



## Department of Human Molecular Genetics

(Established: 1995)



### Head

Prof. Dr. Hans-Hilger Ropers  
Phone: +49 (0)30 8413-1240  
Fax: +49 (0)30 8413-1383  
Email: ropers@molgen.mpg.de

### Secretary

Gabriele Eder  
Phone: +49 (0)30 8413-1241  
Fax: +49 (0)30 8413-1383  
Email: eder@molgen.mpg.de

### Group leaders of the Department

Dr. Vera Kalscheuer (since 07/95)  
Dr. Andreas Tzschach (since 02)  
Dr. Diego Walther (since 02/03)  
Dr. Reinhard Ullmann (since 04)  
Dr. Andreas Kuss (since 06/05)  
Dr. Tim Hucho (since 09/05)  
Prof. Dr. Ulrike Nuber (02/00-07/05)  
Prof. Dr. Constance Scharff (09/01-09/04)  
Dr. Steffen Lenzner (10/96-12/04)  
Dr. Wei Chen (01/07-12/08)

### Heads of associated groups

apl.Prof. Dr. Harry Scherthan (since 01/04)  
Prof. Dr. Susann Schweiger (since 06)  
Dr. Wei Chen (since 01/09)

## Introduction

For more than 10 years, genome research has focused on finding genetic risk factors for common disorders, based on the ‘Common Disease – Common Variant (CDCV)’ hypothesis – the assumption that for most of the common disorders like dementia, diabetes, coronary heart disease, autism and hypertension there are common genetic risk factors. In 2007, after many years of largely futile genome-wide association studies (GWAS), associated markers were identified for a wide variety of complex disorders, which was hailed as a decisive breakthrough in this field. However, these associations were only found after massively increasing cohort sizes and marker densities, meaning that the vast majority of the associated risk factors have small effects and that they are of no diagnostic and prognostic relevance. Therefore, it is now widely believed that for most common disorders, the CDCV hypothesis is wrong<sup>1</sup>.

This certainly applies to mental retardation (MR) – the biggest unsolved problem of clinical genetics and the largest socio-economic burden of health care – where most severe forms are due to defined chromosomal abnormalities or single gene defects, instead of resulting from multifactorial inheritance, i.e. the interaction of many different gene variants and environmental factors. However, there is increasing evidence that single gene defects also play a significant, previously underestimated role in other complex disorders. This has led to growing uneasiness about the validity of the idea that GWAS is the preferred approach for identifying sequence variants in the human genome that predispose to, or cause, disease.

<sup>1</sup> Terwilliger & Hiekkalinna, Eur J Hum Genet 14:426-437, 2006; News Feature, Nature 456:18-21, 2008.

Moreover, it has raised serious doubts about the strategy, first proposed in the early nineties and uncritically adopted by leading genome centres worldwide, to focus exclusively on complex disorders.

After the introduction of massive-parallel next generation sequencing techniques, there are now indications for a paradigm shift in this field, with renewed attention on single gene disorders. At a recent meeting<sup>2</sup>, two groups reported on their efforts to unravel the molecular basis of Mendelian disorders by sequencing all exons in the genomes of patients and their unaffected parents. Moreover, leading genome researchers expressed their belief that instead of GWAS, whole genome sequencing-based, large-scale elucidation of single gene disorders will be the strategy of choice for shedding more light on the molecular architecture of common disorders.

We were among the first to point out the inherent difficulties of GWAS in complex diseases and to stress that single gene disorders are important in their own right<sup>3</sup>. In line with this, our focus has been, and still is, on the elucidation of single gene disorders. Already in 1995, together with a Danish group, we had launched a project to study disease-associated balanced chromosome rearrangements, as a systematic way to identify disease genes. Almost in parallel, we and others founded the European MRX Consortium, a collaboration involving five European groups that soon became a leader in the search for gene defects causing X-linked mental retardation. In 2003, when it became clear that X-linked forms were not as common as previously thought, our group started a formalized collaboration with a potent group from Iran to study autosomal recessive forms of mental retardation. A year later, and in parallel with only four other groups world-wide, we generated whole genome-spanning tiling path BAC arrays, a novel tool for screening the entire genome for submicroscopic Copy Number Variants (CNVs), which had been implicated in MR and were suspected of playing a role in the aetiology of other diseases, too<sup>4</sup>.

## Developments since 2006

### Next generation sequencing

Since our decision to become beta tester and first buyer of the Solexa/Illumina Genome Analyzer on the European continent, Solexa/Illumina has established itself as the leading manufacturer of next generation sequencing (NGS) systems world-wide, and NGS has become indispensable for our research into MR and related disorders. We were also among the very first users of novel genome partitioning methods, based on hybridization in solution (SureSelect, Agilent), array-based hybridization (Nimblegen and Agilent oligonucleotide arrays) and more recently, multiplex PCR amplification-based methods (Raindance)<sup>5</sup>. Moreover, we pioneered the combination of preparative chromosome sorting and NGS for mutation detection in X-linked and autosomal recessive disorders<sup>6</sup>. With substantial bioinformatics support from the Department of Computational Molecular Biology (head: Martin Vingron), these methods were successfully employed for mutation screening in defined genomic intervals, coding sequences and even in entire chromosomes. Together, they have become a valuable asset for gene finding, and ongoing efforts to generate a pipeline for the analysis of high-throughput sequenc-

---

<sup>2</sup> See News Feature, Nature 461:459, 2009.

<sup>3</sup> Ropers, Frankfurter Allgemeine Zeitung, 26.01.2001; Ropers, Am J Hum Genet 81:199, 2007; Ropers, OrphaNews, Dec.24th, 2008, <http://www.orpha.net/actor/EuropaNews/2008/081224.html>.

<sup>4</sup> For more details, see also Research Report 2006.

<sup>5</sup> Hu, Chen, Kalscheuer, Ropers et al, in preparation; see also report of Ullmann and Chen.

<sup>6</sup> See reports of Kalscheuer and Kuss.



ing data (S. Haas et al, Dept. Vingron) promise to overcome the residual limitations of this approach.

### Identification of gene defects and genetic risk factors for MR and related disorders

Various complementary strategies were employed to map and identify genetic defects that underlie, or predispose to, mental retardation or related disorders, as outlined in the previous report. Given the many apparently relevant microdeletions and duplications observed in mental retardation, we extended the *search for copy number variants (CNVs)* to patients with autism, schizophrenia, attention deficit/hyperactivity disorder (ADHD) and several other complex diseases. Reasoning that these CNVs would only be relevant for diagnosis and prognosis if found in at least 1% of these patients, and in view of our budgetary constraints, cohort sizes were mostly limited to 100 well-characterized patients.

Among a wide variety of pathogenetically relevant CNVs, we identified a duplication on chromosome 16p13.1 as a risk factor for autism, and the reciprocal deletion in several patients with MR<sup>7</sup>. Follow-up studies<sup>8</sup> have shown that the del16p13.1 is one of the most common risk factors for MR known to date, and that it also predisposes for epilepsy<sup>9</sup>. Recently, other groups<sup>10</sup> found that the dup16p13.1 is also a risk factor for schizophrenia. Previously, other CNVs identified in our schizophrenia cohort had been implicated in autism. These observations point to pathogenetic links between MR, autism and schizophrenia, indicate that all three disorders are highly heterogeneous and have strengthened our belief that large-scale gene finding will eventually lead to the identification of novel regulatory pathways<sup>11</sup>.

To speed up fine-mapping of breakpoints and gene finding in patients with *disease-associated balanced chromosome rearrangements (DBCRs)*, we have combined preparative sorting and next generation sequencing of derivative chromosomes from mentally retarded patients. In this way, we have identified several additional candidate genes for MR<sup>12</sup>. As pointed out by the reviewers of this article, this was the first application of NGS for finding novel disease genes. More recently, we have shown that genomic paired-read sequencing is sufficiently accurate for breakpoint mapping, i.e. that prior chromosome sorting is not necessary<sup>13</sup>.

According to current estimates<sup>14</sup>, approximately 10 percent of all genetic forms of MR are X-linked. To date (October 2009), about 90 genes have been implicated in *X-linked MR (XLMR)*, and mutations in one third of these have been reported in patients with non-syndromic forms of XLMR, with major contributions from our group and from other members of the European MRX Consortium. In 2006, when the Sanger-Wellcome Institute (Hinxton, UK) obtained funds for sequencing all X-chromosomal genes in 200 XLMR families, it was widely believed that this would lead to the identification of most missing XLMR genes, but in the course of this project, no more than 10 additional genes were found. Moreover, to confirm the status of candidate genes showing mutations in a single family, several hun-

<sup>7</sup> Ullmann et al, Hum Mutat 28.7 :674-682, 2007.

<sup>8</sup> Mefford et al, Genome Res 19:1579-1585, 2009.

<sup>9</sup> de Kovel et al, Brain 2009 online, doi:10.1093/brain/awp262.

<sup>10</sup> Ingason et al, Mol Psychiatry, Sept. 29<sup>th</sup>, 2009 [Epub ahead of print]; Ikeda et al, Biol Psychiatry Oct 30<sup>th</sup>, 2009 [Epub ahead of print].

<sup>11</sup> For details, see report Ullmann.

<sup>12</sup> Chen et al, Genome Research 18.7:1143-9, 2008.

<sup>13</sup> Chen et al, Eur J Hum Genet 2009, in press; for more details concerning DBCRs, see reports of Kalscheuer and Chen.

<sup>14</sup> Ropers & Hamel, Nature Rev Genet 6:46-57, 2005.

dred additional families had to be tested, which is why the Euro MRX Consortium was invited to join in before the results of this study were published<sup>15</sup>. In our opinion, the relatively meagre results of this study are primarily due to the incomplete coverage of coding regions on the X chromosome, which is due to the fact that only slightly more than 700 genes were screened for mutations, and on average, only 65 percent of the exonic nucleotides were screened. Moreover, this study focused on the detection of protein-truncating mutations, whereas about half of the intragenic sequence variants were non-polymorphic missense changes, and sequence variants outside exons and splice sites were not studied at all. Finally, many of the families studied were small, including also kindreds with only two affected males, where X-linkage is possible but not proven. This has encouraged us to embark on an even more ambitious project aiming to identify all sequence variants in the non-repetitive portion of the X-chromosome in >200 Consortium families with proven X-linked inheritance. For this project, which started in 2009 and is just reaching its production phase, we combine exon enrichment and chromosome sorting with state-of-the-art NGS<sup>16</sup>.

*Autosomal recessive MR (ARMR)* has been largely disregarded in the past, probably because in Western populations, it is rarely familiar and often overlooked<sup>17</sup>. When we and our Iranian colleagues published the results of homozygosity mapping in the first 78 consanguineous ARMR families<sup>18</sup>, we did not find any overlapping linkage intervals and concluded that this disorder must be extremely heterogeneous. In the meantime, we have studied more than 200 additional families, and this enabled us to identify several families with overlapping linkage intervals as well as several novel ARMR genes. In several of these, two or even three allelic mutations have been found. These observations appear to refute our earlier statements concerning the extreme heterogeneity of ARMR and argue for the existence of genes that are mutated in several percent of the patients, at least in Iran<sup>19</sup>. Moreover, at least two of these candidate genes seem to directly interact, thereby establishing the first step of a novel MR pathway<sup>20</sup>.

From now on, novel genomic enrichment and NGS techniques will greatly accelerate these studies, and already today, the *recruitment and clinical characterization of patients and families* has become the most important rate-limiting factor (see also report Tzschach). Due to our long-standing international partnerships, we are very well positioned in this field. In 2007, we have initiated the MR-NET (co-ordinator A. Reis, Erlangen), which is part of the German National Genome Research Network (NGFN*plus*) and forms a new platform for recruiting German patients and families. Apart from the large and still growing number of XLMR families recruited by the EuroMRX Consortium, numerous additional families with XLMR have been identified in Iran<sup>21</sup> while recruiting familial cases for ARMR studies, and in collaboration with S. Mundlos (MPIMG and Charité Berlin), sporadic patients with MR are being recruited for CNV screening in the context of the MR-NET. So far, our Iranian partner has collected more than 500 consanguineous families with two or more mentally retarded children. In the majority of these, MR

---

<sup>15</sup> Tarpey et al, Nature Genetics 41.5:535-43, 2009.

<sup>16</sup> See also reports of Chen and Kalscheuer.

<sup>17</sup> See Ropers, Current Opinion in Genetics & Development 16(3):260-269 (2006); id., Am J Hum Genet 81.2:199-207,2007; id., Current Opinion in Genetics & development 18:241-250, 2008..

<sup>18</sup> Najmabadi et al, Hum Genet 121:43-48, 2007.

<sup>19</sup> See report Kuss.

<sup>20</sup> Moheb, Kuss, Tzschach, Kahrizi, Najmabadi and Ropers, unpublished.

<sup>21</sup> Pouya et al, Eur J Med Genet 52:170-3, 2009.



should be due to autosomal recessive gene defects, and to our knowledge, this is by far the largest cohort of its kind.

### Functional studies

During the past few years, the functional expertise available in various groups of our department has been a valuable asset for our research into MR and related disorders, as documented by numerous publications that are co-authored by several group leaders. Still, as predicted in the previous report, research into the function of disease genes can never keep track with their identification, and given the wide range of mechanisms leading to MR, the methodological infrastructure required for such studies will always be a problem.

A possible solution is to focus on the function of specific MR genes (such as PQBP1, CDKL5, ARHGEF9 and DYRK1A)<sup>22</sup> or pathways (e.g., the serotonin metabolism which has been implicated previously in behavioural disorders)<sup>23</sup>. Other groups deal with chromosome dynamics in mitosis and meiosis<sup>24</sup>, mechanisms of pain sensitization and perception involving the brain<sup>25</sup> and chromatin modification, another important mechanism in MR<sup>26</sup>. The work of S. Schweiger is exceptional in that her previous investigation of a monogenic malformation syndrome has paved the way for ongoing research into drug therapies for cancer, Alzheimer and Huntington disease<sup>27</sup>.

As a fast and (almost) general approach to shed more light on the function of novel MR genes, we have joined forces with Matthias Mann (MPIB, Martinsried) and Antony Hyman (MPICBG, Dresden), who have embarked on a large-scale project to study the interaction of all human proteins. This approach entails the transfection of BAC clones carrying GFP-tagged genes into HeLa and mouse ES cells, followed by GFP-mediated isolation and mass spectrometry of the relevant protein complexes<sup>28</sup>. In parallel, functional analyses of individual genes and proteins will be performed through collaboration with specialized groups.

### Outlook

There is now increasing empirical and theoretical support for the notion that large scale identification of MR genes is a viable option for shedding light on their function, as mentioned above<sup>29</sup>: the more genes will be identified, the more likely it is that they will form functional clusters or pathways, and this will be a major asset for understanding their role in the brain and in the pathogenesis of MR. Therefore, and in view of the gradually diminishing resources of our department, which will be closed in Fall 2014, we will increasingly focus on the molecular elucidation of MR and related disorders, as a basis for reliable diagnosis, prevention and eventually, therapy. As of 2011, support from the EU and other sources will partially compensate the gradual loss of structural funding, and various possibilities are being explored to continue this research elsewhere if it is still competitive in 2014.

<sup>22</sup> See report Kalscheuer.

<sup>23</sup> See report Walther.

<sup>24</sup> See report Scherthan.

<sup>25</sup> See report Hucho.

<sup>26</sup> See report Ullmann.

<sup>27</sup> See report Schweiger.

<sup>28</sup> See also report Kuss.

<sup>29</sup> See also Outlook, Research Report 2006.

## Signal Transduction in Pain and Mental Retardation

(Established: 09/2005)

---



### Head

Dr. Tim Hucho (since 09/05)  
Phone: +49 (0)30 8413-1243  
Fax: +49 (0)30 8413-1383  
Email: hucho@molgen.mpg.de

### Scientists

Jörg Isensee\* (since 09)  
Chandan Goswami (05-09)

### PhD students

Julia Kuhn\* (since 06)  
Christine Andres (since 08)  
Juliane Schreier\* (since 09)  
René Buschow (since 09)

### Technicians

Vanessa Suckow (since 05)

142

## Introduction

The clinical approach to pain therapy is still driven by the pain concurrent symptomatic diseases such as *Herpes zoster* infection, diabetes and/or surgical intervention. The attempted leap to a mechanism based therapy by the BMBF funded “Deutsche Forschergruppe Neuropathischer Schmerz” has failed so far in the face of remaining confusion about the underlying molecular mechanisms. This is partially due to a very limited understanding of the intracellular signalling network responsible for peripheral sensitization, as past research has mostly focussed on the large numbers of extracellular mediators and ion channels involved in various pain states. Signalling has been rather inaccessible for research as no cell line system is established and because the sensory neurons are of a puzzling and ill defined heterogeneity.

## Results since 2006

We established and since employ successfully a culture system of primary sensory neurons to study endogenous signalling underlying sensitization. Central to our research is the translocation of one protein kinase C isoform, PKC $\epsilon$ , to the plasma membrane in the course of its activation. Based on our studies giving prove of principle for GPCR $\alpha$ -s/cAMP/Epac/PKC $\epsilon$  crosstalk occurring only in a subpopulation of sensory neurons, we extended our knowledge about intracellular signalling events correlating with pain sensitization. Finishing a protein array approach, we identified 35 novel PKC $\epsilon$ -substrate candidates. These results indicated a novel cellular organelle, the stress granule, to be centrally regulated by PKC $\epsilon$  and thereby introduced a novel aspect to cellular pain sensitization beyond ion channel regula-

\* externally funded



tion. Molecular and cellular details are under investigation, which we pursue in collaboration and technical exchange with Sylvia Krobtsch within the institute. In house collaboration on *in vitro* translation experiments will be established with Knud Nierhaus, and expression clones are shared with Zoltan Konthur.

In parallel, we investigated the action of PKCε signalling on a known phosphorylation target, the capsaicin receptor TRPV1. We describe for the first time that a TRPV ion channel can have a functionality beyond its ion channel properties. We describe PKCε phosphorylation to alter the direct biochemical interaction of TRPV1 with the ends of microtubules, which thereby get released to transfer the sensitizing signal to a nearby effector complex. These data are the very first to describe an ion channel cytoplasmic domain to be a mere signalling intermediate, and show on a cellular level that sensitization signalling results in cytoskeleton rearrangements (manuscript to be submitted by end of 2009).

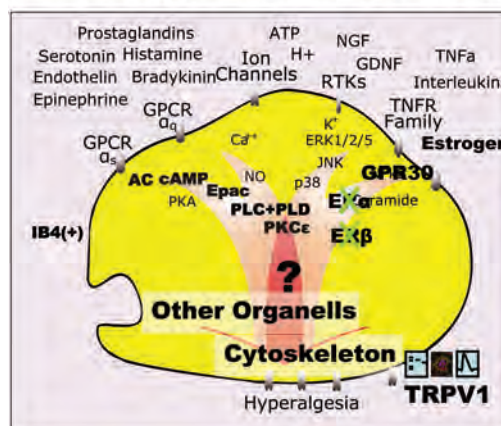
Beyond the effect of sensitization signalling pathways on microtubules in a TRPV1-dependent manner, we also found TRPV1-dependent changes of the acting cytoskeleton. In addition, we found TRPV1-dependent actin reorganization and lamellipodia to filopodia transgression. The ramifications of these observations are presently under investigation.

Beyond the identification of novel cellular mechanisms of PKCε sensitization signalling we investigated if and how the peripheral sensory neuron integrates multiple sensitizing stimuli. Surprisingly we found, that the signalling outcome is less dependent on the input signal but rather on the signalling history of the cell. The signalling history was memorized for over 20 hours and resulted in inversion of the signaling outcome of successive stimuli. Thus, in primary cell cultures, single fibre electrophysiological recordings, animal behaviour as well as human behavioural studies the successive “sensitization” attempt resulted not in sensitization, but in complete erasure of already established sensitization. This opens a completely novel approach to therapeutical intervention. It is also the very first indication that the activation of endogenous signalling pathways can lead to memory deletion (manuscript currently under revision at PNAS).

The number of pain-inhibitory substances is very limited. We introduced two novel substances to the pain field: estrogen and EGF. We provided evidence for a first biological functionality for the novel estrogen receptor GPR30 *in vitro* as well as *in vivo*. This also gave a first rational for the second most common side effect, namely pain, in the course of breast cancer therapy with Fulvestrant, a now known GPR30 agonist (Kuhn et al. 2008).

EGF plays an important role during tissue regeneration after e.g. painful mechanical tissue disruption. Establishing a quantitative single cell based immunofluorescence technique, we found different activation kinetics for the MAPK ERK1/2 if activated through EGF versus NGF exposure. Accordingly in behavioural experiments we did not find EGF to induce pain sensitization but to inhibit PGE2

### Concepts under investigation...



- Novel Pathway Elucidation
- Cellular Correlates of Pain
- Pain Module
- Signal Computation

induced sensitization. Indeed, increased pain sensitivity has been reported in clinical trials of cancer related EGFR-blocking therapy. This is the first investigation of the importance of signaling kinetics for pain sensitization (manuscript in preparation).

Being embedded into the Department of Human Molecular Genetics, we have been instrumental in the investigation of a mutation found to cause mental retardation. We described the mutation to result in a loss of function of the glutamate receptor Grik2, thereby giving the first evidence, that indeed glutamate receptors are in humans involved in higher brain functions (Motazacker et al. 2007).

Further, in collaboration with Andreas Kuss and Eckehard Friedel, we collected blood of fibromyalgia patients to identify in a first level of investigation expression markers for better categorization of this widespread phenotype with partial genetic background (prevalence about 5% of the European population). The underlying mutations have so far not been described, something we attribute first of all to the lack of a clear diagnostic marker. The study is ongoing.

Finally, we are involved in the functional analysis of a balanced chromosomal translocation that had been identified by Vera Kalscheur in the department to underlie mental retardation. The breakpoint was mapped to be close to the ion channel TRPV1. TRPV1 had so far mostly been investigated in the context of pain. We now identified TRPV1 to be a synaptic protein, to modulate strongly endo- as well as exocytosis, and to be an important regulator of dendritic spine like protrusions. Thereby we provided a first rationale for the observed severe mental retardation phenotype (manuscript under revision at JCS).

We expanded our technical methodological abilities in the laboratory to viral techniques (lenti as well as adeno viruses), to live cell imaging (Calcium imaging as well as live observation of morphological changes), and to high content quantitative single cell microscopy. This allowed us to extend the focus of our work from PKC $\epsilon$  to ERK as well as calcium and will facilitate further increase in the number of signaling components under investigation. Further techniques like behavioural experiments and single cell PCR are planned. I am proud to have been instrumental in formation of a BMBF consortium (including Harald Seitz at the MPIMG) around our attempt to identify intracellular signalling modules underlying pain sensitization. In that consortium, which I am coordinating, system biological approaches are initiated.



## General information

### Selected publications

Goswami C, Hucho T. *Submembraneous microtubule cytoskeleton: biochemical and functional interplay of TRP channels with the cytoskeleton*. FEBS J. 2008; 275:4684-4699

plus Editorial for this series about submembraneous cytoskeleton, which we initiated and organised: Goswami C, Hucho T. *Novel aspects of the submembraneous microtubule cytoskeleton*. FEBS J 2008; 275:4653

Kuhn J, Dina OA, Goswami C, Suckow V, Levine JD, Hucho T. *GPR30 Estrogen Receptor Agonists Induce Mechanical Hyperalgesia in the Rat*. Eur J Neuroscience 2008; 27(7):1700-9

Motazacker M, Rost B, Hucho T, Garshasbi M, Kahrizi K, Ullmann R, Abedini S, Nieh S, Amini S, Goswami C, Tzschach A, Jensen L, Schmitz D, Ropers HH, Najmabadi H, Kuss AW. *A Defect in the Ionotropic Glutamate Receptor 6 Gene (GRIK2) is Associated with Autosomal Recessive Mental Retardation*. Am J Hum Genetics 2007; 81(4):792-8

Goswami C, Hucho T. *TRPV1 expression-dependent initiation and regulation of filopodia*. J Neurochem 2007; 103(4):1319-33

Hucho T, Levine JD. *Signaling Pathways in Sensitization: Toward a Nociceptor Cell Biology*. Neuron 2007; 55(3):365-376

### Awards

Poster Prize GBM Herbsttagung 2007

PosterPrize Congress of the International Society of Gender Medicine 2006

### Work as scientific referee

Tim Hucho serves as scientific referee for the following journals: PNAS, FEBS Journal, Cell Biochemistry and Function, Cell Biology International.

Tim Hucho serves as scientific referee for the following institution: DFG, University of Erlangen.

