Institute of Human Genetics

Chair of Human Genetics

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Research Focus
- Genetic factors of intellectual disability
- Genetics of complex diseases
- Growth retardation
- Developmental genetics

Structure of the Institute

Professorships: 2
Personnel: 49
- Doctors (of Medicine): 8
- Scientists: 9 (thereof funded externally: 4)
- Graduate students: 10

Clinical focus areas
- Genetic outpatient clinic for all aspects of genetic diseases
- Interdisciplinary clinic for familial cancer in children and adults
- Wide range of pre- and postnatal genetic analyses including genome sequencing

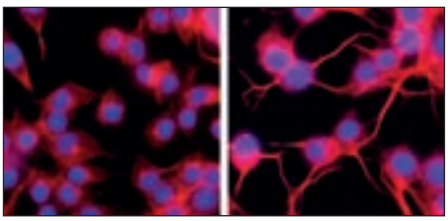
Research

Research at the Institute of Human Genetics focuses on the elucidation of causes and pathomechanisms of genetic disease and genotype/phenotype correlation. In particular, modern genomic technologies such as microarray analysis and exome/genome sequencing are used. For various projects large groups of patients have been recruited and clinically characterized in detail. In addition, cellular models including induced pluripotent stem cells and genome editing using CRISPR-Cas9 are used. The Institute cooperates with numerous departments and institutes within the Faculty and operates the core unit „Next Generation Sequencing".

Genetic factors of intellectual disability

PI: PD Dr. C. Zweier, PD Dr. R. Abou Jamra, Prof. Dr. A. Reis

Genetic factors are the main cause of intellectual disability (ID) in Germany. In many cases, ID co-occurs with additional symptoms and malformations in a syndromic presentation. Genetic causes are very heterogeneous and all modes of Mendelian inheritance occur. Over the recent years, including the reporting period, the working groups at the Institute identified numerous single gene defects. Autozygosity mapping and massively parallel sequencing was used to identify several new autosomal recessive gene defects in multiplex families with consanguineous parents. As autosomal dominant de novo mutations represent the main cause of sporadic ID, sequencing of the entire coding sequence (exome sequencing) of parent-child trios is the ideal strategy. In this group, genetic defects of members of the BAF complex, including ARID1B, are particularly frequent. In functional studies, the effect of this chromatin remodeling complex on the Wnt/ß-catenin signaling pathway could be demonstrated. In addition, the genetic and clinical spectrum of X-linked NAA10 deficiency in girls and boys was extended and the groups made important contributions to the characterization of the clinical and genetic spectrum of FOXP2- and CNTNAP2-associated developmental disorders. Furthermore, a publicly accessible, manually curated database of all ID associated genes has been created. This integrated resource containing genetic and phenotypic data combined with information on biological functions allows novel insights into the clinical and biological landscape of ID.

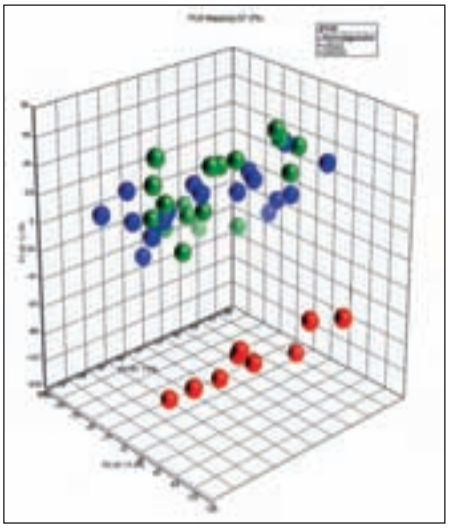


Knock-down of ARID1B in neuronal cells (N2A) induces differentiation. Right control cells