### External funding

BMBF, MedSys: *Modeling of peripheral Pain Switches (MoPS)*, 02/09-01/12

DFG Hu 1636/2-1: *Identification of substrates of PKCε and their role in pain sensitization*, 05/08-04/11

Studienstiftungs-stipend with/for Julia Kuhn, max 3 years

### Teaching activities

Lecture „Biochemie“ at FU Berlin, each term since summer 07

Supervision of the practical „Radionuklidchemie“ at FU Berlin, SS 2008/9, twice per semester one week each, WS 2009 one week

Lecture „Neurobiologische Grundlagen und Modellsysteme“ in the course of the inhouse PhD Programm of the MPIMG (2008, 2009)

### Organization of scientific events

Member of the organizing committee „Studiengruppe Neurochemie (GBM)“ for the „GBM Herbsttagung 2007“

Member of the organizing committee „Studiengruppe Molekulare Neurobiologie (GBM)“ for the „GBM Herbsttagung 2008“

Member of the organizing committee of the Workshop „Molecular Interactions“ 2008

Member of the organizing committee of the Workshop „Molecular Interactions“ 2009

Organization and chairing of the symposium „memory deletion“ at the european neuroscience meetings of the FENS 2010 in Amsterdam

### Public relations

Experimental lecture during the „Lange Nacht der Wissenschaften (Long night of science)“, 2006, 2009

Experimental lecture at the Marie Curie Gymnasium, Ludwigsfelde near Berlin, 11/08

## Chromosome Rearrangements and Disease

(Established: 1995)

### Head

Dr. Vera M. Kalscheuer  
Phone: +49 (0)30 8413-1293  
Fax: +49 (0)30 8413-1383  
Email: kalscheu@molgen.mpg.de

### Scientist

Dr. Luciana Musante (since 02/03)

### PhD students

Nils Rademacher (since 02/05)  
Stella-Amrei Kunde (01/05-06/09)  
Kristine Freude (03/01-01/05)  
Olivier Hagens\* (09/00-01/05)  
Sarah Shoichet\* (09/00-11/04)  
Barbara Dlugaszewska\* (10/00-10/04)  
Jiong Tao (10/00-08/04)  
Magdalena Mayer (02/02-10/04)  
Luciana Musante\* /12/00-02/03)



### Technicians

Ute Fischer (since 08/95)  
Astrid Grimme (since 02/04)  
Kirsten Hoffmann\* (01/02-05/07)  
Corinna Menzel (00-12/06)

### Scientific overview

The Chromosome Rearrangements and Disease Group focuses on the genetic causes of human disorders of the brain, and on the pathogenetic mechanisms underlying known gene mutations.

For finding novel disease genes we apply three complementary approaches. One of these is to map the chromosome breakpoints of patients with a disease-associated balanced chromosome rearrangement. This endeavour was very successful and has resulted in the identification of numerous novel disease genes, both on the X chromosome and on autosomes. To expedite the process of translocation breakpoint mapping we use ultrahigh resolution oligonucleotide arrays and flow sorting of derivative chromosomes (in collaboration with R. Ullmann). For determining inversion breakpoints more rapidly and efficiently we use next generation sequencing (in collaboration with W. Chen). Recently, we have also embarked on systematic mutation screening in families with X-linked mental retardation (MR), employing next generation sequencing strategies (in collaboration with W. Chen). The third approach is to screen novel candidate genes, identified through establishing the protein-protein interaction network for known MR proteins, in patients with the corresponding clinical phenotype.

As a small side project we have continued our search for novel pathogenic mutations in patients with Noonan Syndrome or Noonan Syndrome-like phenotype. In addition to mutation search, functional studies aiming to understand the pathology of known gene mutations include deciphering the molecular networks and protein complexes involving the “disease proteins”. These studies yielded new insights into the underlying molecular mechanisms, promise to reveal new disease genes and modifiers, and eventually might lead to potential therapeutic targets.

\* externally funded



One recent example of successful novel disease gene finding by chromosome breakpoint mapping is *DYRK1A*, which lies on chromosome 21, within both the Down syndrome critical region and in the minimal region for partial monosomy 21. *DYRK1A* encodes a highly conserved dual-specificity tyrosine phosphorylation-regulated kinase. We have found that truncations of *DYRK1A* caused a clinical phenotype comprising prenatal onset of microcephaly, intrauterine growth retardation, feeding problems, developmental delay, and febrile seizures/epilepsy in two unrelated patients who both carried a *de novo* balanced translocation (Møller et al., *Am J Hum Genet.* 2008). Our results highlight the importance of a correct gene dosage of *DYRK1A* for normal brain development and strongly suggest that in humans the dosage of the associated kinase needs to be very tightly regulated. Also recently, fine mapping of the X-chromosome breakpoint in a female patient presenting with a disturbed sleep-wake cycle, late-onset epileptic seizures, increased anxiety, aggressive behavior, and mental retardation indicated disruption of the collybistin gene (*ARHGEF9*). Expression of truncated collybistin proteins in cultured neurons interfered with synaptic localization of endogenous gephyrin and GABA(A) receptors. These results suggest that collybistin has a key role in membrane trafficking of gephyrin and selected GABA(A) receptor subtypes involved in epilepsy, anxiety, aggression, insomnia, and learning and memory (Kalscheuer et al., *Hum Mut.* 2009).

Using the same approach, we have found that truncations of the cyclin-dependent kinase-like 5 (*CDKL5*) gene are a significant cause of infantile spasms and early epileptic seizures in female patients (Kalscheuer et al., *Am J Hum Genet.* 2003, Córdova-Fletes et al., *Clin Genet.* 2009) and of an intractable seizure disorder, called atypical Rett syndrome (Tao et al., *Am J Hum Genet.* 2004 and unpublished results). In the meanwhile the link between atypical Rett syndrome and a mutation in *CDKL5* has been confirmed by several other groups. Likewise, we have shown that truncation of the *Netrin G1* gene caused a highly similar clinical phenotype in a patient with a balanced translocation involving chromosomes 1 and 7 (Borg et al., *Eur J Hum Genet.* 2005).

Along the same lines, our studies indicated that a *de novo* balanced chromosome rearrangement truncated the *FOXG1* gene (Shoichet et al., *Hum Genet* 2005). More recently, several other groups have confirmed that mutations in *FOXG1* cause atypical Rett syndrome.

To date, the functional role of CDKL5 is far from being understood and only two interaction partners have been discussed in the literature: the methyl CpG binding protein 2 (MeCP2) and the DNA methyltransferase1 (DNMT1). Mutations in *MECP2* are the major cause of typical Rett syndrome and CDKL5 has been proposed to regulate MeCP2 function in the nucleus. To gain more insights into the functions of the CDKL5 complex in the normal and diseased brain, we have searched for CDKL5 interaction partners and have investigated protein products that could act in the same signalling pathway. Interestingly, the majority of the newly identified components of the CDKL5 complex are associated with constitu-

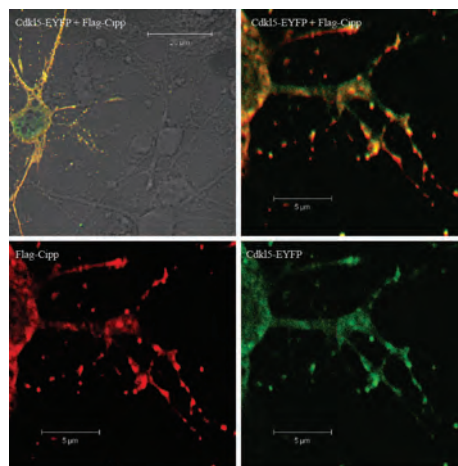


Figure 1: Colocalization of *Cdkl5* and the PDZ-protein *Cipp* (*InaD*-like) in cortical mouse neurons (DIV 10). Primary neurons were transfected with *Cdkl5*-EYFP and *Flag-Cipp* expression constructs. *Cdkl5* and *Cipp* colocalize in a dotted pattern along the neurites.

ents of the cytoskeleton and have an established role in vesicle trafficking and protein turnover, respectively. Our findings suggest that CDKL5 is part of a protein network, which is involved in creating and regulating cell-cell contacts and may act as an upstream effector of MeCP2 (Rademacher and Kalscheuer, unpublished results).

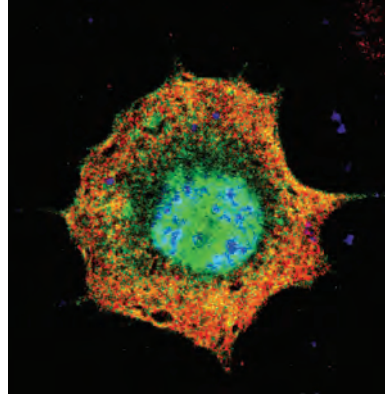


Figure 2: Colocalization of PQBP1 and one of the newly found interaction partners in the cytoplasm of neuronal F11 cells.

In addition, we have found that mutations in the X-linked polyglutamine binding protein 1 (*PQBP1*) gene cause mental retardation, microcephaly, short stature and other midline defects with variation in severity of the phenotypes, both within and between families (Kalscheuer et al., Nat Genet 2003; Cossee et al., Eur J Hum Genet 2006). The pathogenic nature of all but one mutations in the *PQBP1* gene is a premature termination codon (PTC) and we have evaluated the consequences on mRNA and protein expression. We could show that in the patients all frameshift mutations result in the production of a truncated PQBP1 protein (Musante et al., Hum Mutat 2009).

Therefore, it is highly likely that the clinical phenotype is caused by the loss of wild-type PQBP1-associated functions and the presence of defect PQBP1 protein. RT-PCRs revealed mutation-specific reduction of *PQBP1* mRNAs carrying the PTCs that can be partially restored by blocking translation, thus indicating a role for the nonsense-mediated mRNA decay pathway. In addition, these mutations resulted in altered levels of *PQBP1* transcripts which skipped exon 4 probably as a result of affecting important splicing motifs. This hypothesis is supported by transfection experiments using wild-type and mutant *PQBP1* minigenes. These studies provide significant insight into the early events contributing to the pathogenesis of the *PQBP1* related XLMR disease. To get more insight into the possible functions of PQBP1, we have established a PQBP1 interaction network. Interestingly, our results suggest that PQBP1 might have diverse roles in gene or chromatin regulation and RNA metabolism, e.g. binding partners might play a role in transcription regulation, alternative splicing and mRNA stability/transport, particularly in the brain (Musante, Kunde, Kalscheuer, unpublished results). These findings support the hypothesis that PQBP1 protein scaffolds a variety of distinct multiprotein complexes *in vivo*. The role of normal and mutant PQBP1 in these processes is under study.



## General information

### Selected publications

Musante L, Kunde SA, Sulistio TO, Fischer U, Grimme A, Frints SGM, Schwartz CE, Martínez F, Corrado Romano, Ropers HH, Kalscheuer VM. *Common pathological mutations in PQBP1 induce nonsense-mediated mRNA decay and enhance exclusion of the mutant exon*. Hum Mutat. 2009 Oct 21, epub ahead of print.

Kalscheuer VM, Musante L, Fang C, Hoffmann K, Fuchs C, Carta E, Deas E, Venkateswarlu K, Menzel C, Ullmann R, Tommerup N, Dalprà L, Tzschach A, Selicorni A, Lüscher B, Ropers HH, Harvey K, Harvey RJ. *A balanced chromosomal translocation disrupting ARHGEF9 is associated with epilepsy, anxiety, aggression, and mental retardation*. Hum Mutat. 2009 Jan;30(1):61-8.

Møller RS, Kübart S, Hoeltzenbein M, Heye B, Vogel I, Hansen CP, Menzel C, Ullmann R, Tommerup N, Ropers HH, Tümer Z, Kalscheuer VM. *Truncation of the Down syndrome candidate gene DYRK1A in two unrelated patients with microcephaly*. Am J Hum Genet. 2008 May;82(5):1165-70.

Tao J, Van Esch H, Hagedorn-Greiwé M, Hoffmann K, Moser B, Raynaud M, Sperner J, Fryns JP, Schwinger E, Gécz J, Ropers HH, Kalscheuer VM. *Mutations in the X-linked cyclin-dependent kinase-like 5 (CDKL5/STK9) gene are associated with severe neurodevelopmental retardation*. Am J Hum Genet. 2004 Dec;75(6):1149-54.

Kalscheuer VM, Freude K, Musante L, Jensen LR, Yntema HG, Gécz J, Sefiani A, Hoffmann K, Moser B, Haas S, Gurok U, Haesler S, Aranda B, Nshedjan A, Tzschach A, Hartmann N, Roloff TC, Shoichet S, Hagens O, Tao J, Van Bokhoven H, Turner G, Chelly J, Moraine C, Fryns JP, Nuber U, Hoeltzenbein M, Scharff C, Scherthan H, Lenzner S, Hamel BC, Schweiger S, Ropers HH. *Mutations in the polyglutamine binding protein 1 gene cause X-linked mental retardation*. Nat Genet. 2003 Dec;35(4):313-5.

### Selected invited talks

1st European Congress on Rett Syndrome, Milan Italy, 2009, *New insights into the pathomechanism of Rett-related disease entities*

Symposium on Molecular Medicine and Health, Hyderabad India, 2005, *Balanced chromosome rearrangements and disease*

3<sup>rd</sup> Iranian Congress of Genetic Disorders & Disabilities, Tehran Iran, 2004, *Balanced chromosome rearrangements and disease*

Annual meeting of the clinical geneticists of Quebec, Montreal Canada, 2004, *Progress in X-linked mental retardation*

European Society of Human Genetics Meeting, Munich, 2004, *Chromosome rearrangements and disease genes*

### Awards

Award for the best poster presentation in “Molecular and biochemical basis of disease, developmental genetics, neurogenetics” at the German Society of Human Genetics Annual Meeting 2009. Kunde SA, Musante L, Müller EC, Ropers HH, Kalscheuer VM. *Studies on the cytoplasmic polyglutamine binding protein 1 (PQBP1) for understanding its role in mental retardation*. Med Gen (2009)21:288.

Award for the best poster presentation at the European Society of Human Genetics Annual Meeting 2009. Musante L, Kunde SA, Ropers HH, Kalscheuer VM. *Towards understanding the pathogenetic mechanism of PQBP1 mutations in X-linked mental retardation*.

Award of the 29<sup>th</sup> Blankenese conference Protein Processing Meets Synaptic Transmission 2009. Rademacher N, Kalscheuer VM. *New insights into the molecular pathomechanism of Rett-related disease entities*.

Award for the best poster presentation in “Molecular and biochemical basis of disease, developmental genetics, neurogenetics” at the German Society of Human Genetics Annual Meeting 2008. Kunde SA, Musante L, Müller EC, Ropers HH, Kalscheuer VM. *Towards understanding the role of the polyglutamine binding protein 1 (PQBP1) in mental retardation*. Med Gen (2008)20:248.

### Membership in journal editorial boards

Review Editorial Board Member of Frontiers in Molecular Neuroscience

### Scientific referee

Vera Kalscheuer serves as scientific referee for the following journals: Human Molecular Genetics, American Journal of Human Genetics, European Journal of Human Genetics, Journal of Medical Genetics.

In addition, Vera Kalscheuer serves as scientific referee for the Deutsche Forschungsgemeinschaft.

### Memberships in professional societies

Founding member of the German Society of Human Genetics

Scientific advisor for the library of the MPIMG and member of the library committee

### External funding

BMBF, NGFN2: *Identification of genetic risk factors for complex disorders by studying patients with associated balanced chromosomal rearrangements*. Joint with Dr. A. Tzschach, MPIMG, 2005-2008

DFG, SFB 577: *Analysis of Clinical Variability in Mendelian Disorders*, subproject *Search for modifier genes in X-linked mental retardation*, 2003-2009

### Teaching activities

Lecture *Genetik für Bioinformatiker*, Free University Berlin, SS 2006, SS2007

Lecture, Seminar and Practical Course *Biologie für Mediziner*, Humboldt Universität Berlin, WS 2006/2007

### Organization of scientific events

Member of the Dahlem Colloquium committee, an institute wide seminar series



## Familial Cognitive Disorders

(Established: 06/2005)

### Head

Dr. Andreas W. Kuss  
Phone: +49 (0)30 8413-1253  
Fax: +49 (0)30 8413-1383  
Email: kuss\_a@molgen.mpg.de

### Scientists

Dr. Lars Riff Jensen (since 04/02)  
Dr. Masoud Garshasbi (since 05/08)

### PhD students

Lia Abbasi Moheb (since 10/05)  
Joanna Walczak Stulpa (since 10/05)  
Sahar Esmaeli Nieh (since 11/06)  
Lucia Püttmann (since 06/08)  
Agnes Zecha (since 07/08)  
Robert Weißmann (since 12/09)  
Rui Tian<sup>1</sup> (09/05-09/09)  
Masoud Garshasbi (02/04-05/08)  
Mohammad Mahdi Motazacker (02/04-07/07)  
Wei Chen (until 07/05)  
Bartłomiej Budny (03-05)



### Technicians

Bettina Lipkowitz (since 05)  
Marianne Schlicht (since 05)  
Georg Lienke (09/06-03/09)  
Melanie Wendhack (08/02-12/06)  
Marion Amende-Acar (until 03/06)

## Scientific overview

### X-linked forms of mental retardation (XLMR)

As member of the European MRX Consortium, our department has made important contributions to the elucidation of X-linked mental retardation (XLMR, for review see e.g. Gecz et al. 2009, Trends Genet 25:308; Ropers 2008, Curr Opin Genet Dev 18:241; Ropers 2006, Curr Opin Genet Dev 16:260) including the discovery that mutations in the histone demethylase *KDM5C* (*JARID1C*) gene are a frequent cause of XLMR [Jensen et al. 2005, Am J Hum Genet 76:227; Tzschach et al. 2006, Hum Mutat 27:389] or the identification of several mutations in the methyl transferase *Ftsj1* [Freude et al. 2004, Am J Hum Genet 75:305]. Both genes also feature prominently among the recent research activities of our group concerning functional aspects of MR genes. In this context, we have been able to describe a distinct gene expression fingerprint in lymphoblastoid cell lines as well as whole blood from male patients with mutations in *KDM5C* [Jensen et al., Pathogenetics 2009 (accepted)].

Using a murine embryonic stem cell line (RRD143, Baygenomics) with a genetrap in *Ftsj1*, for injection in C57BL/6 blastocysts we have produced mice lacking functional *Ftsj1* (collaboration with Diego Walther), and are presently investigating the effects of *Ftsj1* deficiency in this model.

<sup>1</sup>Supervised by S. Sigrist, FU Berlin

Furthermore, we have designed a resequencing array based on the Affymetrix 50K platform containing the coding and splice site regions of 17 XLMR genes (*ACSL4*, *ARX*, *ATRX*, *DLG3*, *FTSJ1*, *GDII*, *IL1RAPL1*, *JARID1C*, *MECP2*, *NLGN4*, *PAK3*, *PHF6*, *PHF8*, *PQBP1*, *SLC6A8*, *TM4SF2* and *ZNF41*) in order to investigate the genetic basis of MR in unrelated sporadic male NS-MR patients from the cohort of the EURO-MRX consortium. Application of this array to DNA from 135 patients led to the identification of 6 previously unknown putative disease causing mutations in these genes.

### Autosomal recessive forms of mental retardation (ARMR)

Most of our activities are focussed on the molecular causes of ARMR which is thought to be much more common than XLMR (see e.g. Ropers 2008, Curr Opin Genet Dev 18:241). However, until recently only three genes for non-syndromic ARMR (NS-ARMR) were known: *PRSS12* (neurotrypsin) [Molinari et al. 2002, Science 298:1779], *CRBN* (cereblon) [Higgins et al. 2004, Neurology 63:1927] and *CC2D1A* [Basel-Vanagaite et al. 2006, J Med Genet 43:203] due to insufficient family sizes and lack of consanguinity in western societies, which preclude successful mapping and identification of candidate loci. We have therefore joined forces with Prof. Dr. H. Najmabadi for a large-scale project, aiming at the systematic identification of genes that have a role in ARMR (see also Research Report 2006).

Since the beginning of our collaboration in 2004 we have accumulated more than 200 families with NS-ARMR as well as many families with microcephaly and more than 10 with other syndromic forms of ARMR. Autozygosity mapping, based on whole genome SNP genotyping with various platforms in the majority of these families has so far enabled us to define 40 novel ARMR loci (Fig.1). For 10 of these we could identify the underlying gene defect.

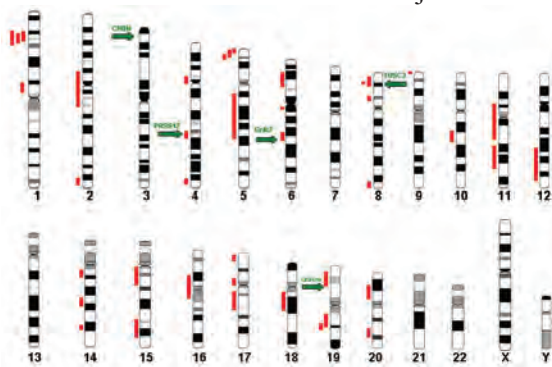


Figure 1. Distribution of ARMR loci throughout the genome. Single linkage intervals identified in 40 different families are represented by red bars. The locations of known genes for NS-ARMR are indicated by green arrows.

The first mutation we found was a deletion of approximately 150 to 200 kb, encompassing the promoter and the first 6 exons of the *MCPH1* gene [Garshasbi et al. 2006, Hum Genet 118:708]. We then identified a complex mutation affecting the kainate receptor subunit encoding gene *GRIK2* [Motazacker et al. 2007, Am J Hum Genet 81:792] and a c.1342C>T nucleotide substitution, which leads to a premature stop codon in exon 10 of *VLDLR*, a gene encoding a member of the low-density lipoprotein receptor (LDLR) superfamily [Moheb et al. 2008, Eur J Hum Genet 16:270]. This was followed by the discovery of a deletion in the *TUSC3* gene [Garshasbi et al. 2008, Am J Hum Genet 82:1158] which is thought to encode a subunit of the oligosaccharyl transferase complex that is involved in the key step of N-glycosylation.

The fifth mutation we found in a family with two branches and four female patients suffering from MR and oligomenorrhea. Here, a sequence change in the *BOD1* gene [Esmaeeli-Nieh et al., presented at the annual ASHG conference, Hawaii, USA, Oct 2009] leads to the loss of all isoforms of the gene product, a kinetochore protein that is involved in spindle attachment and mitotic chromosome segregation [Porter et al. 2007, J Cell Biol 179:187].

Furthermore, a stop mutation (R154X) was identified in the poly-A binding zinc finger protein gene *ZC3H14* in a family with three affected individuals with NS-



ARMR. ZC3H14 and its yeast ortholog NAB are thought to be important regulators of translation [Leung et al. 2009, Gene 439:71] and the functional impact of the stop mutation is being investigated (collaboration with A. Corbett).

Previously we had reported that ARMOR is extremely heterogeneous and that common causes are unlikely to exist [Najmabadi et al. 2007, Hum Genet 121:43]. After having performed homozygosity mapping in many additional consanguineous families, this statement might need qualification. Recently we have identified several ARMOR genes carrying mutations in more than one family (Fig.1).

The first two of these genes are *ZNF526* [Abbasi Moheb et al., presented at the Annual ASHG conference, Hawaii, USA, Oct 2009], where two different mutations occurred in three different families and *NSUN2* with three different mutations in independent families. The ZNF526 protein has nucleic acid binding properties, and whole genome expression profiling in immortalized lymphoblasts from homozygous mutation carriers has enabled us to identify putative target genes may give a clue to the etiology of MR in these patients. In addition, we are performing chromatin immune precipitation experiments followed by next generation sequencing (ChIP-SEQ) to confirm these findings and to identify the DNA targets of the ZNF526 protein.

For ZNF526, NSUN2, BOD1 and an additional selection of >90 MR proteins we are currently performing a large-scale search for interaction partners by a systematic screen of the protein interactome (collaboration with A. Hyman, MPI-CBG, Dresden and M. Mann, MPI-BC, Munich). In these experiments, BACs containing the GFP-labelled murine orthologs of the genes are introduced into HeLa cells. The anti-GFP antibody is then used for pull-down assays followed by mass spectrometry. Functional follow-up studies will be performed in our group.

For the identification of novel MR causing mutations in large homozygous intervals we are currently applying genomic enrichment followed by next generation sequencing (collaboration with W. Chen and H. Hu). This has enabled us to identify apparently pathogenic allelic missense mutations in two families with overlapping linkage intervals on the short arm of chromosome 1 [Najmabadi et al., presented at the 14th X-linked mental retardation workshop, Bahia, Brazil, 2009] affecting the *ST3GAL3* gene. The protein encoded by *ST3GAL3* is a type II membrane protein that catalyzes the transfer of sialic acid from CMP-sialic acid to galactose-containing substrates. Functional investigations are in progress to verify the pathogenicity of these mutations. We expect that this strategy, which also enabled us to identify a plausible novel candidate gene on chromosome 6, will revolutionize the search for novel ARMOR genes.

### Other mendelian disorders

In a consanguineous Polish family with two patients suffering from Cranioectodermal Dysplasia (CED), a rare disorder characterized by craniofacial, skeletal, and ectodermal abnormalities, homozygosity mapping revealed a disease related locus on chromosome 3q21-q24. In the linkage interval from this family we identified a homozygous missense mutation in the IFT122 gene. As a component of the intraflagellar transport complex A, the IFT122 protein plays an important role in the assembly and maintenance of eukaryotic cilia and flagella [Pedersen & Rosenbaum 2008, Curr Top Dev Biol 85:23]. Sequencing of this gene in additional CED patients led to the identification of two further missense changes and a splicing mutation. Functional studies in patient fibroblasts as well as knockdown experiments in Zebrafish provide compelling evidence for the pathogenicity of these mutations and show that CED is a ciliopathy.

## General information

### Selected publications

Mir A, Kaufman L, Noor A, Motazacker MM, Jamil T, Azam M, Kahrizi K, Rafiq MA, Weksberg R, Nasr T, Naeem F, Tzschach A, Kuss AW, Ishak GE, Doherty D, Ropers HH, Barkovich AJ, Najmabadi H, Ayub M, Vincent JB. *Identification of mutations in TRAPPC9, which encodes the NIK and IKK- $\beta$  binding protein (NIBP), in Non-Syndromic Autosomal Recessive Mental Retardation*. Am J Hum Genet 2009; 85: 909-915

Cízková A, Stránecký V, Mayr JA, Tesařová M, Havlíčková V, Paul J, Ivánek R, Kuss AW, Hansíková H, Kaplanová V, Vrbacký M, Hartmannová H, Nosková L, Honzík T, Drahota Z, Magner M, Hejzlarová K, Sperl W, Zeman J, Houštik J, Kmoč S. *TMEM70 mutations cause isolated ATP synthase deficiency and neonatal mitochondrial encephalomyopathy*. Nature Genetics 2008; 40(11): 1288-90.

Garshasbi M, Hadavi V, Habibi H, Kahrizi K, Kariminejad R, Behjati F, Tzschach A, Najmabadi H, Ropers HH, Kuss AW. *A defect in the TUSC3 gene is associated with autosomal recessive mental retardation*. Am J Hum Genet 2008; 82(5): 1158-64

Motazacker MM, Rost BR, Hucho T, Garshasbi M, Kahrizi K, Ullmann R, Abedini SS, Esmaeli-Nieh S, Amini SH, Goswami C, Tzschach A, Jensen LR, Schmitz D, Ropers HH, Najmabadi H, Kuss AW. *A Defect in the Ionotropic Glutamate Receptor 6 Gene (GRIK2) is Associated With Autosomal Recessive Mental Retardation*. Am J Hum Genet 2007; 81(4):792-798.

Najmabadi H, Motazacker MM, Garshasbi M, Kahrizi K, Tzschach A, Chen W, Behjati F, Hadavi V, Nieh SE, Abedini SS, Vazifehmand R, Firouzabadi SG, Jamali P, Falah M, Seifati SM, Gruters A, Lenzner S, Jensen LR, Ruschendorf F, Kuss AW, Ropers HH. *Homozygosity mapping in consanguineous families reveals extreme heterogeneity of non-syndromic autosomal recessive mental retardation and identifies 8 novel gene loci*. Hum Genet 2007; 121(1): 43-48.

### Selected invited talks

*Autosomal recessive intellectual disability: elucidating the molecular basis of a heterogeneous genetic disorder*, Emory University, Atlanta GA, USA, 15.10.2009

*Unravelling the molecular background of autosomal recessive mental retardation*, Institute for Human Genetics, University of Würzburg, Würzburg, Germany, 19.05.2008

### Work as scientific referee

Andreas Kuss serves as scientific referee for the following journals: Human Genetics, Molecular Biology Reports.

### Teaching activities

Lecture *Homozygosity Mapping* in the course of the inhouse PhD Programm of the MPIMG (2008, 2009)

### Public relations

Experimental lecture during the *Lange Nacht der Wissenschaften* (Long night of sciences), 2006



## Clinical Genetics

(Established: 10/2001)

### Head

Andreas Tzschach, MD (since 02)  
Phone: +49 (0)30 8413-1416  
Fax: +49 (0)30 8413-1383  
Email: tzsach@molgen.mpg.de

Maria Hoeltzenbein, MD (10/01-07/07)

### Technicians

Susanne Freier  
Nadine Nowak (since 01/08)



## Scientific overview

The main objective of the “Clinical Genetics” group is the recruitment, evaluation and clinical characterization of patients and families for the various research groups of the “Human Molecular Genetics” department. Access to suitable families and individual patients is crucial for human genetic research that aims at elucidating novel disease genes. Although mental retardation (MR) – the focus of this department’s interest - is not a particularly rare condition (it has a prevalence of approximately 1-2%), only a small subset of these patients qualify as starting points for promising investigations. Generally, this concerns either familial forms of MR in which linkage analysis can be performed, or carriers of chromosome aberrations.

### Autosomal recessive mental retardation

In a large collaboration with the Genetic Research Centre in Tehran/Iran (Prof. Hossein Najmabadi) we are being provided with DNA, blood samples and clinical information of consanguineous families with multiple mentally retarded children. The “Familial Cognitive Disorders” group (AW Kuss) performs homozygosity mapping in these families. The majority of the patients from Iran suffer from unspecific (non-syndromic) mental retardation, but several families also have additional clinical problems. Many of these syndromes are apparently novel and do not resemble other published MR syndromes (e.g. Kahrizi et al., *Eur J Hum Genet.* 2009 Jan;17(1):125-8.; Tzschach et al., *Br J Dermatol.* 2008 Sep;159(3):748-51.). Apart from the clinical evaluation (frequently including proposals for specific investigations such as MRI scans, ophthalmologic examinations and others), we screen the regions of homozygosity for promising functional candidate genes according to morphological similarity or (putative) functional links to other syndromes based on several databases.

In a collaborative project with Dr. A. Rajab (Muscat, Oman), we obtained access to several consanguineous families with syndromic forms of MR. The spectrum of disorders included a form of albinism, ectodermal dysplasia, a muscle disorder

and a large family with MR and epilepsy. We also received material from families with syndromic forms of mental retardation from our partners in Poznan/Poland (Prof A Latos-Bielenska).

### **X-linked mental retardation**

The elucidation of novel genes involved in X-linked mental retardation (XLMR) continues to be a major research focus of our department. Our group recruits families with putative X-linked MR by collaboration with clinical geneticists in Germany and abroad (e.g. Tzschach et al *Hum Mutat.* 2006 Apr;27(4):389., Budny et al *Hum Genet.* 2006 Sep;120(2):171-8.). We also keep clinical data of formerly submitted families updated and communicate the results of mutation analysis to the respective physicians or families. Apart from families with non-syndromic XLMR, we also investigate families with syndromic XLMR. Linkage analysis and mutation analysis in these families is being performed in the “Familial Cognitive Disorders” group (AW Kuss).

### **Disease associated chromosome aberrations**

Breakpoint analysis of disease-associated balanced chromosome rearrangements combining array CGH (R. Ullmann’s group), FISH and recently also next-generation sequencing techniques (V. Kalscheuer’s and W. Chen’s groups) is a fast and efficient strategy to identify novel disease-causing genes (e.g. Chen et al *Genome Res.* 2008 Jul;18(7):1143-9.; Kalscheuer et al *Hum Mutat.* 2009 Jan;30(1):61-8.). Comprehensive clinical characterisation is a prerequisite for the selection of patients suitable for analysis. The identification of a disrupted gene or genes at the breakpoints often raises new questions concerning specific phenotypic details. The “Clinical Genetics” group obtains these data through collaboration with referring doctors or by contacting the patients or their families.

Our group recruits additional patients with *de novo* disease associated balanced chromosome rearrangements by maintaining and extending a network of clinical geneticists and other specialists.

### **Unbalanced chromosome aberrations**

Both large, cytogenetically visible unbalanced chromosome aberrations and small, submicroscopic aberrations which are only detectable by array CGH (R. Ullmann’s group) are an important cause of congenital malformations and mental retardation, and they can point to single genes responsible for a specific phenotype. Our group characterises such patients clinically and aims to establish genotype-phenotype correlations (e.g. Tzschach et al, *Eur J Hum Genet* 2009 (in press)). Our department is a member of the “German Mental Retardation Network (MRNet)” which performs array CGH analysis in a large patient cohort.

### **Cell culture facility**

We establish permanent cell lines from peripheral blood lymphocytes by EBV transformation after obtaining informed consent from patients in whom molecular cytogenetic or molecular genetic investigations are planned. Our cell culture lab performs EBV transformation, stores the cell lines and provides ready-to-use DNA, RNA or metaphase chromosome spreads for FISH investigations to the respective research groups.

### **Genetic counselling**

Andreas Tzschach, who is a board-certified clinical geneticist (“Facharzt für Humangenetik”), offers genetic counselling at the Institute of Medical Genetics (director: Prof. S. Mundlos) of the Charité - Universitätsmedizin Berlin, and he regularly takes part in clinical genetics, dysmorphology and cytogenetics meetings.



## External collaborations

### *Autosomal recessive mental retardation*

- Hossein Najmabadi, Genetic Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran
- Anna Rajab, MD, Genetic Unit, DGHA, Ministry of Health, Muscat, Sultanate of Oman

### *Balanced chromosome rearrangements*

- Niels Tommerup, Wilhelm Johannsen Centre, Copenhagen, Denmark

### *X-linked mental retardation*

- EUROMRX consortium ([www.euomrx.com](http://www.euomrx.com))

### *Mental retardation in Germany*

- German Mental Retardation Network (MRNet, [www.german-mrnet.de](http://www.german-mrnet.de))

We also collaborate with numerous clinical geneticists in Germany and abroad.

## General information

### Selected publications

Tzschach A, Bisgaard AM, Kirchhoff M, Graul-Neumann LM, Neitzel H, Page S, Ahmed A, Müller I, Erdogan F, Ropers HH, Kalscheuer VM, Ullmann R. *Chromosome aberrations involving 10q22: Report of three overlapping interstitial deletions and a balanced translocation disrupting C10orf11*. Eur J Hum Genet. 2009, Oct 21. [Epub ahead of print]

Kahrizi K, Najmabadi H, Kariminejad R, Jamali P, Malekpour M, Garshasbi M, Ropers HH, Kuss AW, Tzschach A. *An autosomal recessive syndrome of severe mental retardation, cataract, coloboma and kyphosis maps to the pericentromeric region of chromosome 4*. Eur J Hum Genet. 2009 Jan;17(1):125-8.

Tzschach A, Bozorgmehr B, Hadavi V, Kahrizi K, Garshasbi M, Motzack MM, Ropers HH, Kuss AW, Najmabadi H. *Alopecia-mental retardation syndrome: clinical and molecular characterization of four patients*. Br J Dermatol. 2008 Sep;159(3):748-51.

Garshasbi M, Hadavi V, Habibi H, Kahrizi K, Kariminejad R, Behjati F, Tzschach A, Najmabadi H, Ropers HH, Kuss AW. *A defect in the TUSC3 gene is associated with autosomal recessive mental retardation*. Am J Hum Genet. 2008 May;82(5):1158-64.

Tzschach A, Lenzner S, Moser B, Reinhardt R, Chelly J, Fryns JP, Kleefstra T, Raynaud M, Turner G, Ropers HH, Kuss A, Jensen LR. *Novel JARID1C/SMCX mutations in patients with X-linked mental retardation*. Hum Mutat. 2006 Apr;27(4):389.

### Work as scientific referee

A. Tzschach serves as scientific referee for the following journals: American Journal of Medical Genetics, Journal of Medical Genetics, Obesity, European Journal of Medical Genetics.

### External funding

BMBF, NGFN2, *Identification of genetic risk factors for complex disorders by studying patients with associated balanced chromosomal rearrangements*. (Joint with V. Kalscheuer, MPIMG).

### Teaching activities

Seminar "Human Genetics" for medical students, Humboldt University Berlin/ Charité-Universitätsmedizin Berlin, Institute of Medical Genetics (7 seminars of 90 minutes each term)

Co-organiser (together with HH Ropers) and lecturer at an educational workshop ("Genetik der geistigen Behinderung") of the "Akademie Humangenetik", Würzburg, 27.-28.2.2009

## Molecular Cytogenetics

(Established: 2004)

---



### Head

Dr. Reinhard Ullmann  
Phone: 0049 30 8413 1251  
Fax: 0049 30 84131383  
Email: ullmann@molgen.mpg.de

### Scientist

Fikret Erdogan (02/04-12/07)

### PhD students

Vivien Boldt (since 03/05)  
Anne Steininger (since 04/06)  
Grit Ebert (since 10/09)  
Artur Muradyan (01/05-05/09)

### Technicians

Ines Müller (since 04)  
Alisho Ahmed (since 06/08)  
Hannelore Madle (11/07-08/09)  
Jan Jurkatis (05/07-03/08)  
Melanie Wendehack (until 12/06)  
Marei Schubert (04/05-04/06)  
Ralph Schulz (until 01/05)  
Barbara Meinck (until 10/04)

## Scientific overview

### Analysis of DNA copy number variants

The Molecular Cytogenetics Group was founded in 2004. The first goal of the group was the creation of a high resolution BAC array platform enabling the genome wide identification of submicroscopic DNA copy number changes. We have accomplished this task in early 2005. In the same year we have also published CGHPRO, a program dedicated to the analysis and visualization of array CGH data. The next years were dominated by our efforts to exploit this array platform in the most efficient way. In cooperation with several partners from the clinics we set out to investigate the impact of copy number variants (CNVs) on the aetiology of various diseases. For most of the bigger screening projects we have invited guest scientists from the partner institution to work in our laboratory in order to get familiar with the array CGH methodology. In this way we have not only increased the manpower in our laboratory, but at the same time accelerated the transfer of this technology to the clinics. This strategy turned out to be very productive also in terms of publications, leading to 57 articles since 2006 alone.

Several of our publications have questioned the current understanding of genotype-phenotype correlation. In one paper published in 2007, for example, we have described a microdeletion/duplication of 16p13.1, which predisposes to mental retardation and autism, respectively. In the meantime the relevance of both the deletion and the duplication has been confirmed by independent groups. Actually, as stated in one of these confirmatory reports, with a frequency of 1.1% in patients



with MR, the 16p13 duplication appears to represent one of the most frequent causes of intellectual disability. Meanwhile the 16p13 paper is cited also for another reason. The duplication has turned out to be a paradigm for the genetic relationship of distinct diseases such as autism, mental retardation and schizophrenia. Up to now four independent studies have linked the very same 16p13 duplication also to schizophrenia.

The paper with the most citations within this year is our report on the first comprehensive screen of CNVs in patients with schizophrenia. In this study we have implicated the mental retardation gene *NRXN1* in the aetiology of schizophrenia and revealed that a direct interaction partner of this gene, *APBA2*, was located in a genomic region lost in another patient. Already one year after publication three independent studies have replicated our findings. In addition the technical quality of the underlying data set was evaluated favourably by an independent group of bioinformaticians in an inter-platform comparison (LaFrambiose, 2009).

### **MRNET: a German wide initiative to investigate the genetic causes of mental retardation**

For many CNVs disease association has been established by identifying recurrent aberrations in unrelated patients. In order to identify the less frequent and maybe low penetrant pathogenic CNVs the number of patients to be investigated has to increase considerably. To cope with this problem in MR research our group is actively participating in a network called the MRNET. Aim of this German wide initiative is to collaboratively analyse around 1200 patients with MR. Up to now our group has already screened 185 patients in the course of this project and has established a pipeline for the high throughput verification of CNVs based on custom designed oligonucleotide arrays. We have also developed the software for filtering and displaying the data, which is used by all participants of this network.

### **Integrative analysis of genetic and epigenetic changes and their consequences on gene expression**

One goal of our current work is to gain more insights into the consequence of DNA copy number changes by considering additional levels of information such as data on gene expression or epigenetic modifications. For that purpose we have established CHIP on Chip and MeDIP, two methods enabling the genome wide analysis of histone modifications and DNA methylation, respectively. Yet, in contrast to others, we have not focused on transcription start sites and CpG Islands, but instead studied epigenetic changes genome wide by means of our BAC array platform. Our results indicate that, at least in tumor cell lines, the correlation of moderate DNA copy number changes with gene expression is surprisingly low and that only a few genes are regularly deregulated when comparing different cases with the very same chromosomal change. Strikingly, according to our data global hypomethylation leads to downregulation of gene expression. We have also observed that regions sharing the same trend of chromatin modifications can extend to several megabases and are recurrent in many cell lines. Some of these recurrent intervals overlap with regions involved in genomic disorders such as the Williams Beuren syndrome. We are currently investigating this unexpected connection in more detail. One aspect under study in this context is the dynamics of large scale chromatin modifications during differentiation.

### **Collaborations within the Institute**

The Molecular Cytogenetics group participates in the project “Balanced Chromosome Rearrangement and Disease”, which currently involves four groups of the department. In this project we are responsible for the array based fine mapping of

chromosomal breakpoints and the exclusion of CNVs elsewhere in the genome. The high-throughput sequencing projects of the department are supported by our group in two ways. Firstly, we perform CNV analysis in patients prior to sequencing and secondly, we are actively involved in the array-based sequence enrichment for specific chromosomal intervals.

### Outlook

In the recent years the commercial availability of DNA microarrays has promoted the rapid introduction of array CGH into clinical routine. Consequently, the systematic search for CNVs is no longer confined to specialized research laboratories and we are able to shift our focus from the mainly descriptive analysis of CNVs to studies dedicated to an improved understanding of their phenotypic consequences. We will continue our multi-dimensional analysis of genetic and epigenetic modifications. However, given the growing competition in this field, we will refrain from a purely descriptive genome-wide inventory of epigenetic marks. Instead we will focus on specific aspects such as the dynamics of epigenetic modifications during certain phases of differentiation.

## General information

### Selected publications

Kirov G, Gumus D, Chen W, Norton N, Georgieva L, Sari M, O'Donovan MC, Erdogan F, Owen MJ, Ropers HH, Ullmann R. *Comparative genome hybridization suggests a role for NRXN1 and APBA2 in schizophrenia*. Hum Mol Genet. 2008 Feb 1;17(3):458-65.

Ullmann R, Turner G, Kirchhoff M, Chen W, Tonge B, Rosenberg C, Field M, Vianna-Morgante AM, Christie L, Krepischi-Santos AC, Banna L, Brereton AV, Hill A, Bisgaard AM, Müller I, Hultschig C, Erdogan F, Wiczorek G, Ropers HH. *Array CGH identifies reciprocal 16p13.1 duplications and deletions that predispose to autism and/or mental retardation*. Hum Mutat. 2007 Jul; 28(7):674-82.

Chen W, Erdogan F, Ropers HH, Lenzner S, Ullmann R. *CGHPRO — a comprehensive data analysis tool for array CGH*. BMC Bioinformatics. 2005 Apr 5;6:85.

### Selected invited talks

*Array CGH in tumor cytogenetics*. Tumor Cytogenetics Meeting, Semmering, Austria 2005

*The variable consequences of chromosomal aberrations*. Cytomics Symposium, Tokyo, Japan; 11/2007

*Technical aspects of array CGH*. Modern methods in cancer research; Vilnius, Lithuania, 2008

### Grant evaluation

R. Ullmann serves as referee for the following institutions/calls: Netherlands Genomics Initiative, Horizon Breakthrough project grant application 2008; Jubilee Funds of the National Bank/ Austria, single grant application 2008; GIS-Institute for Rare Diseases in France, Rare diseases and structural variation 2007.



## Work as scientific referee

R. Ullmann serves as scientific referee for the following journals: American Journal of Human Genetics, American Journal of Medical Genetics, Bioinformatics, BMC Bioinformatics, BMC Genomics, European Journal of Human Genetics, Gene, Human Genetics, Human Molecular Genetics, Journal of Medical Genetics, Nature Protocols.

## External funding

Jose Carreras Stiftung: *Einsatz von Array-CGH und anderer molekularzytogenetischer Techniken zum Nachweis kryptischer genetischer Imbalancen und Translokationen bei akuten lymphatischen Leukämien (ALL) im Kindesalter*, 2006-2009 (application together with Prof. Dr. Karl Seeger, Charite Berlin)

## Teaching activities

### Teaching at Universities

*Molecular Cytogenetics in Tumor Biology*, University of Salzburg, Austria, 2005, 2006

*Human Genetics for Bioinformaticians*, Freie Universität Berlin, Germany (together with Ropers, Schweiger, Kalscheuer), 2004, 2005, 2006

*Molecular Biology and Genetics II*, Freie Universität Berlin, Germany (together with Ropers, Schweiger & Kalscheuer, Wittig, Huber, Hinderlich, Klein, Peiser, Dobrinski), 2007

*Modern methods for the genome wide analysis of genetic and epigenetic changes in tumor biology and human genetics*, University of Salzburg, Austria, 2008, 2009

### Summerschools/Courses

*Principles of array CGH*, International Summer School in Functional Genomics, Wilhelm Johannsen Centre for Functional Genome Research, Copenhagen, Denmark, 2007, 2008

*Principles of arrayCGH & DNA copy number variation*, Postgraduate Course in Cytogenetics, Wilhelm Johannsen Centre for Functional Genome Research, Copenhagen, Denmark, 2007

*How next generation sequencing can benefit from molecular cytogenetic techniques*, course in integration of cytogenetics, microarrays and massive sequencing in biomedical and clinical research, European School of Genetic Medicine/EuroMediterranean University Centre of Ronzano. Bologna, Italy, 2008, 2009

*The role of DNA copy number changes in congenital disorders and tumorigenesis*, PhD program of the Max Planck Institute for Molecular Genetics, 2008, 2009

### Public relations

Up to now the Molecular Cytogenetics group participated four times in the “Long Night of Science”, which takes place once a year in Berlin. This year’s title of our presentation was: “*What makes tumor cells so dangerous?*”

## Neurochemistry Group & Mouse Lab; Monoamine signalling and disease

(Established: 02/2003)

---

### Head

Dr. Diego J. Walther  
Phone: +49 (0)30 8413-1664  
Fax: +49 (0)30 8413-1383  
Email: [dwalther@molgen.mpg.de](mailto:dwalther@molgen.mpg.de)

### Scientists

Dr. Maik Grohmann (since 03/08,  
guest scientist)  
Dr. Nils Paulmann (since 04/08)

### PhD students

Jakob Vowinckel (since 07/06)  
Paul Hammer (since 01/07)  
Silke Stahlberg (since 07/08)  
Jens-Uwe Peter (02/03-12/08)  
Maik Grohmann (04/03-03/08)  
Nils Paulmann (09/03-03/08)



### Technicians

Angela Lüttges  
Sabine Otto  
Monika Dopatka (until 12/08)

162

### Scientific overview



Figure 1. Sugar and Serotonin-deficient Mice helped identify a link between Diabetes mellitus and serotonin.

Our group is focused on the elucidation of molecular causes of human diseases by the generation, analysis, and rescue experiments of transgenic and knockout mouse models. The use of transgenic mice is one of the most straightforward tools to study gene function. Our facility offers the generation of transgenic and knockout mice to all groups in the Department, the Max-Planck-Institute and other interested laboratories. Our facility constituted in part the Central Facility for Animal Model Generation of the SFB577: "Molecular Basis of Clinical Variability in Mendelian Disorders". Currently we work on animals with defined genetic dysfunctions in genes involved in mental retardation (e.g. *Mcp1* and *Ftsj1*) and in monoaminergic systems (e.g. *Tph1* and *Tph2*) aiming the elucidation of the numerous hormonal and neurotransmitter effects of serotonin (5-HT), histamine (HA), and the catecholamines dopamine (DA) and norepinephrine (NE). Furthermore, we closely cooperate with the Department of Computational Molecular Biology in order to combine bioinformatics with experimental verification of computational results.



## The dichotomy of the serotonergic system

Nine low-molecular weight neurotransmitters have been identified in the central nervous system of vertebrates and four of them are the above-mentioned evolutionary ancient primary monoamines. 5-HT, one of these nine neurotransmitters, is not only the messenger of some thousands of neurons [*Science* 299 (2003) 76; *Biochem. Pharmacol.* 66 (2003) 1673], but an ubiquitous substance in peripheral tissues and fluids, from which 5-HT was first isolated six decades ago identifying it as the vasoconstrictor compound in serum, which appears in conjunction with platelet degranulation [*Cell* 115 (2003) 851; *Mol. Cell. Biochem.*, 295 (2007) 205]. Tryptophan hydroxylase (TPH) catalyzes the rate-limiting step in the biosynthesis of 5-HT biasing the serotonergic system in its whole.

A dichotomy of the serotonergic system consisting of two 5-HT-synthesizing TPH isoforms was recently characterized by us, using *Tph* gene-targeted (*Tph1*<sup>-/-</sup>) mice. TPH1, the enzyme known for decades, is broadly expressed in non-neuronal tissues and the novel TPH2 is almost restricted to neurons [*Science* 299 (2003) 76; *Biochem. Pharmacol.* 66 (2003) 1673]. Thus, TPH2 catalyses the rate-limiting step of 5-HT biosynthesis in the central nervous system [*Science* 299 (2003) 76; *Biochem. Pharmacol.* 66 (2003) 1673]. The neurotransmitter 5-HT is involved in multiple facets of mood control and the regulation of sleep, anxiety, alcoholism, drug abuse, food intake, and sexual behaviour. For these reasons, we work on the biochemical properties of TPH2 in order to understand the central nervous system 5-HT biosynthesis [*J. Biol. Chem.*, 281 (2006) 28105; *J. Neurochem.* 2007 102 (2007) 1887]. Furthermore, we and our collaborators are working on the elucidation of TPH2-dependent human psychiatric disorders [*Mol. Psychiatry* 9 (2004) 980; *Biol. Psychiatry*, 62 (2007) 1288].

A novel intracellular mechanism of 5-HT signalling was discovered in the viable *Tph1*<sup>-/-</sup> mice, a mechanism depending on the 5-HT transporter (SERT)-driven entry of 5-HT into cells in conjunction with Ca<sup>2+</sup> mobilization, which culminates in the constitutively activating covalent modification of small GTPases of the Rho and Rab families with 5-HT in a transglutaminase-mediated reaction [*Cell* 115 (2003) 851; *PLoS Biol.* 7 (2009) e1000229]. We termed this post-translational protein modification 'serotonylation'.

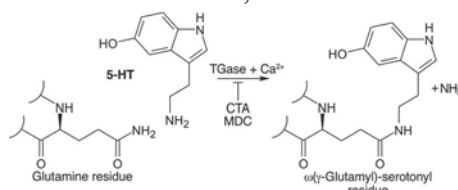


Figure 2: Scheme of protein serotonylation of glutamine residues by transglutaminase.

Extraneuronal serotonin is involved in primary haemostasis [*Cell* 115 (2003) 851], mammary gland involution [*Dev. Cell* 6 (2004) 193], liver regeneration [*Science* 312 (2006) 104], and insulin secretion [*J. Endocrinol.* 200 (2009) 23; *PLoS Biol.* 7 (2009) e1000229]. Our collaborators and we are working on these items and also on the analysis of tissue-specific expression of splicing isoforms of TPH1. 5-HT also functions as a growth factor, particularly in early embryonic development [*Mol. Brain Res.* 68 (1999) 55]. Mitogenic effects of 5-HT in adult tissues are also gaining attention, for example, in the pathological hyperplasia of the pulmonary artery smooth muscle cells (PA-SMCs) in pulmonary hypertension [*Hypertension* 49 (2007) 232]. However, the underlying mechanisms for such processes have remained elusive, while a growing body of evidence points to a crucial involvement of the SERT in the aetiology of this disease. Finally, the functional analysis revealed an involvement of RhoA serotonylation in the aetiology, as previously postulated [*Cell* 115 (2003) 851].

Platelets contain large amounts of 5-HT and can be easily obtained from peripheral blood. Washed platelets are an accepted model for synaptic vesicle metabolism mechanisms. Therefore, the platelets of our *Tph1*<sup>-/-</sup> mice deliver the first

opportunity to study transmitter-devoid vesicles. We are cooperating with G. Ahnert-Hilger to elucidate vesicular trafficking mechanisms. We have reported that the vesicular monoamine content regulates VMAT2 activity through Gaq in mouse platelets based on evidence for autoregulation of vesicular transmitter uptake [*J. Biol. Chem.* 278 (2003) 15850]. Similar autoregulation is also given in other neurotransmitter storage systems [*J. Neurosci.* 25 (2005) 4672]. In addition, under physiological conditions, platelets are crucial players in delivering serotonin to a variety of target organs and play a central role for instance in the immune response and in liver regeneration [*Science* 312 (2006) 104].

### Primary monoamines and protein monoamination

Recently, we have identified a novel signalling mechanism in platelets, the ‘serotonylation’ of small GTPases [*Cell* 115 (2003) 851]. In addition, the other biogenic monoamines HA, DA, and NE can cause an analogous transglutaminase-mediated activation of signalling proteins by ‘hisaminylation’ and ‘catecholaminylation’, wherefore we coined the generic term ‘monoamination’ [*Cell* 115 (2003) 851].

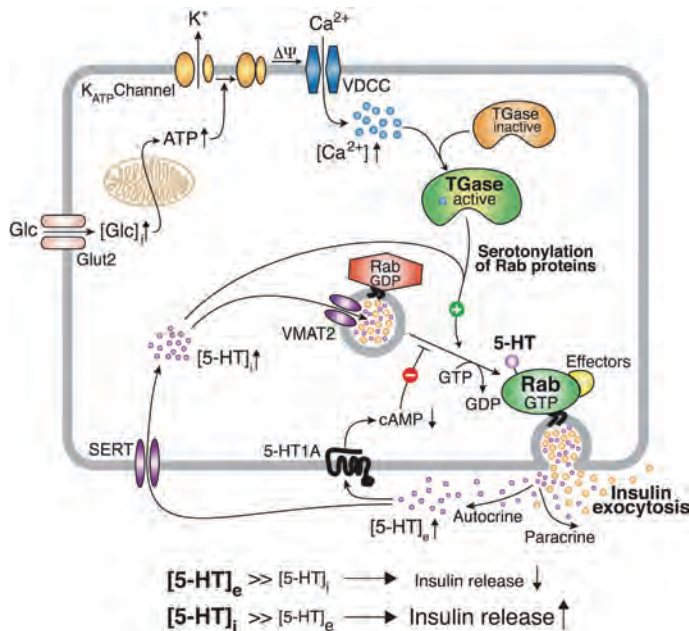


Figure 3. Proposed model of 5-HT-induced exocytosis of  $\beta$ -granules from glucose-stimulated  $\beta$ -cells. The classic mechanism of glucose induced  $\text{Ca}^{2+}$  influx is represented in the upper part of the scheme. This  $\text{Ca}^{2+}$  activates transglutaminases that serotonylate central signalling proteins, which promote insulin secretion [*PLoS Biol.* 7 (2009) e1000229].

serotonylation highlights the general physiological relevance of protein monoamination exemplarily. Like the phosphorylation of proteins, also the monoamination has a deep impact on several cellular processes. In contrast to what was assumed for a long time, water-soluble hormones like 5-HT, HA, and catecholamines act not only at the cell’s face *via* surface receptors, but also within cells *via* monoamination.

We now identified this mechanism also in  $\beta$ -cells of the pancreas [*PLoS Biol.* 7 (2009) e1000229]. As in platelets, serotonylation regulates the secretion of storage granules from these cells. Under normal conditions 5-HT controls the release of insulin. When the 5-HT levels are low like in 5-HT-deficient mice, proper insulin secretion is hampered and blood glucose concentration rises to noxious levels after a meal, a hallmark of diabetes. Thus, the identification of the insulin-releasing action of 5-HT may open new avenues for intervention in diabetes, a main research objective for further studies.

The pancreas is the third disease-associated context of serotonylation identified since the first description of this mechanism in bleeding disorders by us [*Cell* 115 (2003) 851]. In addition to the finding’s contribution to the understanding of 5-HT’s role in the widespread disease diabetes, the special case of serotonylation highlights the general physiological relevance of protein monoamination exemplarily.



## Internal cooperations

- Vera Kalscheuer, MPIMG
- Susann Schweiger, Charité Berlin/MPIMG
- Stefan Mundlos, Charité Berlin/MPIMG
- Martin Vingron, MPIMG
- Stefan Roepcke, MPIMG

## External cooperations

- Prof. Gudrun Ahnert-Hilger, Charité Berlin
- Prof. Michael Bader, Max-Delbrück-Center (MDC) for Molecular Medicine, Berlin
- Prof. Peter Beyerlein, TFH Wildau
- Prof. Pierre-Alain Clavien, Universitätsspital Zürich, Switzerland.
- Prof. Heidrun Fink, Freie Universität Berlin

- Prof. Christian Gachet, EFS Strasbourg, INSERM, France
- Dr. Katrin Hoffmann, Charité Berlin
- Prof. Joachim Klose, Charité Berlin
- Prof. Josef Priller, Charité Berlin
- Prof. Marjan Rupnik, University of Maribor, Slovenia
- Prof. Margharet McLean, University of Glasgow, UK
- Prof. Annette Schürmann, DIFE Potsdam
- Prof. Karl Sperling, Charité Berlin
- Prof. Kent Vrana, Penn State University, Pennsylvania, USA
- Prof. Erich Wanka, Max-Delbrück-Center (MDC) for Molecular Medicine, Berlin
- Priv.-Doz. Peter Zill, Ludwig-Maximilians-Universität (LMU) Munich

## General information

### Selected publications

Paulmann N, Grohmann M, Voigt J-P, Bert B, Vowinckel J, Bader M, Skelin M, Jevšek M, Fink H, Rupnik M, Walther DJ. *Intracellular serotonin modulates insulin secretion from pancreatic  $\beta$  cells by protein serotonylation*. PLoS Biol 2009;7: e1000229

Scheuch K, Lautenschlager M, Grohmann M, Stahlberg S, Kirchheiner J, Zill P, Heinz A, Walther DJ\*, Priller J\*. *Characterization of functional promotor polymorphisms of the human tryptophan hydroxylase-2 gene in serotonergic raphe neurons*. Biol. Psychiatry 2007; 62:1288-1294 (\*shared authorship)

Lesurtel M, Graf R, Aleil B, Walther DJ, Tian Y, Jochum W, Gachet C, Bader M, Clavien P-A. *Platelet-derived serotonin mediates liver regeneration*. Science 2006; 312:104-107.

Walther DJ, Peter J-U, Winter S, Höltje M, Paulmann N, Grohmann M, Vowinckel J, Alamo-Bethencourt V, Wilhelm CS, Ahnert-Hilger G, Bader M. *Serotonylation of Small GTPases is a Signal Transduction Pathway that Triggers Platelet  $\alpha$ -Granule Release*. Cell 2003; 115:851-862.

Walther DJ, Peter JU, Bashammakh S, Hörtnagl H, Voits M, Fink H, Bader M. *Synthesis of serotonin by a second tryptophan hydroxylase isoform*. Science 2003;299:76.

### Work as scientific referee

Since 2003, D. Walther serves as scientific referee for the following journals: Journal of Histochemistry & Cytochemistry, Cephalalgia, Biological Psychiatry, Behavioural Brain Research, and Molecular Psychiatry.

In addition, D. Walther served as referee for the following institutions: Higher Education Authority (HEA) of Ireland (evaluation of animal facilities, 09/06), county court Munich (expert assessment about the use of 5-hydroxytryptophan as antidepressive compound, 10/08)

### Teaching activities

Lectures on „Tragenic Animals in Research and Production – Overview and Perspectives“ at the Freie Universität Berlin, since 04/07

University lectureship at the Technische Fachhochschule Berlin, FB Biotechnologie, since 07/08

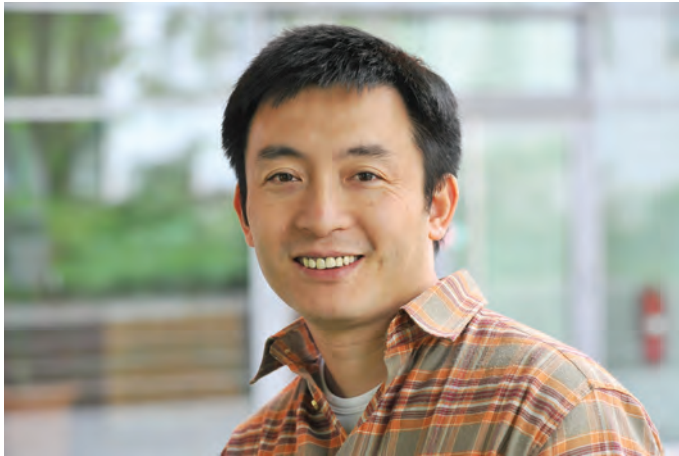
### External funding

DFG, SFB 577: *Analysis of the clinical variability in Mendelian disorders* (subprojects B1 and Z1)

## Associated Group: Applied Bioinformatics

(Established: 01/2007)

---



### Head

Dr. Wei Chen (since 01/07)  
Phone: +49 (0)30 8413-1214  
Fax: +49 (0)30 8413-1383  
Email: wei@molgen.mpg.de

### Scientist

Dr. Hao Hu (since 05/09)

### Graduate students

Na Li (since 10/00)  
Hui Kang (since 09/00)  
Raghu Bhushan (02/00 - 06/09)

### Technicians

Corinna Menzel (since 01/07)  
Melanie Bienek (since 06/09)

## Scientific overview

The recent introduction of massive parallel sequencing technology has revolutionized genomic research. These so-called next generation sequencing platforms, such as Roche/454, Illumina/solexa and ABI/SOLiD system can sequence DNA orders of magnitude faster and at much lower cost than conventional Sanger method. With their incredible sequencing capacity, my lab has been focused on developing and implementing various genomic assays based on this new generation of sequencers. We are now applying the assays in identifying genetic factors underlying human diseases as well as studying transcriptional and posttranscriptional regulation of miRNA genes.

### Characterisation of breakpoints in disease-associated balanced chromosome rearrangements

The frequency of *de novo* balanced translocations in patients associated with congenital malformations and/or developmental delay is twice that among the general population, suggesting a causative link between the rearrangements and the observed phenotype in at least half of the disease-associated balanced translocations (DBCRs). The phenotype in these cases can be caused by the disruption or inactivation of specific gene(s) at the translocation breakpoints. Therefore, characterisation of the breakpoints in DBCRs has often been a promising starting point in molecular elucidation of early-onset Mendelian disorders. Recently such a strategy has also been applied to search for genetic risk factors for complex and late-onset diseases.

Mapping translocation breakpoints using conventional methods, such as *in situ* hybridization with fluorescent dye-labeled bacterial artificial chromosome clones (BAC-FISH), is rather laborious, time consuming and often provides limited reso-



lution of breakpoint positions. With the development of array painting techniques, which combine DNA array and chromosome sorting technologies, the efficiency has been greatly improved and the ultra-high resolution was achieved by the sequential painting with two arrays, a tiling path large insert array and a region-specific, ultra-high-resolution oligonucleotide array. Using 'next generation' massive parallel sequencing technology, we have introduced a novel and rapid method to map translocation breakpoint by shotgun sequencing flow-sorted derivative chromosomes. The coverage attained by this method was sufficient to bridge the breakpoints by PCR amplification, and the procedure allows to determine their exact nucleotide positions in a short time frame. Recently, to further improve the method and in order to characterise the breakpoints in all types of balanced chromosome rearrangements more efficiently and more accurately, we performed massively parallel sequencing using Illumina 1G analyser and ABI SOLiD systems to generate short sequencing reads from both ends of DNA fragments. By identifying read pairs spanning the breakpoints, we were able to map the breakpoints to a region of a few hundred base pairs that could be confirmed by subsequent PCR amplification and Sanger sequencing of the junction fragments. Collaborating with Vera Kalscheuer and Andreas Tzschach, we are now implementing our method in large-scale breakpoint mapping and gene finding.

### **Molecular elucidation of genetic factors underlying mental retardation by genome partitioning and large-scale next generation sequencing**

Using Sanger sequencing, mutation screening in genomic intervals defined by linkage analysis or in a large number of candidate genes is often extremely tedious. Recently advance in massive parallel sequencing technology has dramatically improved the efficiency and reduced the cost. However, the cost of sequencing the complete genome using presently available instruments is still too high to apply to a large number of human patients. Therefore, robust methods to isolate relevant genomic regions for targeted sequencing are required. In this project, we evaluated different genome partitioning strategies including droplet-based PCR from RainDance Technologies, solution hybrid selection from Agilent Technologies and chromosome sorting. With different strengths, they are eventually combined to identify genetic factors underlying mental retardation.

### **Transcriptional and posttranscriptional regulation of miRNA genes**

miRNAs are small non-coding RNAs that control the expression of target genes at the posttranscriptional level. Recently, more and more miRNAs have been implicated in a variety of biological processes including brain development and function. Whereas much attention has been focus on finding the target genes regulated by miRNAs, little is known about the system which regulates miRNA expression. One major focus of the lab is to study transcription and posttranscriptional regulation of miRNA genes. In the study of transcriptional regulation, we are involved in genome wide discovery of miRNA promoters in pre-B cells using ChIP-seq, mRNA-seq and small RNA sequencing methods.

It has been demonstrated that the Drosha or Dicer processing of individual miRNA can be regulated. Though, it is yet not known how generalized the phenomena are. We are therefore interested in studying the posttranscriptional regulation of miRNAs, especially regulation of Dicer processing at the genomic level by genome-wide profiling of miRNA precursor (pre-miRNA) and mature miRNA from the same sample and comparing their relative abundance across different samples. Currently, we are developing a novel assay to efficiently profile pre-miRNA based on new sequencing technology.

### **De novo transcriptome sequencing using 454 pyrosequencing**

New sequencing technologies are not only robust tools for the investigation of transcriptome in model organisms, but also manifest great potential in studying non-model organisms. To facilitate comprehensive transcriptome characterization, we are developing methods for transcriptome sequencing using 454 pyrosequencing. With long read length and high accuracy, it is particularly suitable for *de novo* sequence assembly. To be fit for 454 sequencing, our methods consist of steps to remove poly A+ tails and cDNA library normalization. The sequencing data would provide a comprehensive reference resource for further functional studies.

### **General information**

#### **Selected publications**

Fu X, Fu N, Guo S, Yan Z, Xu Y, Hu H, Menzel C, Chen W\*, Li Y, Zeng R, Khaitovich P\* (2009). *Estimating accuracy of RNA-Seq and microarrays with prote-omics*. BMC Genomics 10:161-169 (\* shared corresponding authors)

Stoeckius M, Maaskola J, Colombo T, Rahn HP, Friedländer MR, Li N, Chen W, Piano F, Rajewsky N (2009). *Large-scale sorting of C. elegans embryos reveals the dynamics of small RNA expression*. Nat Methods. 2009 Sep 6. [Epub ahead of print]

Kuss AW, Chen W (2008). *MicroRNAs in brain function and disease*. Curr Neurol Neurosci Rep 3:190-197.

Friedländer MR, Chen W, Adamidi C, Maaskola J, Einspanier R, Knespel S, Rajewsky N (2008). *Discovering microRNAs from deep sequencing data using miRDeep*. Nat Biotechnol. 26(4), 407-415.

Chen W, Kalscheuer V, Tzschach A, Menzel C, Ullmann R, Schulz M, Erdogan F, Li N, Kijas Z, Arkesteijn G, Pajares IL, Goetz-Sothmann M, Heinrich U, Rost I, Dufke A, Grasshoff U, Glaeser BG, Vingron M, Ropers HH (2008). *Mapping translocation breakpoints by next-generation sequencing*. Genome Res. 18: 1143-1149.

#### **Teaching activities**

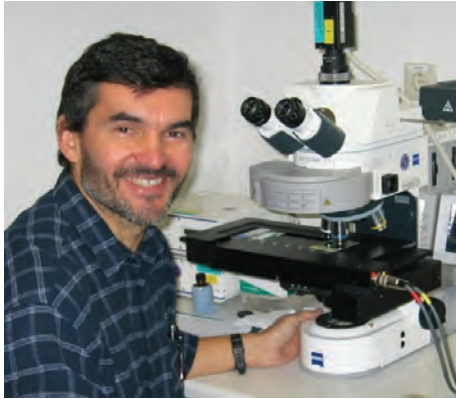
22nd course in Medical Genetics, 04/2009, Bertinoro di Romagna

Integration of Cytogenetics, Microarrays and Massive Sequencing in Biomedical and Clinical Research, 10/2008 Bologna



## Associated Group: Meiosis & Chromosome Dynamics

(Established: 01/2004)



### Head

apl. Prof. Dr. Harry Scherthan (guest scientist since 01/04)

Email: [schertha@molgen.mpg.de](mailto:schertha@molgen.mpg.de)

### Scientist

Dr. Caroline Adelfalk (06/03-12/05, guest scientist since 01/06)

### Scientific overview

The germ line is particularly vulnerable to genotoxic agents. DNA damage and recombinational misrepair can lead to mutation & chromosomal aberrations and amongst others to mental retardation and congenital genetic defects. A major interest and focus of our group is to understand chromosome behavior in meiotic prophase and the genesis of chromosomal aberrations. Besides genotoxic influences, homologous recombination at illegitimate sites is thought to fuel the chromosome rearrangements, those seen in patients as well as in an evolutionary context. It is thus imperative to understand the nature of DNA double strand break repair, break points and recombinogenic sequences in the context of genome architecture and nuclear topology. Genes expressed in brain are also expressed in testis and given our interest in meiosis, we have established tools for high resolution analysis of first meiotic prophase progression in the genetic model systems budding yeast and mouse.

Since 2006 we moved on with our comparative analysis of the impact of mutations in genes involved in DNA repair and telomere stability in the mouse and yeast and developed a highly sensitive live cell imaging microscope system (TILL) for live cell analysis in the light sensitive prophase I stage of the model species *S. cerevisiae*. By this, we pioneered work that for the first time showed in live meiocytes exceeding meiotic movements of telomeres and entire nuclei, and that these dynamics required the expression of a functional telomere complex, cohesin and an actin network independent of recombination. We continued this line of research and showed that the telomere mobility translates to whole chromosomes (Fig. 1) much surprisingly during all of prophase I. This gave new impetus to the perception how meiotic telomere and chromosome be-

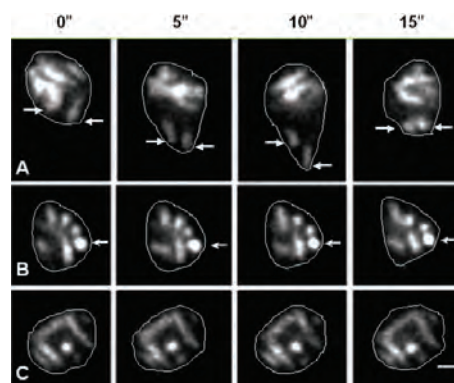


Figure 1: Zip1-GFP-marked chromosomes in live yeast pachytene meiocytes. Frames in 5s intervals and nuclear border outlines are shown. (A) In the wild type the nucleus undergoes constant shape changes and often “maverick” chromosomes (arrows) rapidly move from and back to the mass of chromosome. (B) Nucleus of a *ndj1Δ* cell whose SCs and nucleus undergo only limited mobility due to defective telomeres, with the arrow marking a stationary polycomplex as reference. (C) Chromosome & nuclear mobility is paralyzed in a WT nucleus treated with the actin poison LatB. Bar: 1μm.

havior is regulated and linked to recombination. These observations have sparked new hypotheses and work in the meiosis field.

We also investigated a number of mouse strains with mutations in DNA-damage-responsive genes and telomere genes for alterations in meiotic chromosome behavior. Our efforts have established a first integrated view of telomere and chromosome mobility phenotypes in relation to mutations with altered prophase I and recombination progression, and provide a first circuitry around the meiotic telomere, which will aid analysis of failure of germ cell differentiation in infertile patients and mice. Furthermore, our analysis will help to understand why up to one third of fertilized human eggs are aneuploid, the leading genetic cause of developmental failure and pregnancy loss.

Currently, we are cooperating with A. Kuss on the role of Bod1 protein in meiosis, whose gene has been found to be mutated in a family with two branches and four female patients suffering from mental retardation and oligomenorrhea, where all isoforms of the BOD1 gene product have been lost. Since BOD1 appears to be a kinetochore protein likely involved in spindle attachment and mitotic chromosome segregation, we work to localize the BOD1 protein in meiotic cells. In a cooperation with R. Ullmann and A. Muradyan we study the genomic signature left by acute high dose radiation in single cell survivor clones derived from irradiated A549 tumour cells by array-CGH, expression profiling and molecular cytogenetics to highlight genomic damage elicited by ionising radiation, to better understand the signatures elicited by genotoxic agent that may alter a cells fate towards misdifferentiation.

## General information

### Selected publications

[Adelfalk C](#), Janschek J, Revenkova E, Liebe B, Göb E, Alsheimer M, Benavente R, de Boer E, Novak I, Höög C, [Scherthan H](#) and Jessberger R. *Cohesin SMC1 $\beta$  protects telomeres in meocytes*. *J Cell Biol* 2009; 187:185-99.

Erenpreisa J, Cragg MS, Salmina K, Hausmann M, [Scherthan H](#). *The role of meiotic cohesin REC8 in chromosome segregation in g irradiation-induced endopolyploid tumour cells*. *Exp Cell Res* 2009; 315:2593-2603.

[Scherthan H](#), Trelles-Sticken E. *Absence of yKu/Hdf1 but not myosin-like proteins alters chromosome dynamics during prophase I in yeast*. *Different* 2008; 76:91-98.

[Scherthan H](#), Wang H, [Adelfalk C](#), White EJ, Cowan C, Cande WZ, Kaback DB. *Chromosome mobility during meiotic prophase in Saccharomyces cerevisiae*. *Proc Natl Acad Sci USA* 2007; 104:16934-16939.

Liebe B, Petukhova G, Barchi M, Bellani M, Braselmann H, Nakano T, Pandita TK, Jasin M, Fornace A, Meistrich ML, Baarends WM, Schimenti J, de Lange Z, Keeney S, Camerini-Otero RD, [Scherthan H](#). *Mutations that affect meiosis in male mice influence the dynamics of the mid-preleptotene and bouquet stages*. *Exp Cell Res* 2006; 312:3768-3781.

### Open access activities

There are 22 free full-text articles in PubMed Central as of 10/2009

### Selected invited talks

*DNA-repair and chromosome dynamics in meiosis*. Invited lecture at the Heinrich-Pette-Institute, Hamburg, Germany, 02/2009

*Meiotic chromosome dynamics*. Chair and invited plenary lecture at the 16<sup>th</sup> Int. Chromosome Conference. Amsterdam, NL, 08/2007



*Modulation of meiotic telomere dynamics.* Invited plenary lecture at the joint meeting of the Biochemical Society and the Genetics Society “Meiosis and the causes and consequences of recombination”. 28.-31.03.2006, University of Warwick, UK

*Telomeres in space and time, evolutionary and germ cell aspects.* Invited plenary lecture, Minisymposium, Biocenter, Vienna, Austria, 10/2006

### Scientific honors / awards

Rank 48 among the top 50 cited German Molec. Biologists (Labor J. 5/2008).

1<sup>st</sup> place, CNRS Concours Chercheurs no. 21/01, DR2, 2006

### Work as scientific referee

H. Scherthan serves as scientific referee for the following journals: BOR, Dev. Cell, Dev. Biology, J. Cell Biol., J. Cell Sci., Eur. J. Cell Biol., Chromosoma, Chromos. Res., Health Physics.

In addition, H. Scherthan serves as referee for the following institutions: DFG, The Wellcome Trust, Deutsche Krebshilfe.

### Membership in journal editorial boards

Editorial Advisory Board of *Chromosome Research*, since 2009

### Teaching activities

Special Practical Course *Molekulare Cytologie/Cytogenetik*; Lecture: *Grundlagen der Molekularen Cytologie/Cytogenetik*. Lecture and seminar series *Chromosome Biology* (since 2007) each term; Technical Univ. of Kaiserslautern.

### Organization of scientific events

Workshop organizer & Chair of the session *Meiosis and the regulation of recombination*, 16<sup>th</sup> Int. Chromosome Conference, Amsterdam, The Netherlands, 2007.

## Associated Group: Clinical Genetics and Biochemistry

(Established: 2000)



### Head

Professor Dr. Susann Schweiger  
Email: [schweiger@molgen.mpg.de](mailto:schweiger@molgen.mpg.de)

### PhD student

Eva Kickstein\* (since 06)

### Technician

Melanie Kunath\* (since 05)

### Scientists

Dr. Sybille Krauss\* (since 00)  
Prof. Rainer Schneider (since 07,  
associate fellow)

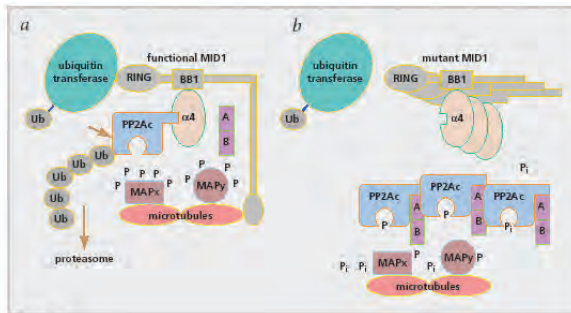
172

## Scientific overview

### Scientific achievements

Some time ago we had identified mutations in the *MID1* gene to be causative for the X-linked form of Opitz BBB/G syndrome (OS, Quaderi et al., 1997, *Nature Genetics*). Since then the scientific focus of my group has been at the characterization of the physiological function of the *MID1* gene product and the analysis of the mechanisms of disease development in OS patients. Our work has led to the identification of a microtubule-associated protein complex that plays a central role in insulin receptor and mTOR signalling and is a translation control unit for the regulation of compartmentalized protein translation.

Figure 1: (a) The microtubule-associated protein MID1 together with the regulatory PP2A subunit  $\alpha 4$  targets the catalytic subunit of PP2A towards ubiquitin dependent modification and degradation by the proteasome. (b) In OS patients MID1 loses its contact to the microtubules, the microtubule-associated pool of PP2A can no longer be ubiquitinated and accumulates at the microtubules. This leads to the hypophosphorylation of microtubule-associated proteins.



The MID1 protein is a multidomain protein with a RING finger domain and two zinc-binding B-Boxes in its N-terminus. We have shown that the C-terminus of the MID1 protein associates to microtubules (Schweiger et al. 1999, *PNAS*) and *via* the two B-Boxes it binds to the  $\alpha 4$  protein, which is a regulatory subunit of protein phosphatase 2A (PP2A). The close vicinity of the ubiquitin ligase MID1 to PP2A results in the ubiquitin dependent modification and degradation of the microtubule-associated pool of the catalytic subunit of PP2A. In OS patients

\* externally funded



this mechanism is disrupted and the catalytic subunit of PP2A accumulates at the microtubules (Fig. 1, Trockenbacher et al. 2001, *Nature Genetics*).

We have further found that the MID1/ $\alpha$ 4/PP2A protein complex assembles a microtubule-associated ribonucleoprotein (RNP) complex, that, in addition to the three proteins, contains (i) active ribosomes, (ii) several translation factors and (iii) mRNAs that bind to the complex *via* G-rich RNA motifs (Aranda-Origillés et al., 2008, *Human Genetics*, Fig. 2). Unpublished results show that the MID1/ $\alpha$ 4 protein complex regulates the translation efficiency of mRNAs that are attached to it and that up-regulation of its activity by, for example, over-expression of MID1 result in an increase in protein synthesis from these mRNAs (manuscript in preparation).

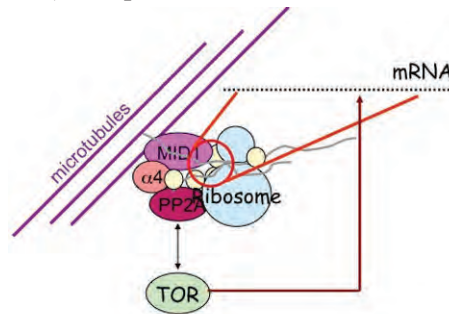


Figure 2: MID1,  $\alpha$ 4 and PP2A assemble a microtubule-associated protein complex that contains active polyribosomes, translation factors and mRNAs, that associate to the complex *via* G-rich RNA motifs. PP2A and its counteracting enzyme, mTOR regulate the translation efficiency of these mRNAs.

Interestingly, it seems to be a set of mRNAs with very specific functions that bind to the MID1/ $\alpha$ 4/PP2A RNP complex. In a database search with MID1 binding RNA motifs we could identify close to 100 mRNAs, all of which are coding for proteins either involved in protein translation, functioning at the synapse or playing central roles in polarizing and migrating cells. Interestingly, translation efficiencies of several of these mRNAs are impaired in cell lines from OS patients. This observation together with FRAP data showing that the MID1 protein complex is actively transported along the microtubules (Aranda-Origillés et al., 2008, *PLoSone*) led us hypothesize that the MID1 protein complex would function as a translation regulator for compartmentalized protein synthesis in either neurons or cells comprising protein gradients such as polarizing and migrating cells.

Furthermore, by comparing clinical genetic phenotypes we were able to establish a novel and unexpected connection of the MID1/ $\alpha$ 4/PP2A complex and shh signalling. The shh pathway is involved in body patterning and limb and brain development. It also is an oncogenic pathway, gain of function of which seems to be a critical factor during carcinogenesis. Loss of function of components of the shh signalling cascade have been linked to syndromes that significantly overlap clinically with the phenotype seen in OS patients. We could show that PP2A activity and the MID1 protein complex regulate the transcriptional activity of GLI3, one of the three transcriptional effector molecules of the shh pathway (Krauss et al. 2008, *Cancer Research*; Kraus et al., *PLoS One*). Interestingly, increase of the activity of PP2A *via* the MID1 protein complex can significantly decrease the activity of the shh signalling cascade, which makes the MID1/ $\alpha$ 4/PP2A protein complex a very promising target for an anti-shh cancer therapy.

Furthermore, by comparing clinical genetic phenotypes we were able to establish a novel and unexpected connection of the MID1/ $\alpha$ 4/PP2A complex and shh signalling. The shh pathway is involved in body patterning and limb and brain development. It also is an oncogenic pathway, gain of function of which seems to be a critical factor during carcinogenesis. Loss of function of components of the shh signalling cascade have been linked to syndromes that significantly overlap clinically with the phenotype seen in OS patients. We could show that PP2A activity and the MID1 protein complex regulate the transcriptional activity of GLI3, one of the three transcriptional effector molecules of the shh pathway (Krauss et al. 2008, *Cancer Research*; Kraus et al., *PLoS One*). Interestingly, increase of the activity of PP2A *via* the MID1 protein complex can significantly decrease the activity of the shh signalling cascade, which makes the MID1/ $\alpha$ 4/PP2A protein complex a very promising target for an anti-shh cancer therapy.

### Future plans - the MID1/ $\alpha$ 4 ubiquitin ligase complex, a promising drug target for cancer and neurodegenerative disorders

PP2A is not only a very potent tumour suppressor, but it is also by far the most important enzyme to de-phosphorylate microtubule-associated tau protein. Hyperphosphorylated tau is the major component of paired helical filaments, a pathological hallmark in brains from Alzheimer's Disease (AD) patients. In addition to that, our data show that the MID1 /  $\alpha$ 4 / PP2A influences the synthesis of several proteins, gain of function of which are the pathogenic factors driving the development of other neurodegenerative disorders such as amyotrophic lateral sclerosis, Parkinson's Disease and Huntington's Disease. Taken together this suggests that a

mechanism that influences the activity of a specific pool of PP2A would be a very promising drug target for several cancer entities as well as neurodegenerative disorders. Although this is widely accepted in the literature and the development of inhibitory molecules for kinases has been very successful, until now it has not been possible to accelerate phosphatase activity in small molecule drug discovery approaches.

The MID1/ $\alpha$ 4 ubiquitin ligase complex seems to regulate the turn over and the activity of the microtubule-associated pool of PP2A quite specifically (Trockenbacher et al. 2001, *Nature Genetics*). In several validation approaches using knock-down technology we could show that a decrease of MID1/ $\alpha$ 4 ubiquitin ligase activity indeed leads to an increase of PP2A activity and influences several of the mentioned pathogenic processes including tau phosphorylation and the production of pathological protein in neurodegenerative disorders. From mutation and deletion analysis data of the MID1 protein and the NMR structures of the B-Box domains of the MID1 protein and the  $\alpha$ 4 protein we have concluded that the interface between MID1 and  $\alpha$ 4 would be targetable by small molecules. Together with our collaboration partners from the University of Innsbruck and the Lead Discovery Unit in Dortmund we have set up an alpha screen to screen for small molecules that disturb the interaction of MID1 and  $\alpha$ 4 and thereby inhibit ubiquitin ligase activity and increase PP2A activity. In addition we are currently developing several cell free and cell based assays and establish animal models to validate potential hits that will be produced in the alpha screen.

In summary, the discovery of a microtubule-associated protein complex that controls microtubule-associated PP2A activity has become a promising drug target for a potential therapy of cancer and neurodegeneration. In addition, the nature of the interaction of the MID1 protein and the  $\alpha$ 4 protein seems to be ideal for a small molecule approach targeting a protein-protein interaction.

## General information

### Selected publications

Aranda-Orgillés B, Aigner J, Kunath M, Lurz R, [Schweiger S](#). *Active Transport of the Ubiquitin Ligase MID1 along the Microtubules Is Regulated by Protein Phosphatase 2A*. PLoS One 2008; 3(10): e3507

Winter J, Roepcke S, Krause S, Mueller EM, Otto A, Vingron M, [Schweiger S](#). *Comparative 3'UTR analysis allows identification of regulatory clusters that drive Eph/ephrin expression in cancer cell lines*. PLoS One 2008;3(7): e2780

Krauß S, Foerster J, Schneider R, [Schweiger S](#). *PP2A and rapamycin regulate the nuclear localization and activity of the transcription factor GLI3*. Cancer Research 2008; 68(12): 4658-65

Aranda-Orgillés B, Winter J, Aigner J, Köhler A, Jastrzebska E, Stahl J, Müller EC, Otto A, Wanker EE, Schneider R, [Schweiger S](#). *The Opitz syndrome gene product MID1 assembles a microtubule-associated ribonucleoprotein complex*. Hum Genet 2008; 123(2):163-76

Winter J, Kunath M, Roepcke S, Krause S, Schneider R, [Schweiger S](#). *Alternative polyadenylation signals and promoters act in concert to control tissue-specific expression of the Opitz Syndrome gene MID1*. BMC Mol Biol 2007; 8:105.



### Work as scientific referee

S. Schweiger serves as scientific referee for the following journals (selection): Journal of Neuroscience, Human Molecular Genetics, Experimental Cell Research and Cancer Research.

### Special achievements

S. Schweiger was board certificated for the Speciality of Human Genetics in November 2006 (Fachärztin für Humangenetik)

### Appointments of former members of the group

Jennifer Winter: Group leader at the Max Planck Institute of Immunobiology, Freiburg / Breisgau

Susann Schweiger - Chair for Molecular Medicine and Head of the Centre for Oncology and Molecular Medicine at the University of Dundee (Medical School)

### Patents

US-preliminary patent # 60/380,590: *Intervention in intracellular PP2A levels via its interaction with the a4 protein: implications for Alzheimer and cancer treatment.*

German patent office invention disclosure: *Strategies to enhance production of proteins in eukaryotic cells.*

### External funding

Volkswagen Foundation Germany: *The renaissance of the human model: monogenic phenotypes as gateways to signaling networks in development and disease*, 04/05 - 03/10

AtaxiaUK: *Translation control of mRNAs with CAG repeat expansions and its implication for pathogenesis and therapy of SCA2 and other spinocerebellar ataxias*, 08/08-07/11

Tenovus Scotland: *The microtubule-associated MID1/PP2A mRNP and its role in the pathogenesis of Chorea Huntington*, 04/08-03/11

Chief Scientist Office: *The MID1/PP2A protein complex: a novel tool to develop therapies for Spinocerebellar Ataxias*, 10/09- 09/10

## General information about the whole Department

### Complete list of publications (2006-2009)

#### 2009

Adelfalk, C., Janschek, J., Revenkova, E., Liebe, B., Göb, E., Alsheimer, M., Benavente, R., de Boer, E., Novak, I., Höög, C., Scherthan, H. and Jessberger, R. *Cohesin SMC1 $\beta$  protects telomeres in meiocytes*. J Cell Biol 187:185-99 (2009).

Attarbaschi, A., Pisecker, M., Inthal, A., Mann, G., Janousek, D., Dworzak, M., Pötschger, U., Ullmann, R., Schrappe, M., Gadner, H., Haas, O.A., Panzer-Grümayer, R., and Strehl, S. *Prognostic relevance of TLX3 (HOX11L2) expression in childhood T-cell acute lymphoblastic leukaemia treated with Berlin-Frankfurt-Münster (BFM) protocols containing early and late re-intensification elements*. British Journal of Hematology, accepted (2009).

Barrionuevo, F., Georg, I., Scherthan, H., Lécureuil, C., Guillou, F., Wegner, M. and Scherer, G. *Testis cord differentiation after the sex determination stage is independent of Sox9 but fails in the combined absence of Sox9 and Sox8*. Developmental Biology 327:301-12 (2009).

Bashiardes, S., Kousoulidou, L., van Bokhoven, H., Ropers, H.H., Chelly, J., Moraine, C., de Brower, A.P., Van Esch, H., Froyen, G., Patsalis, P.C. *A New Chromosome X Exon-specific Microarray Platform for Screening of Patients with X-Linked Disorders*. J Mol Diagn Sep24[epub ahead of print] (2009).

Chen, W., Ullmann, R., Langnick, C., Menzel, C., Wotschofsky, Z., Hu, H., Döring, A., Hu, Y., Kang, H., Tzschach, A., Hoeltzenbein, M., Neitzel, H., Markus, S., Wiedersberg, E., Kistner, G., Van Ravenswaaij-Arts, C.M.A., Kleefstra, T., Kalscheuer, V.M., Ropers, H.H. *Breakpoint analysis of balanced chromosome rearrangements by next-generation paired-end sequencing*. Eur J Hum Genet, advance online publication, 2 December 2009; doi:10.1038/ejhg.2009.211 (2009).

Cordova-Fletes, C., Rademacher, N., Ullmann, R., Mundo-Ayala, J.N., Morales-Jeanhs, E.A., Garcia-Ortiz, J.E., Leon-Gil, A., Rivera, H., Dominguez, M.G., Kalscheuer, V.M. *CDKL5 truncation due to a t(X;2)(p22.1;p25.3) in a girl with X-linked infantile spasm syndrome*. Clin Genet 75 (accepted) (2009).

Erenpreisa, J., Cragg, M.S., Salmina, K., Hausmann, M., Scherthan, H. *The role of meiotic cohesin REC8 in chromosome segregation in  $\gamma$ irradiation-induced endopolyploid tumour cells*. Exp. Cell Res. 315:2593-2603 (2009).

Fu, X, Fu, N., Guo, S., Yan, Z., Xu, Y., Hu, H., Menzel, C., Chen, W., Li, Y., Zeng, R., Khaitovich, P., *Estimating accuracy of RNA-Seq and microarrays with proteomics*. BMC Genomics 10;161-169 (2009).

Garcia-Cruz, R., Roig, I., Robles, P., Scherthan, H., and Garcia, M. *ATR, BRCA1 and  $\gamma$ H2AX localize to unsynapsed chromosomes at the pachytene stage in human oocytes*. Reprod. BioMedicine Online 18:37-44 (2009).

Graul-Neumann, L.M., Stieler, K.M., Blume-Peytavi, U., Tzschach, A. *Autosomal dominant inheritance in a large family with focal facial dermal dysplasia (Brauer-Setleis syndrome)*. Am J Med Genet A. Mar16;149A(4): 746-750 (2009).

Grohmann, M., Paulmann, N., Fleischhauer, S., Vowinkel, J., Priller, J., Walther, D.J. *A mammalianized synthetic nitroreductase gene for high-level expression*. BMC Cancer Aug27;9:301 (2009)

Haensel, J., Kohlschmidt, N., Pitz, S., Keilmann, A., Zenker, M., Ullmann, R., Haaf, T., Bartsch, O. *Case report supporting that the Barber-Say and ablepharon macrostomia syndromes could represent one disorder*. Am J Med Genet A, Sep16.[Epub ahead of print] (2009).

Hilhorst-Hofstee, Y., Tümer, Z., Born, P., Knijnenburg, J., Hansson, K., Yatawara, V., Steensberg, J., Ullmann, R., Arkesteijn, G., Tommerup, N., Larsen, L.A. *Molecular characterization of two patients with de novo interstitial deletions in 4q22-q24*. Am J Med Genet A. Aug;149A(8):1830-3 (2009).

Hu, H.Y., Yan, Z., Xu, Y., Hu, H., Menzel, C., Zhou, Y.H. Chen, W., Khaitovich, P. *Sequence features associated with microRNA strand selection in humans and flies*. BMC Genomics. Sep4;10(1):413 [Epub ahead of print] (2009).

Kahrizi, K., Najmabadi, H., Kariminejad, R., Jamali, P., Malekpour, M. Garshasbi, M., Ropers, H.H., Kuss, A.W., Tzschach, A. *An autosomal recessive syndrome of severe mental retardation, cataract, coloboma and ky-*



- phosis maps to the pericentromeric region of chromosome 4.* Eur J Hum Genet, 17(1), 125-8 (2009).
- Kalscheuer, V.M., Musante, L., Fang, C., Hoffmann, K., Fuchs, C., Carta, E., Deas, E., Venkateswarlu, K., Menzel, C., Ullmann, R., Tommerup, N., Dalprà, L., Tzschach, A., Selicorni, A., Lüscher, B., Ropers, H.H., Harvey, K., Harvey, R.J. *A balanced chromosomal translocation disrupting ARHGEF9 is associated with epilepsy, anxiety, aggression, and mental retardation.* Hum Mutat Jan;30(1):61-8 (2009).
- Kariminejad, A., Kariminejad, R., Tzschach, A., Ullmann, R., Ahmed, A., Asghari-Roodsari, A., Salehpour, S., Afroozan, F., Ropers, H.H., Kariminejad, M.H. *Craniosynostosis in a patient with 2q37.3 deletion 5q34 duplication: association of extra copy of MSX2 with craniosynostosis.* Am J Med Genet A. Jul;149A(7):1544-9 (2009).
- Kim, G.-J., Georg, I., Scherthan, H., Merken-schlager, M., Guillou, F., Scherer, G. and Barrionuevo, F. *Dicer is required for Sertoli cell function and survival.* Int J Dev Biol., in press (2009).
- Krauß, S., So, J., Hambrock, M., Köhler, A., Kunath, M., Scharff, C., Wessling, M., Grzeschick, K.H., Schneider, R., Schweiger, S. *Point Mutations in GLI3 Lead to Misregulation of its Subcellular Localization.* PLoS One Oct 15;4(10):e7471 (2009).
- Laumonnier, F., Shoubridge, C., Antar, C., Nguyen, L.S., Van Esch, Kleefstra, T., Briault, S., Fryns, J.P., Hambel, B., Chelly, J., Ropers, H.H., Ronce N., Blesson, S., Moraine, C., Gecz, J., Raynaud, M. *Mutations of the UPF3B gene, which encodes a protein widely expressed in neurons, are associated with non-specific mental retardation with or without autism.* Mol Psychiatry Feb 24 [Epub ahead of print] (2009).
- Lugtenberg, D., Kleefstra, T., Oudakker, A.R., Nillesen, W.M., Yntema, H.G., Tzschach, A., Raynaud, M., Rating, D., Journal, H., Chelly, J., Goizet, C., Lacombe, D., Pedespan, J.M., Echenne, B., Tariverdian, G., O'Rourke, D., King, M.D., Green, A., van Kogelenberg, M., Van Esch, H., Gecz, J., Hamel, B.C., van Bokhoven, H., de Brouwer, A.P. *Structural variation in Xq28: MECP2 duplications in 1% of patients with unexplained XLMR and in 2% of male patients with severe encephalopathy.* Eur J Hum Genet Apr;17(4):444-53 (2009).
- Mangerich, A., Scherthan, H., Diefenbach, J., Kloz, U., van der Hoeven, F., Beneke, S. and Bürkle, A. *A Caveat in Mouse Genetic Engineering: Ectopic Gene Targeting in ES Cells by Bidirectional Extension of Homology Arms of a Gene Replacement Vector Carrying Human PARP-1.* Transgenic Research, 18:261-79 (2009).
- Mir A, Kaufman L, Noor A, Motazacker MM, Jamil T, Azam M, Kahrizi K, Rafiq MA, Weksberg R, Nasr T, Naeem F, Tzschach A, Kuss AW, Ishak GE, Doherty D, Ropers HH, Barkovich AJ, Najmabadi H, Ayub M, Vincent JB. *Identification of mutations in TRAPPC9, which encodes the NIK and IKK-β binding protein (NIBP), in Non-Syndromic Autosomal Recessive Mental Retardation.* Am J Hum Genet 2009; 85: 909-915
- Musante, L., Kunde, S.A., Sulistio, T.O., Fischer, U., Grimme, A., Frints, S.G.M., Schwartz, C.E., Martinez, F., Romano, C., Ropers, H.H., Kalscheuer, V.M. *Common pathological mutations in PQBP1 induce nonsense-mediated mRNA decay and enhance exclusion of the mutant exon.* Hum Mut, accepted for publication Sept (2009).
- Najm, J., D. Horn, I. Wimplinger, J.A. Golden, V.V. Chizhikov, J. Sudi, S.L. Christian, R. Ullmann, A. Kuechler, C.A. Haas, A. Flubacher, L.R. Charnas, G. Uyanik, U. Frank, E. Klopocki, W.B. Dobyns, K. Kutsche. *Mutations of CASK cause an X-linked brain malformation phenotype with microcephaly and hypoplasia of the brainstem and cerebellum.* Nat Genet 40(9):1065-7 (2009).
- Neumann, T.E., Allanson, J., Kavamura, I., Kerr, B., Neri, G., Noonan, J., Cordeddu, V., Gibson, K., Tzschach, A., Krüger, G., Hoeltzenbein, M., Goecke, T.O., Kehl, H.G., Albrecht, B., Luczak, K., Sasiadek, M.M., Musante, L., Laurie, R., Peters, H., Tartaglia, M., Zenker, M., Kalscheuer, V. *Multiple giant cell lesions in patients with Noonan syndrome and cardio-facio-cutaneous syndrome.* Eur J Hum Genet Apr;17(4):420-5 (2009).
- Pouya, A.R., Abedini, S.S., Mansoorian, N., Behjati, F., Nikzat, N., Mohseni, M., Nieh, S.E., Abbasi Moheb, L., Darvish, H., Monajemi, G.B., Banihashemi, S., Kahrizi, K., Ropers, H.H., Najmabadi, H. *Fragile X syndrome screening of families with consanguineous and non-consanguineous parents in the Iranian population.* Eur J Med Genet Jul-Aug;52(4):170-3 (2009).

- Raile, K., Klopocki, E., Holder, M., Wessel, T., Galler, A., Deiss, D., Müller, D., Riebel, T., Horn, D., Maringa, M., Weber, J., Ullmann, R., Grütters, A. *Expanded clinical spectrum in hepatocyte nuclear factor 1 $\beta$ -maturity-onset diabetes of the young*. J Clin Endocrinol Metab. Jul;94(7):2658-64 [Epub May5] (2009).
- Ropers, H.H. *Single gene disorders come into focus – again*. Dialogues in Clinical Neuroscience 44, in press (2009).
- Ropers, H.H. *Vom Mütterchen die Frohnatur: neue Perspektiven für die Aufklärung der Funktion des menschlichen Genoms und Konsequenzen für die Krankenversorgung*. In: Gaterslebener Begegnungen XI, in press (2009).
- Scherthan, H. *Analysis of telomere dynamics in mouse spermatogenesis*. Methods Molec Biol 558:383-99 (2009).
- Schmidt, S., Hommel, A., Gawlik, V., Augustin, R., Junicke, N., Florian, S., Richter, M., Walther, D.J., Montag, D., Joost, H.G., Schürmann, A. *Essential role of glucose transporter GLUT3 for post-implantation embryonic development*. J Endocrinol Jan;200(1):23-33 [Epub 2008Oct23] (2009).
- Seifert, W., Holder-Espinasse, M., Kühnisch, J., Kahrizi, K., Tzschach, A., Garshasbi, M., Najmabadi, H., Kuss, A.W., Kress, W., Laureys, G., Loeys, B., Brilstra, E., Mancini, G.M., Dollfus, H., Dahan, K., Apse, K., Hennies, C.H., Horn, D. *Expanded mutational spectrum in Cohen syndrome, tissue expression, and transcript variants of COH1*. Hum Mutat Feb;30(2):E404-20 (2009).
- Shoichet, S.A., Waibel, S., Endruhn, S., Sperfeld, A.D., Vorwerk, B., Müller, I., Erdogan, F., Ludolph, A.C., Ropers, H.H., Ullmann, R. *Identification of candidate genes for sporadic amyotrophic lateral sclerosis by array comparative genomic hybridization*. Amyotroph Lateral Scler Jun;10(3):162-9 (2009).
- Stoeckius, M., Maaskola, J., Colombo, T., Rahn, H.P., Friedländer, M.R., Li, N., Chen, W., Piano, F., Rajewsky, N. *Large-scale sorting of C.elegans embryos reveals the dynamics of small RNA expression*. Nat Methods Sep6[Epub ahead of print] (2009).
- Tarpey, P.S., Smith, R., Pleasance, E., Whibley, A., Edkins, S., Hardy, C., O'Meara, S., Latimer, C., dicks, E., Menzies, A., Stephens, P., Blow, M., Greenman, C., Xue, Y., Tyler-Smith, C., Thompson, D., Gray, K., Andrews, J., Barthorpe, S., Buck, G., Cole, J., Dunmore, R., Jones, D., Maddison, M., Mironenko, T., Turner, R., Turell, K., Varian, J., West, S., Widaa, S., Wray, P., Teague, J., Butler, A., Jenkinson, A., Jia, M., Richardson, D., Shepherd, R., Wooster, R., Tejada, M.I., Martinez, F., Carvill, G., Goliath, R., de Brouwer, A.P., van Bokhoven, H., Van Esch, H., Chelly, J., Raynaud, M., Ropers, H.H., Abidi, F.E., Srivastava, A.K., Cox, J., Luo, Y., Mallya, U., Moon, J., Parnau, J., Mohammed, S., Tolmie, J.L., Shoubbridge, C., Corbett, M., Gardner, A., Haan, E., Rujirabanjert, S., Shaw, M., Vandeleur, L., Fullston, T., Easton, D.F., Boyle, J., Partington, M., Hackett, A., Field, M., Skinner, C., Stevenson, R.E., Bobrow, M., Turner, G., Schwartz, C.E., Gecz, J., Raymond, F.L., Futreal, P.A., Stratton, M.R. *A systematic, large-scale resequencing screen of X-chromosome coding exons in mental retardation*. Nat Genet May;41(5):535-43 [Epub 2009Apr19] (2009).
- Türkmen, S., Guo, G., Garshasbi, M., Hoffmann, K., Alshalah, A.J., Mischung, C., Kuss, A.W., Humphrey, N., Mundlos, S., Robinson, P.N. *CA8 mutations cause a novel syndrome characterized by ataxia and mild mental retardation with predisposition to quadrupedal gait*. PLoS Genetics 5(5):e1000487 (2009).
- Tzschach, A., Bisgaard, A.-M., Kirchhoff, M., Graul-Neumann, L.M., Neitzel, H., Page, S., Ahmed, A., Müller, I., Erdogan, F., Ropers, H.H., Kalscheuer, V.M., R. Ullmann. *Chromosome aberrations involving 10q22: Report of three overlapping interstitial deletions and a balanced translocation disrupting C10orf11*. Eur J Hum Genet, accepted (2009).
- Tzschach, A. *Genetik der nichtsyndromalen geistigen Behinderung*. Medgen 21:231-236 (2009).
- Tzschach, A., Ramel, C., Kron, A., Seipel, B., Wüster, C., Cordes, U., Liehr, T., Hoeltzenbein, M., Menzel, C., Ropers, H.H., Ullmann, R., Kalscheuer, V., Decker, J., Steinberger, D. *Hypergonadotropic hypogonadism in a patient with inv ins (2;4)*. Int J Androl. Jun;32(3):226-30 (2009).
- Tzschach, A., Graul-Neumann, L.M., Konrat, K., Richter, R., Ebert, G., Ullmann, R., Neitzel, H. *Interstitial deletion 2p11.2-p12: report of a patient with mental retardation and review of the literature*. Am J Med Genet A. Jan15;149A(2):242-5 (2009).



Ullmann, R. *Array Comparative Genomic Hybridization in Pathology*, pp87-96. In: Basic concepts of Molecular Pathology, Eds: Cagle, P.T. and Craig, A., Springer Verlag Heidelberg [ISBN: 978-0-387-89625-0] (2009).

Urcan, E., Haertel, U., Styllou, M., Hickel, R., Scherthan, H., Reichl, F.-X. *Real-time xCelligance impedance analysis of the cytotoxicity of dental composite components on human gingival fibroblasts*. Dent Mater doi:10.1016/j.dental.2009.08.007 (2009).

Zanni, G., van Esch, H., Bensalem, A., Saillour, Y., Poirer, K., Castelnaud, L., Ropers, H.H., de Brouwer, A.P., Laumonnier, F., Fryns, J.P., Chelly, J. *A novel mutation in the DLG3 gene encoding the synapse-associated protein 102 (SAP102) causes non-syndromic mental retardation*. Neurogenetics Oct [Epub ahead of print] (2009).

Zatkova, A., Merk, S., Wendehack, M., Bilban, M., Muzik, E.M., Muradyan, A., Haferlach, C., Haferlach, T., Wimmer, K., Fonatsch, C., Ullmann, R. *AML/MDS with 11q/MLL amplification show characteristic gene expression signature and interplay of DNA copy number changes*. Genes Chromosomes Cancer. Jun;48(6):510-20 (2009).

Zhang, L., Tümer, Z., Mollgard, K., Barbi, G., Rossier, E., Bendsen, E., Moller, R.S., Ullmann, R., He, J., Papadopoulos, N., Tommerup, N., Larsen, L.A. *Characterization of a t(5;8)(q31;q21) translocation in a patient with mental retardation and congenital heart disease: implications for involvement of RUNX1T1 in human brain and heart development*. Eur J Hum Genet Aug;17(8):1010-8 [Epub Jan 28] (2009).

## 2008

Al Yacoub, N., M. Romanowska, S. Krauss, S. Schweiger, and J. Foerster: *PPARdelta is a Type 1 IFN target gene and inhibits apoptosis in T cells*. J Invest Dermatol, 128(8), 1940-9 (2008)

Aranda-Orgillés, B., J. Aigner, M. Kunath, R. Lurz, R. Schneider, S. Schweiger: *Active transport of the ubiquitin ligase MID1 along the microtubules is regulated by protein phosphatase 2A*. PLoS ONE 3(10), e3507 (2008).

Aranda-Orgillés, B. A. Trockenbacher, J. Winter, J. Aigner, A. Köhler, E. Jastrzebska, J. Stahl, E.C. Müller, A. Otto, E.E. Wanker, R. Schneider, and S. Schweiger: *The Opitz syndrome gene product MID1 assembles a microtubule-associated ribonucleoprotein complex*. Hum Genet. 123(2), 163-76 (2008).

Busche, A., E. Klopocki, R. Ullmann, S. Mundlos, and D. Horn: *A cryptic unbalanced translocation t(2;9)(p25.2;q34.3) causes the phenotype of 9q subtelomeric deletion syndrome and additional exophthalmos and joint contractures*. Eur J Med Genet, Jul 12 (2008).

Chen, W., V. Kalscheuer, A. Tzschach, C. Menzel, R. Ullmann, M. Schulz, F. Erdogan, N. Li, Z. Kijas, G. Arkesteijn, I.L. Pajares, M. Goetz-Sothmann, U. Heinrich, I. Rost, A. Dufke, U. Grasshoff, B.G. Glaeser, M. Vingron and H.H. Ropers: *Mapping translocation breakpoints by next-generation sequencing*. Genome Research 18(7), 1143-9 (2008).

Cízková, A., V. Stránecký, J.A. Mayr, M. Tesarová, V. Havlíčková, R. Ivánek, A.W. Kuss, H. Hansíková, V. Kaplanová, M. Vrbacký, H. Hartmannová, L. Nosková, T. Honzík, Z. Drahota, M. Magner, K. Heizlarová, W. Sperl, J. Zeman, J. Houstek, and S. Kmoch: *TMEM70 mutations cause isolated ATP synthase deficiency and neonatal mitochondrial encephalomyopathy*. Nature Genetics 40(11), 1288-90 (2008).

Ender, C., A. Krek, M.R. Friedländer, M.B. Weinmann, W. Chen, S. Pfeffer, N. Rajewsky, and G. Meister: *A human snoRNA with microRNA-like functions*. Molecular Cell 32(4), 519-528 (2008).

Engenheiro, E., R.S. Møller, M. Pinto, G. Soares, M. Nikanorova, I.M. Carreira, R. Ullmann, N. Tommerup, Z. Tümer: *Mowat-Wilson syndrome: an underdiagnosed syndrome?* Clin Genet. 73(6):579-84 (2008).

Erdogan F., J.M. Belloso, E. Gabau, K.D. Ajbro, M. Guitart, H.H. Ropers, N. Tommerup, R. Ullmann, Z. Tümer, LA Larsen: *Fine mapping of a de novo interstitial 10q22-q23 duplication in a patient with congenital heart disease and microcephaly*. Eur J Med Genet, 51(1), 81-6 (2008).

Erdogan, F., L.A. Larsen, L. Zhang, Z. Tümer, N. Tommerup, W. Chen, J.R. Jacobsen, M. Schubert, J. Jurkatis, A. Tzschach, H.H. Ropers, and R. Ullmann: *High frequency of submicroscopic genomic aberrations detected by tiling path array CGH in patients with isolated congenital heart disease*. Journal of Medical Genetics 45(11), 704-9 (2008).

Friedlander, M.R., W. Chen, C. Adamidi, J. Maaskola, R. Einspanier, S. Knespel, and N. Rajewsky: *Discovering microRNAs from deep sequencing data using miRDeep*. Nature Biotechnology 26(4),407-15 (2008).

- Frints, S.G., S. Lenzner, M. Bauters, L.R. Jensen, H. Van Esch, V. Des Portes, U. Moog, M.V. Macville, K., van Roozendaal, C.T. Schrandt-Stumpel, A. Tzschach, P. Marynen, J.P. Fryns, B. Hamel and H. van Bokhoven, J. Chelly, C. Beldjord, G. Turner, J. Gecz, C. Moraine, M. Raynaud, H.H. Ropers, G. Froyen, and A.W. Kuss: *MCT8 mutation analysis and identification of the first female with Allan-Herndon-Dudley syndrome due to loss of MCT8 expression*. European Journal of Human Genetics 16(9), 1029-37 (2008).
- Froyen, G., M. Corbett, J. Vandewalle, I. Jarvela, O., Lawrence, C. Meldum, M. Bauters, K. Govaerts, L. Vandeleur, H. Van Esch, J. Chelly, D. Sanlaville, H. van Bokhoven, H.H. Ropers, F. Laumonnier, E. Ranieri, C.E. Schwartz, F. Abidi, P.S. Tarpey, P.A. Futreal, A. Whibley, F.L. Raymond, M.R. Stratton, J.P. Fryns, R. Scott, M. Peippo, M. Sipponen, M. Partington, D. Mowat, M. Field, A. Hackett, P. Marynen, G. Turner, and J.Géczy: *Submicroscopic duplications of the hydroxysteroid dehydrogenase HSD17B10 and the E3 ubiquitin ligase HUWE1 are associated with mental retardation*. Am J Hum Genet, 82(2), 432-43 (2008).
- Garshasbi, M., V. Hadavi, H. Habibi, K. Kahrizi, R. Karimnejad, F. Behjati, A. Tzschach, H. Najmabadi, H.H. Ropers and A.W. Kuss: *A defect in the TUSC3 gene is associated with autosomal recessive mental retardation*. Am J Hum Genet 82(5), 1158-1164 (2008).
- Gilling, M., M.B. Lauritsen, M. Møller, K.F. Henriksen, A. Vicente, G. Oliveira, C. Cintin, H. Eiberg, P.S. Andersen, O. Mors, T. Rosenberg, K. Brøndum-Nielsen, R.M. Cotterill, C. Lundsteen, H.H. Ropers, R. Ullmann, I. Bache, Z. Tümer and N. Tommerup: *A 3.2 Mb deletion on 18q12 in a patient with childhood autism and high-grade myopia*. Eur J Hum Genet 16(3), 312-9 (2008).
- Goswami, C. Hucho T: *Submembraneous microtubule cytoskeleton: biochemical and functional interplay of TRP channels with the cytoskeleton*. FEBS J 275(19), 4684-99 (2008).
- Goswami, C. and T. Hucho: *Novel aspects of the submembraneous microtubule cytoskeleton*. Editorial to review series. FEBS J. 275(19), 4653 (2008).
- Heazlewood, J.L. P. Durek, J. Hummel, J. Selbig, W. Weckwerth, D. Walther, and W.X. Schulze: *PhosPhAt: a database of phosphorylation sites in Arabidopsis thaliana and a plant-specific phosphorylation site predictor*. Nucleic Acids Res Jan;36(Database issue): D1015-21. [Epub 2007 Nov] (2008).
- Kaalund, S.S., R.S. Møller, A. Tészás, M. Miranda, G. Kosztolanyi, R. Ullmann, N. Tommerup, Z. Tümer: *Investigation of 4q-deletion in two unrelated patients using array CGH*. Am J Med Genet A, 146A(18), 2431-4 (2008).
- Kalscheuer, V.M., I. Feenstra, C.M.A. Van Ravenswaaij-Arts, D.F.C.M. Smeets, C. Menzel, R. Ullmann, L. Musante and H.H. Ropers: *Disruption of the TCF4 gene in a girl with mental retardation but without the classical Pitt-Hopkins syndrome*. Am J Med Genet Part A, 146A(16), 2053-9 (2008).
- Kalscheuer, V.M., L. Musante, C. Fang, K. Hoffmann, C. Fuchs, E. Carta, E. Deas, K. Venkateswarlu, C. Menzel, R. Ullmann, N. Tommerup, L. Dalprà, A. Tzschach, A. Selicorni, B. Lüscher, H.H. Ropers, K. Harvey and R.J. Harvey: *A balanced chromosomal translocation disrupting ARHGEF9 is associated with epilepsy, anxiety, aggression, and mental retardation*. Human Mutations, Jul 9 [Epub ahead of print] (2008).
- Kahrizi, K., H. Najmabadi, R. Karimnejad, P. Jamali, M. Malekpour, M. Garshasbi, H.H. Ropers, A.W. Kuss, and A. Tzschach: *An autosomal recessive syndrome of severe mental retardation, cataract, coloboma and kyphosis maps to the pericentromeric region of chromosome 4*. European Journal of Human Genetics 17(1), 125-128 [Epub 2008 Sep10] (2008).
- Kirov, G., D. Gumus, W. Chen, N. Norton, L. Georgieva, M. Sari, M.C. O'Donovan, F. Erdogan, M.J. Owen, H.H. Ropers, R. Ullmann: *Comparative genome hybridization suggests a role for NRXN1 and APBA2 in schizophrenia*. Hum Mol. Genet 17(3), 458-65 [Epub 2007, Nov 6] (2008).
- Klopocki, E., L.M. Graul-Neumann, U. Grieben, H. Tönnies, H.H. Ropers, D. Horn, S. Mundlos, and R. Ullmann: *A further case of the recurrent 15q24 microdeletion syndrome, detected by array CGH*. Eur J Pediatr 167(8), 903-8 [Epub 2007 Oct 12] (2008).



- Klopocki, E., C.E. Ott, N. Benatar, R. Ullmann, S. Mundlos, and K. Lehmann: *A microduplication of the long range SHH limb regulator (ZRS) is associated with triphalangal thumb-polysyndactyly syndrome*. J Med Genet 45(6), 370-5 (2008).
- Krauß, S., J. Foerster, R. Schneider, and S. Schweiger: *Protein Phosphatase 2A and Rapamycin regulate the nuclear localization and activity of the transcription factor GLI3*. Cancer Research 68(12), 4658-4665 (2008).
- Kuhn, J., O.A. Dina, C. Goswami, V. Suckow, J.D. Levine, and T. Hucho: *GPR30 estrogen receptor agonists induce mechanical hyperalgesia in the rat*. Eur J of Neuroscience 27(7):1700-9 (2008).
- Kuss, A.W. and W. Chen: *MicroRNAs in brain function and disease*. Current Neurology and Neuroscience Reports 8, 190-197 (2008).
- Lugtenberg, D., T. Kleefstra, A.R. Oudakker, W.M. Nillesen, H.G. Yntema, A. Tzschach, M. Raynaud, D. Rating, H. Journel, J. Chelly, C. Goizet, D. Lacombe, J.M. Pedespan, B. Echenne, G. Tariverdian, D. O'Rourke, M.D. King, A. Green, M. van Kogelenberg, H. Van Esch, J. Geetz, B.C. Hamel, H. van Bokhoven, and A.P. de Brouwer: *Structural variation in Xq28: MECP2 duplications in 1% of patients with unexplained XLMR and in 2% of male patients with severe encephalopathy*. Eur J Hum Genet [Epub 2008 Nov 5] (2008).
- Møller, R.S., S. Kübart, M. Hoeltzenbein, B. Heye, I. Vogel, C.P. Hansen, C. Menzel, R. Ullmann, N. Tommerup, H.H. Ropers, Z. Tümer and V.M. Kalscheuer: *Truncation of the Down syndrome candidate gene DYRK1A in two unrelated patients with microcephaly*. Am J Hum Genet. 82(5):1165-70 (2008).
- Møller, R.S., L.M. Schneider, C.P. Hansen, M. Bugge, R. Ullmann, N. Tommerup and Z. Tümer: *Balanced translocation in a patient with severe myoclonic epilepsy of infancy disrupts the sodium channel gene SCN1A*. Epilepsia, 49(6), 1091-4 (2008).
- Moheb, L.A., A. Tzschach, M. Garshasbi, K. Kahrizi, H. Daruishi, Y. Heshmati, A. Kordi, H. Najmabadi, H.H. Ropers, and A.W. Kuss: *Identification of nonsense mutation in the very low density lipoprotein receptor gene (VLDLR) in an Iranian family with dysequilibrium syndrome*. Eur J Hum Genet 16(2), 270-273 (2008).
- Muradyan, A., V. Boldt, A. Steininger, S. Stabentheiner, K. Tebel, J. Kreutzberger, I. Müller, H. Madle, H. Popper and R. Ullmann: *An integrative approach for analyzing the interplay of genetic and epigenetic changes in tumors*. Archives of Pathology & Laboratory Medicine, 132(10), 1557-61 (2008).
- Najm, J., D. Horn, I. Wimplinger, J.A. Golden, V.V. Chizhikov, J. Sudi, S.L. Christian, R. Ullmann, A. Kuechler, C.A. Haas, A. Flubacher, L.R. Charnas, G. Uyanik, U. Frank, E. Klopocki, W.B. Dobyns, K. Kutsche: *Mutations of CASK cause an X-linked brain malformation phenotype with microcephaly and hypoplasia of the brainstem and cerebellum*. Nat Genet (Aug 19), (2008).
- Neumann, T.E., J. Allanson, I. Kavamura, B. Kerr, G. Neri, J. Noonan, V. Cordeddu, K. Gibson, A. Tzschach, G. Krüger, M. Hoeltzenbein, T.O. Goecke, H.G. Kehl, B. Albrecht, K. Luczak, M.M. Sasiadek, L. Musante, R. Laurie, H. Peters, M. Tartaglia, M. Zenker, and V. Kalscheuer: *Multiple giant cell lesions in patients with Noonan syndrome and cardio-facio-cutaneous syndrome*. Eur J Hum Genet, Oct 15 [Epub 2008Oct15] (2008).
- Novak, I., H. Wang, E. Revenkova, R. Jessberger, H. Scherthan, and C. Höög: *Cohesin Smc1 $\beta$  determines meiotic chromatin axis loop organization*. J. Cell Biology, 180, 83-90 (2008).
- Raile K., E. Klopocki, T. Wessel, D. Deiss, D. Horn, D. Müller, R. Ullmann, and A. Grüters: *HNF1B Abnormality (Mature-Onset Diabetes of the Young 5) in Children and Adolescents: High prevalence in autoantibody-negative type 1 diabetes with kidney defects*. Diabetes Care, 31(11), e83 (2008).
- Romanowska, M., al Yacoub, N., Seidel, H., Donando, S., Germen, H., Phillip, S., Haritonova, N., Artuc, M., Schweiger, S., Sterry, W., Foerster, J. *PPARdelta enhances keratinocyte proliferation in psoriasis and induces heparin-binding EGF-like growth factor*. Invest Dermatol 128(1):110-24 (2008).
- Ropers, H.H.: *Genetics of intellectual disability*. Current Opinion in Genetics & Development 18, 241-250 (2008).

- Scheffler, I.E., S.J. Turner, L.M. Dibbens, M.A. Bayly, K. Friend, B. Hodgson, L. Burrows, M. Shaw, C. Wei, R. Ullmann, H.H. Ropers, P. Szepietowski, E. Haan, A. Mazarib, Z. Afawi, M.Y. Neufeld, P.I. Andrews, G. Wallace, S. Kivity, D. Lev, T. Lerman-Sagie, C.P. Derry, A.D. Korczyn, J. Gecz, J.C. Mulley, and S.F. Berkovic: *Epilepsy and mental retardation limited to females: an under-recognized disorder*. Brain 131(4), 918-27 (2008).
- Schell-Apacik, C.C., K. Wagner, M. Bihler, B. Ertl-Wagner, U. Heinrich, E. Klopocki, V.M. Kalscheuer, M. Muenke, and H. Von Voss: *Agenesis and dysgenesis of the corpus callosum: clinical, genetic and neuroimaging findings in a series of 41 patients*. Am J Med Genet A, 146A(19), 2501-11 (2008).
- Scherthan, H. *FISH targeting of chromosomes and subchromosomal regions in yeast*. In: Springer Protocols: Fluorescence in situ hybridization (FISH)—Application Guide. T. Liehr, ed. Springer Berlin, Heidelberg. p347-361 (2008).
- Scherthan, H. and Trelles-Sticken, E. *Absence of yKu/Hdf1 but not myosin-like proteins alters chromosome dynamics during prophase I in yeast*. Differentiation 76;91-98. DOI: 10.1111/j.1432-0436.2007.00212.x (2008).
- Scherthan, H., Hieber, L., Braselmann, H., Meineke, V., Zitzelsberger, H. *Accumulation of DSBs in gamma-H2AX domains fuel chromosomal aberrations*. Biochem Biophys Res Commun 371;694-97 (2008).
- Schmidt, S., A. Hommel, V. Gawlik, R. Augustin, N. Junicke, S. Florian, M. Richter, DJ Walther, D. Montag, H.G. Joost, A. Schürmann: *Essential role of glucose transporter GLUT3 for post-implantation embryonic development*. J Endocrinol. [Epub Oct 23] (2008).
- Seifert, W., M. Holder-Espinasse, J. Kühnisch, K. Kahrizi, A. Tzschach, M. Garshasbi, H. Najmabadi, A.W. Kuss, W. Kress, G. Laureys, B. Loeys, E. Brilstra, G. M.S. Mancini, H. Dollfus, K. Dahan, K. Apse, H.C. Hennies, and D. Horn: *Expanded mutational spectrum in Cohen Syndrome, tissue expression, and transcript variants of COH1*. Human Mutation 29, E404-E420 (online) (2008).
- So, J., I. Müller, M. Kunath, S. Herrmann, R. Ullmann, and S. Schweiger: *Diagnosis of a terminal deletion of 4p with duplication of Xp22.31 in a patient with clinical features of Opitz BBB/G Syndrome*. Am J Med Genet A 146A(1), 103-9 (2008).
- Steichen-Gersdorf, E., I. Gaßner, A. Superti-Furga, R. Ullmann, S. Stricker, E. Klopocki, and S. Mundlos: *Triangular tibia with fibular aplasia associated with a microdeletion on 2q11.2 encompassing LAF4*. Clin Genet 74(6);560-5 (2008).
- Tészás, A., R.S. Møller, R. Kellermayer, M. Czakó, K.W. Kjaer, R. Ullmann, B. Meleg, N. Tommerup, G. Kosztolányi: *A cryptic unbalanced translocation resulting in del 13q and dup 15q*. Am J Med Genet A. 146A(19), 2570-3 (2008).
- Tzschach, A., B. Bozorgmehr, V. Hadavi, K. Kahrizi, M. Garshasbi, M.M. Motazacker, H.H. Ropers, A.W. Kuss and H. Najmabadi: *Alopecia-mental retardation syndrome: clinical and molecular characterization of four patients*. British Journal of Dermatology, Sep;159(3):748-51 (2008).
- Tzschach, A., W. Chen, F. Erdogan, A. Hoeller, H.H. Ropers, C. Castellan, R. Ullmann, and A. Schinzel: *Characterization of Interstitial Xp duplications in two families by tiling path array CGH*. American Journal of Medical Genetics, Part A.146A(2), 197-203 (2008).
- Tzschach, A., S. Tinschert, E. Kaminsky, E. Lusga, S. Mundlos, L.M. Graul-Neumann: *Czech dysplasia: report of a large family and further delineation of the phenotype*. American Journal of Medical Genetics, Jul 15; 164A(14):1859-64 (2008).
- Tzschach, A., C. Kelbova, S. Weidensee, H. Peters, H.H. Ropers, R. Ullmann, F. Erdogan, J. Jurkatis, C. Menzel, V. Kalscheuer and S. Demuth: *Blepharophimosis-ptosis, epicanthus inversus syndrome in a girl with chromosome translocation t(2;3) (q33;q23)*: Ophthalmic Genetics, 29(1), 37-40 (2008).
- Ullmann, R.: *Array Comparative Genomic Hybridization in Pathology*. In: Molecular Pathology of Lung Diseases (Series Ed. Philip T. Cagle) (2008).
- Ullmann R., *Strukturelle Genomvarianten – Ausmaß, Entstehung und phänotypische Konsequenzen*. Medizinische Genetik 20(4), 401-405 (2008).
- Walczak-Sztulpa, J., M. Wisniewska, A. Latos-Bielenska, M. Linné, C. Kelbova, B. Belitz, L. Pfeiffer, V. Kalscheuer, F. Erdogan, A.W. Kuss, H.H. Ropers, R. Ullmann, and A. Tzschach: *Chromosome deletions in 13q33-34: Report of four patients and review of the literature*. Am J Med Genet A. 146(3), 337-42 (2008). Review



Winter, J., S. Roepcke, S. Krauss, E.C. Müller, A. Otto, M. Vingron, and S. Schweiger: *Comparative 3'UTR analysis allows identification of regulatory clusters that drive Eph/ephrin expression in cancer cell lines*. PLoS ONE 3(7), e2780 (2008).

## 2007

Belloso, J.M., I. Bache, M. Guitart, M.R. Caballin, C. Halgren, M. Kirchhoff, H.H. Ropers, N. Tommerup and Z. Tümer: *Disruption of the CNTNAP2 gene in a t(7;15) translocation family without symptoms of Gilles de la Tourette syndrome*. Eur J Hum Genet 15(6), 711-713 (2007).

Bisgaard, A.M., M. Kirchhoff, J.E. Nielsen, C. Brandt, H. Hove, B. Jepsen, T. Jensen, R. Ullmann, F. Skovby: *transmitted cytogenetic abnormalities in patients with mental retardation: Pathogenic or normal variants?* Eur J Med Genet, 50(4), 243-55 (2007).

Chen, W., L.R. Jensen, J. Gecz, J.P. Fryns, C. Moraine, A. de Brouwer, J. Chelly, B. Moser, H.H. Ropers and A.W. Kuss: *Mutation screening of brain-expressed X-chromosomal miRNA genes in 464 patients with nonsyndromic X-linked mental retardation*. Eur J Hum Genet 15, 375-378 (2007).

De Brouwer, A.P., H.G. Yntema, T. Kleefstra, D. Lugtenberg, A.R. Oudakker, B.B. de Vries, H. van Bokhoven, H. van Esch, S.G. Frints, G. Froyen, J.P. Fryns, M. Raynaud, M.P. Moizard, N. Ronce, A. Bensalem, C. Moraine, K. Poirier, L. Castenau, Y. Saillour, T. Bienvenu, C. Beldjord, V. des Portes, J. Chelly, G. Turner, T. Fullston, J. Gecz, A.W. Kuss, A. Tzschach, L.R. Jensen, S. Lenzner, V.M. Kalscheuer, H.H. Ropers and B.C. Hamel: *Mutation frequencies of X-linked mental retardation genes in families from the EuroMRX consortium*. Human Mutations 28(2), 207-208 (2007).

Engenheiro E., Saraiva J., Carreira I., Ramos L., Ropers H.H., Silva E., Tommerup N., Tümer Z.: *Cytogenetically invisible microdeletions involving PITX2 in Rieger syndrome*. Clinical Genetics 72, 464-470 (2007)

Erdogan, F., R. Ullmann, W. Chen, M. Schubert, S. Adolph, C. Hultschig, V. Kalscheuer, H.H. Ropers, C. Spaich and A. Tzschach: *Characterization of a 5.3 Mb deletion in 15q14 by Comparative Genomic Hybridization using a whole genome "tiling path" BAC array in a girl with heart defect, cleft palate and developmental delay*. Am J Med Gen A 143(2), 172-178 (2007).

Estrugo, D., Fischer, A., Hess, F., Scherthan, H., Belka, C., Cordes, N. *Beta1 integrins inhibit procaspase-8 via PI3K/Akt for mediating cell adhesion mediated drug and radiation resistance of human leukemia cells*. PLoS ONE, 2:e269 (2007).

Goswami, C., T. Hucho: *TrPV1 expression-dependent initiation and regulation of filopodia*. Journal of Neurochemistry, 103(4), 1319-33 (2007).

Goswami, C., T. Hucho and F. Hucho: *Identification and characterization of novel tubulin-binding motifs located within the C-terminus of TRPV1*. Journal of Neurochemistry 101(1), 250-262 (2007).

Gratias, S., H. Rieder, R. Ullmann, L. Kleinhitpass, S. Schneider, R. Boloni, M. Kappler and D.R. Lohmann: *Allelic loss in a minimal region on chromosome 16q24 is associated with vitreous seeding of retinoblastoma*. Cancer Research 67(1), 408-416 (2007).

Jakobsen, L.P., R. Ullmann, S.B. Christensen, K.E. Jensen, K. Molsted, K.F. Henriksen, C. Hansen, M.A. Knudsen, L.A. Larsen, N. Tommerup and Z. Tümer: *Pierre Robin sequence may be caused by dysregulation of SOX9 and KCNJ2*. Journal of Medical Genetics 44(6), 381-386 (2007).

Jensen, L.R., S. Lenzner, B. Moser, K. Freude, A. Tzschach, W. Chen, J.P. Fryns, J. Chelly, G. Turner, C. Moraine, B. Hamel, H.H. Ropers and A.W. Kuss: *X-linked mental retardation: a comprehensive molecular screen of 47 candidate genes from a 7.4 Mb interval in Xp11*. European Journal of Human Genetics 15, 68-75 (2007).

Kalscheuer VM, D FitzPatrick, N Tommerup, M Bugge, E Niebuhr, LM Neumann, A Tzschach, SA Shoichet, C Menzel, F Erdogan, G Arkesteijn, HH Ropers and R Ullmann: *Mutations in Autism Susceptibility Candidate 2 (AUTS2) in patients with mental retardation*. Human Genetics 121(3-4), 501-509 (2007).

Kirov, G., D. Gumus, W. Chen, N. Norton, L. Georgieva, M. Sari, M.C. O'Donovan, F. Erdogan, M.J. Owen, H.H. Ropers and R. Ullmann: *Comparative genome hybridization suggests a role for NRXN1 and APBA2 in schizophrenia*. Human Molecular Genetics 17,3;458-65 [Epub 2007, Nov 6] (2007).

- Klopocki, E., H. Schulze, G. Strauss, C.E. Ott, J. Hall, F. Trotier, S. Fleischhauer, L. Greenhalgh, R.A. Newbury-Ecob, L.M. Neumann, R. Habenicht, R. König, E. Seemanova, A. Megarbane, H.H. Ropers, R. Ullmann, D. Horn and S. Mundlos: *Complex inheritance pattern resembling autosomal recessive inheritance involving a microdeletion in thrombocytopenia-absent radius (TAR) syndrome*. Am J Hum Genet 80(2), 232-240 (2007).
- Klopocki E, LM Neumann, U Grieben, H Tönnies, HH Ropers, D.Horn, S Mundlos, R Ullmann: *A further case of the recurrent 15q24 microdeletion syndrome, detected by array CGH*. Eur J Pediatrics [Epub 2007 Oct12]
- Kousoulidou L, S Parkel, O Zilina, P Palta, H Puusepp, M Remm, G Turner, J Boyle, H van Bokhoven, A de Brouwer, H Van Esch, G Froyen, HH Ropers, J Chelly, C Moraine, J Gecz, A Kurg, PC Patsalis: *Screening of 20 patients with X-linked mental retardation using chromosome X-specific array-MAPH*, Eur J Med Genet, 50(6), 399-410 (2007).
- Mefford, H.C., S. Clauin, A.J. Sharp, R.S. Moller, R.Ullmann, R. Kapur, D. Pinkel, G.M. Cooper, M. Ventura, H.H. Ropers, N. Tommerup, E.E. Eichler and C. Bellanne-Chantelot: *Recurrent reciprocal genomic rearrangements of 17q12 are associated with renal disease, diabetes and epilepsy*. Am J Hum Genet 81, 1057-1069 (2007)
- Meyer, S., W.D. Fergusson, A.D. Whetton, F. Moreira-Leite, S.D. Pepper, C. Miller, E.K. Saunders, D.J. White, A.M. Will, T. Eden, H. Ikeda, R.Ullmann, S. Tuerkmen, A. Gerlach, E. Klopocki and H. Tönnies: *Amplification and translocation of 3q26 with overexpression of EVI1 in Fanconi anemia-derived childhood acute myeloid leukemia with biallelic FANCD1/BRCA2 disruption*. Genes, Chromosomes & Cancer 46(4), 359-372 (2007)
- Moheb, L.A., A. Tzschach, M. Garshasbi, K. Kahrizi, H. Daruishi, Y. Heshmati, A. Kordi, H. Najmabadi, H.H. Ropers, and A.W. Kuss: *Identification of nonsense mutation in the very low density lipoprotein receptor gene (VLDLR) in an Iranian family with dysequilibrium syndrome*. Eur J Hum Genet 16,2; 270-3 [Epub 2007] (2007).
- Moller, R., C. Hansen, G. Jackson, R. Ullmann, H. Ropers, N. Tommerup, Z. Tumer: *Interstitial deletion of chromosome 4p associated with mild mental retardation, epilepsy and polymicrogyria of the left temporal lobe*. Clinical Genetics, 72,6;593-8 (2007).
- Morecroft, I., Y. Dempsie, M.Bader, D.J. Walther, K. Kotnik, L. Loughlin, M. Nilsen and M.R. MacLean: *Effect of Tryptophan Hydroxylase 1 Deficiency on the Development of Hypoxia-Induced Pulmonary Hypertension*. Hypertension 49, 232-236 (2007).
- Motazacker MM, BR Rost, T Hucho, M Garshasbi, K Kahrizi, R Ullmann, SS Abedini, S Esmaeeli Nieh, SH Amini, C Goswami, A Tzschach, LR Jensen, D Schmitz, HH Ropers, H Najmabadi, AW Kuss: *A defect in the ionotropic glutamate receptor 6 gene (GRIK2) is associated with autosomal recessive mental retardation*. Am J Hum Genet 81(4), 792-798 (2007).
- Najmabadi, H., M.M. Motazacker, M. Garshasbi, K. Kahrizi, A. Tzschach, W. Chen, F. Behjati, V. Hadavi, S. Esmaeeli Nieh, S.S. Abedini, R. Vazifehmand, S.G. Firouzabadi, P. Jamali, M. Falah, S.M. Seifati, A. Grueters, S. Lenzner, L.R. Jensen, F. Rueschendorf, A. Kuss and H.H. Ropers: *Homozygosity mapping in consanguineous families reveals extreme heterogeneity of non-syndromic autosomal recessive mental retardation and identifies 8 novel gene loci*. Human Genetics 121(1), 43-48 (2007).
- Peter, J.-U., N. Alenina, M. Bader and D.J. Walther: *Development of anti-thrombotic miniribozymes that target peripheral tryptophan hydroxylase*. Molecular and Cellular Biochemistry 295(1-2), 205-215 (2007).
- Ropers, H.H.: *New perspectives for the elucidation of genetic disorders*. Am J Hum Genet 81(2), 199-207 (2007).
- Scherthan, H.: *Telomere attachment and clustering during meiosis*. Cellular and Molecular Life Sciences 64,2;117-24 (2007).
- Scherthan, H. *Chromosome numbers in Mammals, 2<sup>nd</sup> vs.* In: Encyclopedia of Life Sciences. John Wiley & Sons, Ltd: Chichester, <http://www.els.net/doi:10.1002/9780470015902.a0005799.pub2> (2007).
- Scherthan, H., H. Wang, D.B. Kaback and C. Adelfalk: *Chromosome and nuclear dynamics in first meiotic prophase*. Chromosome Research 15(2), 89 (2007).
- Scherthan, H., Abend, M., Müller, K., Beinke, C., Braselmann, H., Zitzelsberger, H., Köhn, F.M., Pillekamp, H., Schiener, R., Das, O., Peter, R.U., Herzog, G., Tzschach, A., Dörr, H.D., Fliedner, T.M., Meineke, V. *Radiation-induced late effects in two affected individuals of the Lilo radiation accident*. Radiation Res 167;615-23 (2007).



- Scherthan, H., H. Wang, C. Adelfalk, E.J. White, C. Cowan, Z. Cande and D.B. Kaback: *Chromosome mobility during meiotic prophase in Saccharomyces cerevisiae*. Proceedings of the National Academy of Sciences, 104,43;16934-9 (2007).
- Scheuch, K., M. Lautenschlager, M. Grohmann, S. Stahlberg, J. Kirchheiner, P. Zill, A. Heinz, D.J. Walther and J. Priller: Biol. Psychiatry 62,11;1288-94 (2007).
- Tenner, K., D. Walther, and M. Bader: *Influence of human tryptophan hydroxylase 2 N- and C-terminus on enzymatic activity and oligomerization*. Journal of Neurochemistry, 102,6;1887-94 (2007).
- Tzschach, A., C. Menzel, F. Erdogan, M. Schubert, M. Hoeltzenbein, G. Barbi, C. Petzenhauser, H.H. Ropers, R. Ullmann and V. Kalscheuer: *Characterization of a 16 Mb interstitial chromosome 7q21 deletion by tiling path array CGH*. American Journal of Medical Genetics 143A(4), 333-337 (2007).
- Tzschach, A., C. Ramel, A. Kron, B. Seipel, C. Wüster, U. Cordes, T. Liehr, M. Hoeltzenbein, C. Menzel, H.H. Ropers, R. Ullmann, V. Kalscheuer, J. Decker and D. Steinberger: *Hypergonadotropic hypogonadism in a patient with inv ins (2;4)*. Int J Andrology 32,3;226-30 [Doi:10.1111/j.1365-2605.2007.00839x] (2007).
- Tzschach, A. and H.H. Ropers: *Genetik der mentalen Retardierung*. Deutsches Ärzteblatt Heft 20, A-1400-1405 (2007).
- Ullmann, R., G. Turner, M. Kirchhoff, W. Chen, B. Tonge, C. Rosenberg, M. Field, A.M. Vianna-Morgante, L. Christie, A.C. Krepischi-Santos, L. Banna, A.V. Breerton, A. Hill, A.M. Bisgaard, I. Muller, C. Hultschig, F. Erdogan, G. Wiczorek and H.H. Ropers: *Array CGH identifies reciprocal 16p13.1 duplications and deletions that predispose to autism and/or mental retardation*. Human Mutation 28(7), 674-682 (2007).
- Winter, J., Kunath, M., Roepcke, S., Krauss, S., Schneider, R., Schweiger, S. *Alternative polyadenylation signals and promoters act in concert to control tissue-specific expression of the Opitz Syndrome gene MID1*. BMC Mol Biol. 8:105 (2007).
- 2006**
- Baekvad-Hansen, M., Z. Tumer, A. Delicado, F. Erdogan, N. Tommerup and L.A. Larsen. *Delineation of a 2.2 Mb microdeletion at 5q35 associated with microcephaly and congenital heart disease*. Am J Med Genet 140(5), 427-33 (2006).
- Bartsch, O., S. Rasi, A. Delicado, S. Dyack, L.M. Neumann, E. Seemanová, M. Volleth, T. Haaf and V.M. Kalscheuer. *Evidence for a new contiguous gene syndrome, the chromosome 16p13.3 deletion syndrome alias severe Rubinstein-Taybi syndrome*. Human Genetics 120(2), 179-186 (2006).
- Budny, B., W. Chen, H. Omran, M. Fliegau, A. Tzschach, M. Wiesniewska, L.R. Jensen, M. Raynaud, S.A. Shoichet, M. Badura, S. Lenzner, A. Latos-Bielenska and H.H. Ropers: *A novel X-linked recessive mental retardation syndrome comprising macrocephaly and ciliary dysfunction is allelic to oral-facial-digital type I syndrome*. Human Genetics 120(2), 171-178 (2006).
- Brunk, I., C. Blex, K. Rachakonda, M. Höltje, S. Winter, I. Pahner, D.J. Walther and G. Ahnert-Hilger: *The first luminal domain of vesicular monoamine transporters mediates G-protein-dependent regulation of transmitter uptake*. Journal of Biological Chemistry 281, 33373-33385 (2006).
- Carkaci-Salli, N., J.M. Flanagan, M.K. Martz, U. Salli, D.J. Walther, M. Bader and K.E. Vrana: *Functional domains of human tryptophan hydroxylase 2 (hTPH2)*. J Biol Chem 281(38), 28105-28112 (2006).
- Cingoz, S., A.M. Bisgaard, I. Bache, T. Bryndorf, M. Kirchoff, W. Petersen, H.H. Ropers, N. Maas, G. van Buggenhout, N. Tommerup and Z. Tumer: *4q35 deletion and 10p15 duplication associated with immunodeficiency*. Am J Med Genet A. 140(20), 2231-2235 (2006).
- Cossee, M., B. Demeer, P. Blanchet, B. Echenne, D. Singh, O. Hagens, M. Antin, S. Finck, L. Vallee, H. Dollfus, S. Hegde, K. Springell, B.K. Thelma, G. Woods, V. Kalscheuer, J.L. Mandel: *Exonic microdeletions in the X-linked PQBP1 gene in mentally retarded patients: a pathogenic mutation and in-frame deletions of uncertain effect*. Eur J Hum Genet 14(4), 418-425 (2006).
- Dadgar S., O. Hagens, S.R. Dadgar, E. Nobakht Haghighi, S. Schimpf, B. Wissinger and M. Garshasbi: *Structural model of the OPA1 GTPase domain may explain the molecular consequences of a novel mutation in a family with autosomal dominant optic atrophy*. Experimental Eye Research 83(3), 702-706 (2006).

- Dantzer, F., M. Mark, D. Quenet, H. Scherthan, A. Huber, B. Liebe, L. Monaco, A. Chicheportiche, P. Sassone-Corsi, G. de Murcia, J. Menissier-de Murcia: *Poly(ADP-ribose) polymerase-2 contributes to the fidelity of male meiosis I and spermiogenesis*. Proceedings of the National Academy of Sciences 103(40), 14854-14859 (2006).
- Dlugaszewska, B., A. Silaharoglu, C. Menzel, S. Kuebart, M. Cohen, S. Mundlos, Z. Tümer, K. Kjaer, U. Friedrich, H.H. Ropers, N. Tommerup, H. Neitzel and V.M. Kalscheuer: *Breakpoints around the HOXD cluster result in various limb malformations*. J Medical Genetics 43, 111-118 (2006)
- Erdogan, F., W. Chen, M. Kirchhoff, V.M. Kalscheuer, C. Hultschig, I. Müller, R. Schulz, C. Menzel, T. Bryndorf, H.H. Ropers and R. Ullmann: *Impact of low copy repeats on the generation of balanced and unbalanced chromosomal aberrations in mental retardation*. Cytogenetics and Genome Research 115(3-4), 247-253 (2006).
- Gamerding, U., K. Bosse, T. Eggermann, V.M. Kalscheuer, G. Schwanitz and H. Engels: *First report of a partial trisomy 3q12-q23 de novo—FISH breakpoint determination and phenotypic characterization*. Eur J Hum Genet 49(3), 225-234 (2006).
- Garshasbi, M., M.M. Motazacker, K. Kahrizi, F. Behjati, S.S. Abedini, S.E. Nieh, S.G. Firouzabadi, C. Becker, F. Ruschendorf, P. Nürnberg, A. Tzschach, R. Vazifehmand, F. Erdogan, R. Ullmann, S. Lenzner, A.W. Kuss, H.H. Ropers and H. Najmabadi: *SNP array-based homozygosity mapping reveals MCPH1 deletion in family with autosomal recessive mental retardation and mild microcephaly*. Hum Genet 118(6), 708-715 (2006).
- Gilling, M., J.S. Dullinger, S. Gesk, S. Metzke-Heidemann, R. Siebert, T. Meyer, K. Brondum-Nielsen, N. Tommerup, H.H. Ropers, Z. Tümer, V.M. Kalscheuer and N.S. Thomas: *Breakpoint cloning and haplotype analysis indicate a single origin of the common Inv(10)(p11.2q21.2) mutation among Northern Europeans*. Am J Hum Genet 78(5), 878-883 (2006).
- Haesler, S.: *Also sprach der Zebrafink*. Gehirn & Geist, Heft 12 (2006).
- Hagens, O., A. Ballabio, V. Kalscheuer, J.P. Kraehenbuhl, M.V. Schiaffino, P. Smith, O. Staub, J. Hildebrand and J.B. Wallingford: *A new standard nomenclature for proteins related to Apx and Shroom*. BMC Cell Biology 7, 18-19 (2006).
- Hagens, O., A. Dubos, F. Abidi, G. Barbi, L. Van Zutven, M. Hoeltzenbein, N. Tommerup, C. Moraine, J.-P. Fryns, J. Chelly, H. van Bokhoven, J. Gécz, H. Dollfus, H.H. Ropers, C.E. Schwartz, R. de Cassia, S. dos Santos, V. Kalscheuer and A. Hanauer: *Disruptions of the novel KIAA1202 gene are associated with X-linked mental retardation*. Human Genetics 118(5), 578-590 (2006).
- Hagens, O., E. Minina, S. Schweiger, H.H. Ropers and V. Kalscheuer: *Characterization of FBX25, encoding a novel brain-expressed F-box protein*. Biochimica et Biophysica Acta 1760(1), 110-118 (2006).
- Hausmann, M., B. Perner, A. Rapp, L. Wollwerber, H. Scherthan and K.-O. Greulich: *Near-Field scanning optical microscopy in cell biology and cytogenetics*. Methods in Molecular Biology 319, 275-294 (2006).
- Hucho, T., O. Dina, J. Kuhn and J.D. Levine: *Estrogen controls PKCe-dependent mechanical hyperalgesia through direct action on nociceptive neurons*. European Journal of Neuroscience 24(2), 527-534 (2006).
- Klopocki, E., B. Fiebig, P. Robinson, H. Tönnies, F. Erdogan, H.H. Ropers, S. Mundlos and R. Ullmann: *A novel 8 Mb interstitial deletion of chromosome 8p12-p21.2*. Am J Med Genet A 140(8), 873-877 (2006).
- Klopocki, E., L.M. Neumann, H. Tönnies, H.H. Ropers, S. Mundlos and R. Ullmann: *Ulnar-mammary syndrome with dysmorphic facies and mental retardation caused by a novel 1.28 Mb deletion encompassing the TBX3 gene*. Eur J Hum Genet 14(12), 1274-1279 (2006).
- Lesurtel, M., R. Graf, B. Aleil, D.J. Walther, Y. Tian, W. Jochum, C. Gachet, M. Bader and P.-A. Clavien: *Platelet-derived serotonin mediates liver regeneration*. Science 312, 104-107 (2006).
- Liebe, B., G. Petukhova, M. Barchi, M. Bellani, H. Braselmann, T. Nakano, T.K. Pandita, M. Jasin, A. Fornace, M.L. Meistrich, W.M. Baarends, J. Schimenti, T. de Lange, S. Keeney, R.D. Camerini-Otero and H. Scherthan: *Mutations that affect meiosis in male mice influence the dynamics of the mid-preleptotene and bouquet stages*. Experimental Cell Research 312(19), 3768-3781 (2006).
- Lugtenberg, D., H.G. Yntema, M.J.G. Banning, A.R. Oudakker, H.V. Firth, L. Willatt, M. Raynaud, T. Kleefstra, J.-P. Fryns, H.H. Ropers, J. Chelly, C. Moraine, J. Gécz, J. van Reeuwijk, S.B. Nabuurs, B.B.A. de Vries,



- B.C.J. Hamel, A.P.M. de Brouwer and H. van Bokhoven: *ZNF674: a new KRAB-containing zinc finger gene involved in non-syndromic X-linked mental retardation*. Am J Hum Genet 78, 265-278 (2006).
- Müller, D., E. Klopocki, L.M. Neumann, S. Mundlos, M. Taupitz, I. Schulze, H.H. Ropers, U. Querfeld and R. Ullmann: *A complex phenotype with cystic renal disease*. Kidney International 70(9), 1656-1660 (2006).
- Piovani, G., G. Borsani, V. Bertini, V.M. Kalscheuer, P. Viertel, D. Bellotti, D. Valseriati and S. Barlati : *Unexpected identification of two interstitial deletions in a patient with a pericentric inversion of a chromosome 4 and an abnormal phenotype*. Eur J Med Genet 49(3), 215-23 (2006).
- Ropers, H.H.: *X-linked mental retardation: many genes for a complex disorder*. Current Opinion in Genetics & Development 16(3), 260-269 (2006).
- Scherthan, H.: *Meiotic telomeres*. In: Telomeres, 2nd ed., Monograph 45 (T. De Lange, V. Lundblad, E. Blackburn, eds.) CSH Press, Cold Spring Harbor, pp. 225-259 (2006).
- Scherthan, H.: *Factors directing telomere dynamics in synaptic meiosis*. Biochemical Society Transactions 34(4), 550-553 (2006).
- Schubert, S., M. Zenker, S.L. Rowe, S. Boll, C. Klein, G. Bollag, I. van der Burgt, L. Musante, V. Kalscheuer, L.E. Wehner, H. Nguyen, B. West, K.Y. Zhang, E. Siermans, A. Rauch, C.M. Niemeyer, K. Shannon and C.P. Kratz: *Germline KRAS mutations cause Noonan syndrome*. Nature Genetics 38(3), 331-336 (2006).
- Schwarzbraun, T., R. Ullmann, M. Schubert, M. Ledinegg, L. Ofner, C. Windpassinger, K. Wagner, P.M. Kroisel and E. Petek: *Characterisation of a de novo complex chromosome rearrangement (CCR) involving chromosomes 2 and 12, associated with mental retardation and impaired speech development*. Cytogenetics and Genome Research 115(1), 84-89 (2006).
- Seifert W, M Holder-Espinasse, S Spranger, M Hoeltzenbein, E Rossier, H Dollfus, D Lacombe, A Verloes, KH Chrzanowska, GH Maegawa, D Chitayat, D Kotzot, D Huhle, P Meinecke, B Albrecht, I Mathijssen, B Leheup, K Raile, HC Hennies, D. Horn: *Mutational spectrum of COH1 and clinical heterogeneity in Cohen syndrome*. Journal of Medical Genetics 43(5), e22 (2006).
- Shoichet, S.A., L. Duprez, O. Hagens, V. Waetzig, C. Menzel, T. Herdegen, S. Schweiger, B. Dan, E. Vamos, H.H. Ropers and V.M. Kalscheuer: *Truncation of the CNS-expressed JNK3 in a patient with a severe developmental epileptic encephalopathy*. Human Genetics 118(5), 559-567 (2006).
- Tagariello, A., R. Heller, A. Greven, V.M. Kalscheuer, T. Molter, A. Rauch, W. Kress and A. Winterpacht: *Balanced translocation in a patient with craniosynostosis disrupts the SOX6 gene and an evolutionary conserved non-transcribed region*. Journal of Medical Genetics 43, 534-540 (2006).
- Tzschach A, M Hoeltzenbein K Hoffmann, C Menzel, A Beyer, V Ocker, G Wurster, M Raynaud, HH Ropers, VM Kalscheuer, H Heilbronner: *Heterotaxy and cardiac defect in a girl with chromosome translocation t(X;1)(q26;p13.1) and involvement of ZIC3*: Eur J Hum Genet 14(12), 1317-1320 (2006).
- Tzschach A, K Hoffmann, M Hoeltzenbein, I. Bache, N. Tommerup, C. Bommer, H. Körner, V.M. Kalscheuer and H.H. Ropers: *Molecular characterization of a balanced chromosome translocation in psoriasis vulgaris*. Clin Genetics 69(2), 189-193 (2006).
- Tzschach A, I Krause-Plonka, C Menzel, VM Kalscheuer, H Tönnies, H Scherthan, A Knoblauch, M Radke, HH Ropers, M Hoeltzenbein: *Molecular cytogenetic analysis of a de novo interstitial deletion 5q23.3q31.2 and its phenotypic consequences*. Am J Med Genet A 140(5), 496-502 (2006).
- Tzschach, A., S. Lenzner, R. Reinhardt, B. Moser, J. Chelly, J.-P. Fryns, T. Kleefstra, M. Raynaud, J. Gécz, H.H. Ropers, A.W. Kuss and L.R. Jensen: *Novel JARID1C mutations in patients with X-linked mental retardation*. Human Mutation 27(4), 389 (2006).
- Tzschach, A. and H.H. Ropers: *X-chromosomale Retardierung*. Medizinische Genetik 2, 187-193 (2006).
- Tzschach, A., I. Krause-Plonka, C. Menzel, A. Knoblauch, H. Toennies, M. Hoeltzenbein, M. Radke, H.H. Ropers, V.M. Kalscheuer: *Molecular Cytogenetic Analysis of a De Novo Interstitial Chromosome 10q22 Deletion*. Am J Med Genet A 140(10), 1108-1110 (2006).

Wada K., J.T. Howard, P. McConnell, O. Whitney, T. Lints, M.V. Rivas, H. Horita, M.A. Patterson, S.A. White, C. Scharff, S. Haesler, S. Zhao, H. Sakaguchi, M. Hagiwara, T. Shiraki, T. Hirozane-Kishikawa, P. Skene, Y. Hayashizaki, P. Carninci and E.D. Jarvis: *A molecular neuroethological approach for identifying and characterizing a cascade of behaviorally regulated genes.* [erratum appears in *Proc Natl Acad Sci U S A.* 2006 Nov 7;103(45):17064]. Proceedings of the National Academy of Sciences of the United States of America 103(41), 15212-15217 (2006).

Yan, K.-L., X.-J. Zhang, Z.-M. Wang, S. Yang, G.-L. Zhang, J. Wang, F.-L. Xiao, M. Gao, Y. Cui, J.-J. Chen, X. Fan, L.-D. Sun, Q. Xia, K.-Y. Zhang, Z.-M. Niu, S.-J. Xu, A. Tzschach, H.H. Ropers, J.-J. Liu and W. Huang: *A novel MGST2 non-synonymous mutation in a Chinese pedigree with psoriasis vulgaris.* Journal of Investigative Dermatology 126(5), 1003-1005 (2006).

Zahn, C., A. Hommel, L. Lu, W. Hong, D. Walther, S. Florian, H.-G. Joost and A. Schürmann: *Knockout of Arfrp1 leads to disruption of ARF-like1 (ARL1) targeting to the trans-Golgi in mouse embryos and HeLa cells.* Molecular and Membrane Biology 23, 475-485 (2006).

### Selected invited talks (H.-Hilger Ropers)

*Molecular elucidation of MR: Strategies and progress report*, XXIII Spanish Genetic Congress, Valladolid, 15.06.2006

*Genetic dissection of MR by high resolution array CGH and other approaches*, Lecture at Dept. of Genetics and Evolutionary Biology, Institute of Biosciences, Univ. Sao Paulo, Brasil. 01.08.2006.

*High resolution array CGH*, AP Echo conference 2006, Shanghai, 28.08.2006

*Frequent genomic imbalances in Mendelian and complex diseases: why association studies often fail.* Nederlands Anthropogenetische Vereniging, Utrecht, 24.11.2006.

*Nieuwe perspectieven voor het ophelderen van erfelijke ziekten*, The Royal Netherlands Academy of Arts and Sciences, Amsterdam, 26.02.2007

Speaker at the *3rd International Meeting on Cryptic Chromosomal Rearrangements, MR and autism*, Troina, Italy, 13.04.2007

*Evangelischer Hochschuldialog : "Gott in den Genen?"*, Albert-Ludwigs-Universität, Freiburg, 07.07.2007 (public discussion)

*New perspectives for the elucidation of human diseases*, Berlin Brandenburg Academy of Sciences and Humanities, 22.06.2007

Lecture at the 1<sup>st</sup> International Congress on Health, Genomics, and Biotechnology, Teheran, 24.11.2007

*Disease related genome research: novel opportunities for developing countries*, HGM 2008, Hyderabad, India, 30.09.2008

Lecture at the Deutsch-Koreanisches Symposium on Biotechnology, Seoul, January 15-16, 2009

*Ethical and social Issues of the Human Genome Project*, Annual Meeting of the Indian Society of Human Genetics, New Delhi, India, 17.03.2009 (plenary lecture)

*Cognitive impairment: what have we learned, what lies ahead*, University of Nijmegen, 03.04.2009

Lecture at the Regpot Conference (EU 7<sup>th</sup> Framework), Ankara, 20.04.2009

*Vom Mütterchen die Frohnatur..': neue Perspektiven für die Aufklärung der Funktion des menschlichen Genoms und Konsequenzen für die Krankenversorgung*, 11. Gaterslebener Begegnung, Leibniz-Institut für Pflanzengenetik und Kulturpflanzenforschung, Gatersleben, 08.05.2009

*The sequencing revolution: Implications for genome research and health care*, Rudbek Seminar Series, Uppsala, 08.10.2009

### Selected memberships (H.-Hilger Ropers)

- Elected member of HUGO Council (since 2003) and member of HUGO Scientific Program Committee
- Elected member of the Royal Netherlands Academy of Arts and Sciences
- Elected member of the Berlin-Brandenburg Academy of Sciences and Humanities
- Elected Secretary of the Biomedical class of the Berlin-Brandenburg Academy of Sciences and Humanities, 2007
- Honorary medal of the Society for Human Genetics (GFH) 2009



### Membership in journal editorial boards (H.-Hilger Ropers)

- Genome Medicine
- Human Genetics
- Clinical Genetics

### Service to the scientific community (H.-Hilger Ropers)

- Evaluation of Telethon, Italy 2009
- Member of the scientific advisory board Biozentrum Würzburg, since 2003

### Appointments of former members of the department

Susann Schweiger - Chair for Molecular Medicine (2006) and Head of the Centre for Oncology and Molecular Medicine (2007) at the University of Dundee (Medical School)

### PhD theses 2009

Masoud Garshasbi (2009) *Identification of 31 genomic loci for autosomal recessive mental retardation and molecular genetic characterization of novel causative mutations in four genes*, PhD Thesis, Freie Universität Berlin (supervisor: Andreas Kuss)

Stella-Amrei Kunde (2009): *Untersuchung zur Funktion des PQBP1-Komplexes*, PhD thesis submitted in 06/09, Freie Universität Berlin (supervisor: Vera Kalscheuer)

Artur Muradyan (2009) *SPON2 and its implication in epithelial-mesenchymal transition*, Freie Universität Berlin (supervisor: Reinhard Ullmann)

Nils Rademacher (2009) *Untersuchungen zur Funktion der Kinase CDKL5 / STK9*, PhD thesis submitted in 09/09, Freie Universität Berlin (supervisor: Vera Kalscheuer)

### 2008

Maik Grohmann (2008) *Die Rolle der Tryptophan-Hydroxylase 2 bei der Entstehung psychiatrischer Erkrankungen*, PhD Thesis, Freie Universität Berlin (supervisor: Diego Walther)

Mohammad Mahdi Motazacker (2008) *Identification of novel genetic loci for non-syndromic autosomal recessive mental retardation and molecular genetic characterization of a causative GRIK2 mutation*, PhD Thesis, Freie Universität Berlin (supervisor: Andreas Kuss)

Nils Paulmann (2008) *Die Serotonylierung kleiner GTPasen moduliert die Insulinsekretion*, PhD Thesis, Freie Universität Berlin (supervisor: Diego Walther)

Joyce So (2007): *Molecular and phenotypic analysis of Opitz syndrome patients and characterization of the relationship between the RBCC protein MID1 and the tumour suppressor CYLD*. PhD Thesis, Freie Universität Berlin (supervisor: Susann Schweiger)

### 2006

B. Budny (2006) *Molecular background of X-linked mental retardation*. PhD Thesis, Karol Marcinkowski University, Poznan, Poland.

Beatriz Aranda-Origillés (2006) *Characterization of the MID1/a4 multiprotein complex*. PhD Thesis, Freie Universität Berlin (supervisor: Susann Schweiger)

Wei Chen (2006) *Development and application of CGHPRO, a novel software package for retrieving, handling and analysing array CGH data*. PhD Thesis, Freie Universität Berlin

Sebastian Haesler (2006) *Studies on the evolution and function of FoxP2, a gene implicated in human speech and language, using songbirds as a model*. PhD Thesis, Freie Universität Berlin (supervisor: Constanze Scharff)

Olivier Hagens (2006) *Search for genes involved in Human Cognition. Molecular characterization of two novel genes, FBXO25 and KIAA1202, disrupted by a translocation in a mentally retarded patient*. PhD Thesis, Freie Universität Berlin (supervisor: Vera Kalscheuer)

Jens-Uwe Peter (2006) *Molekularbiologische und pharmakologische Manipulation der Tryptophanhydroxylasen*. PhD Thesis, Freie Universität Berlin 2006 (supervisor: Diego Walther)

## Student Theses 2009

C. Bähr (2009) *Monoaminylierung von Transkriptionsfaktoren am Beispiel des CLOCK*, Bachelor Thesis, Freie Universität Berlin (supervisor: Diego Walther)

B. Behrendt (2009) *Modellierung der serotonininduzierten Ausschüttung densesgranulärer Botenstoffe aus Thrombozyten*, Bachelor Thesis, Technische Fachhochschule Wildau (supervisor: Diego Walther)

M. Bienemann (2009) *Modellierung der serotonininduzierten Ausschüttung des Insulins aus  $\beta$ -Zellen des Pankreas*, Bachelor Thesis, Technische Fachhochschule Wildau (supervisor: Diego Walther)

René Buschow (2009) *Quantitative Analyse neuronaler Subgruppen mit Hilfe automatisierter Immunfluoreszenz*, Diploma Thesis, Institut für Biologie, Universität Kassel (supervisor: Tim Hucho)

Grit Ebert (2009) *Veränderungen der Genexpressionsmuster im Verlauf der Retinsäureinduzierten Zelldifferenzierung*, Diploma Thesis, Humboldt Universität zu Berlin (supervisor: R. Ullmann)

A. Funke (2009) *Identifikation von BRN2-regulierten Genkandidaten und Untersuchung der Auswirkung des SNPs rs16967794 auf die Bindungsaffinität von BRN2*, Bachelor Thesis, Technische Fachhochschule Wildau (supervisor: Diego Walther)

S. Mucha (2009) *Studien zum Einfluss von Serotonin auf die Glucose-induzierte Insulinsekretion*, Bachelor Thesis, Technische Fachhochschule Wildau (supervisor: Diego Walther)

F. Roske (2009) *Die Veränderung der Aufnahme und Inkorporation von biogenen Monoaminen durch Adipogenese in 3T3-L1-Zellen*, Bachelor Thesis, Universität Bayreuth (supervisor: Diego Walther)

B. Schoder (2009) *Vergleich viraler Promotoren mit dem humanen ribosomalen RPL12-Promotor in eukaryotischen Expressionssystemen*, Bachelor Thesis, Technische Fachhochschule Wildau (supervisor: Diego Walther)

C. Schwarzer (2009) *Etablierung eines immunologischen Nachweissystems zur Erfassung des Aktivierungszustandes der kleinen GFTPase Cdc42*, Bachelor Thesis, Universität Bayreuth (supervisor: Diego Walther)

C. Technau (2009) *Monoaminylierung von Transkriptionsfaktoren am Beispiel des CREB*, Bachelor Thesis, Freie Universität Berlin, 2009 (supervisor: Diego Walther)

Lars Theobald (2009) *Untersuchung und Charakterisierung transaktivierender Eigenschaften monoaminylierter Transkriptionsfaktoren*, Diploma Thesis, Technische Fachhochschule Berlin (supervisor: Diego Walther)

Zofia Wotschofsky (2009) *Translocation breakpoint mapping by Illumina/Solexa technology*, Diploma Thesis, Technische Universität Berlin (supervisor: Wei Chen)

## 2008

Christine Andres (2008) *Relative Immunofluoreszenz - Eine Mikroskop basierte Methode zur Untersuchung der Aktivierung von Signalwegen in heterogenen Zellsystemen wie DRG-Neuronen*, Diploma Thesis, Freie Universität Berlin (supervisor: Tim Hucho)

Vivien Boldt (2008) *Chromosomale Veränderungen in Präneoplasien und Karzinomen der Brust und deren Auswirkungen auf die Genexpression*, Diploma Thesis, Freie Universität Berlin (supervisor: R. Ullmann)

Barbara Glowacka (2008) *Funktionelle Untersuchungen zur Rolle von PQBP1 (Polyglutamin-Bindungsprotein1) bei der Genexpression*, Diploma thesis, Freie Universität Berlin (supervisor: Vera Kalscheuer)

Melanie Krüger (2008) *Die Rolle der TPH1 in der Ätiologie von Alkoholismus*, Diploma Thesis, Freie Universität Berlin (supervisor: Diego Walther)

Ann Schöler (2008) *Die Bedeutung der Monoaminylierung in neuronalen Differenzierungsprozessen*, Diploma Thesis, Technische Universität Berlin (supervisor: Diego Walther)

Juliane Schreier (2008) *Untersuchungen der Östrogen-Effekte auf die MAP-Kinase ERK in primären sensorischen Neuronen und F-11 Zellen*, Diploma Thesis, Freie Universität Berlin (supervisor: Tim Hucho)

Karsten Sollich (2008) *Establishment of a lenti-virus-based gene knock-down system in rat sensory neurons*, Diploma Thesis, Technische Universität Berlin (supervisor: Tim Hucho)

Anne Steininger (2008) *Genetische und epigenetische Veränderungen bei kutanen T-Zell-Lymphomen*, Diploma Thesis, Freie Universität Berlin (supervisor: R. Ullmann)



Tina Sulistio (2008) *Determination of transgene integration sites in mutant PQBP1 transgenic mice and characterization of the expression pattern of various PQBP1 mutations*, Diploma thesis, Mannheim University of Applied Sciences (supervisor: Vera Kalscheuer)

Anke Walther (2008) *Untersuchungen zur Rolle von CDKL5 Interaktionspartnern beim atypischen Rett-Syndrom*, Diploma thesis, Technische Universität Berlin (supervisor: Vera Kalscheuer)

## 2007

A. von Bock (2007) *Untersuchung von RNA-Editierungen in der Tryptophan Hydroxylase 2*. Master Thesis, Freie Universität Berlin (supervisor: Diego Walther)

F. Baumkötter (2007) *Monoaminylierung in der Hyperproliferation humaner pulmonärer glatter Muskelzellen*. Diploma Thesis, Freie Universität Berlin (supervisor: Diego Walther)

S. Gohlke (2007) *Monoaminylierung von Huntingtin*. Diploma Thesis, Freie Universität Berlin (supervisor: Diego Walther)

Paul Hammer (2007) *Molekulare Untersuchungen zur Genregulation von TPH2*. Master Thesis, Technische Fachhochschule Wildau (supervisor: Diego Walther)

M. Mehnert (2007) *Einfluss von Monoaminen auf Differenzierungs- und Proliferationsprozesse von embryonalen und adulten neuronalen Stammzellen*. Diploma Thesis, Freie Universität Berlin (supervisor: Diego Walther)

A. Nauman (2007) *Herabregulierung der Expression muriner Transglutaminasen durch RNA-Interferenz*. Master Thesis, Technische Fachhochschule Wildau (supervisor: Diego Walther)

S. Pohl (2007) *Serotoninkataboliten in der Ätiologie des Alkoholismus*. Diploma Thesis, Albert-Ludwigs-Universität Freiburg (supervisor: Diego Walther)

Silke Stahlberg (2007) *Funktionelle Charakterisierung des MI-Motivs in Promotoren der Gene humaner ribosomaler Proteine*. Diploma Thesis, Freie Universität Berlin (supervisor: Diego Walther)

A. Walter (2007) *Identifizierung von monoaminylierten Proteinen in neuronalen Zellen*. Diploma Thesis, Freie Universität Berlin (supervisor: Diego Walther)

## 2006

K. Albers (2006) *Development of a laboratory information management system (LIMS) for medical genetic investigations*. Bachelor Thesis, Freie Universität Berlin

T. Döser (2006) *Monoaminylierung in der zellulären Immunantwort*. Diploma Thesis, Technische Fachhochschule Berlin (supervisor: Diego Walther)

S. Grabow (2006) *Welche Proteine sind Ziel der Monoaminylierung in T-Lymphozyten?* Diploma Thesis, Freie Universität Berlin (supervisor: Diego Walther)

Dejan Ninkovic (2006) *Untersuchungen zu PQBP1 und einigen wahrscheinlichen Proteininteraktionspartnern*, Diploma Thesis, Freie Universität Berlin (supervisor: Vera Kalscheuer)

A. Salamon (2006) *Functional Aspects of a Mutation in the PLP2 Promoter Region of Patients with Non-Syndromic X-Linked Mental Retardation*. Technische Universität Berlin

Jakob Vowinkel (2006) *Monoaminylierung von Signalproteinen*. Diploma Thesis, Freie Universität Berlin (supervisor: Diego Walther)

M. Walther (2006) *Der Einfluß von Ethanol auf den Metabolismus von Serotonin*. Diploma Thesis, Technische Fachhochschule Berlin (supervisor: Diego Walther)

## Guest scientists

Prof. Klaus Wrogemann, MD, PhD, Dept. of Biochemistry & Medical Genetics, University of Manitoba, Canada, 02-08/09

Roxana Karaminejad, MD, Kariminejad-Najmabadi Pathology & Genetics Center, Tehran, Iran, 03-05/07; 10-12/07; 07/08

Anne Thorwarth, MD, Institute for Experimental Pediatric Endocrinology, Charité University Medicine Berlin, 09/06-12/07

Markus Pisecker, PhD, St. Anna Kinderkrebsforschung, CCRI, Children's Cancer Research Institute, Vienna, Austria, 01-04/07

Dilihan Gumus, MD, MSc, PhD Student Cardiff University, Cardiff, UK, 01-07/06

Sandra Selch, PhD student, University of Würzburg, Germany, 04-06/06

Rikke Moeller, MD, The Wilhelm Johannsen Centre for Functional Genome Research, University of Copenhagen, Denmark