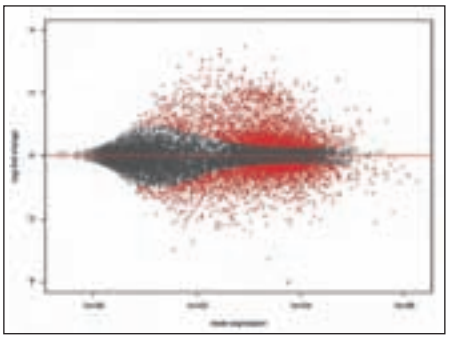
Genetics of complex diseases

PI: PD Dr. U. Hüffmeier, Prof. Dr. A. Reis

Complex or multifactorial diseases are caused by a combination of mostly unknown environmental and genetic factors. Numerous genetic variants, each with a small effect size, act as susceptibility factors. These can be detected with genetic association studies in large patient groups and promise insights into the pathomechanisms of the particular disease or trait. At the Institute, psoriasis, psoriasis arthritis and glaucoma are of particular interest. In the reporting period, a long-standing international association study on secondary glaucoma with exfoliation syndrome was completed and a common risk-variant mapping to CACNA1A could be newly identified. Based on previous studies in patients with psoriasis and psoriatic arthritis, the previously identified susceptibility locus at the RUNX3 gene was investigated in search for the causative variant and the associated signaling pathway. In addition, the working group analyzed generalized and palmoplantar forms of pustular psoriasis for genetic variants in the IL36RN gene and CARD14.



PCA plot showing clustering of three tissue types based on genome wide expression profiles



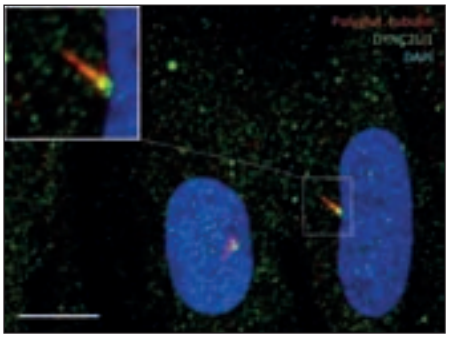
MA plot showing distribution of genome wide gene expression values

Growth retardation

PI: PD Dr. C. Thiel

The elucidation of genetic causes of growth disturbances allows insights into the regulation of fundamental cellular processes. The working group combines genetic and genomic techniques with functional characterization of factors involved in idiopathic short stature and ciliary growth disorders. In close cooperation with the Department of Pediatric and Adolescent Medicine and external partners, large patient groups were established. With a genome-wide approach

using exome sequencing, the molecular and clinical spectrum of known entities could be extended and novel causes for idiopathic short stature identified. Moreover, exome sequencing combined with functional characterization of the ciliary protein NEK1 led to the identification of the interaction partner DYNC2LI1 as novel candidate gene for autosomal recessive short stature. Defects of DYNC2LI1 disrupt the retrograde protein transport and finally the function of the primary cilium.



Immunofluorescence of the primary cilium in a human fibroblast cell line
The primary cilium is localized on nearly all vertebrate cells and plays an important role in many processes during development. It is composed of the basal body (green) and the axoneme (red). During mitosis the basal body breaks down into the centrioles involved in spindle formation.

Developmental genetics

PI: Prof. Dr. A. Winterpacht

This group is interested in the molecular basis of developmental processes and their individual variability. This includes epigenetic mechanisms and regulatory networks of organogenesis and cell differentiation as well as the identification of variants in specific components of these processes. The group focused on the gene SPOC1 (PHF13) whose expression is associated with survival time in ovarian cancer patients. The group was able to show that SPOC1 functions as an epigenetic reader and writer of histone modifications and plays a role in mitosis and in the epigenetic regulation of meiosis as well as spermatogonial stem cell maintenance and differentiation.

Teaching

The Institute of Human Genetics is involved in curricular teaching activities in Medicine and in the B.Sc. and M.Sc. degree programs in Molecular Medicine as well as M.Sc. in Cellular and Molecular Biology, respectively.
Bachelor's and Master's theses as well as MD and PhD theses were supervised.

Selected Publications

Aung T et al. A common variant mapping to CACNA1A is associated with susceptibility to exfoliation syndrome. Nat Genet. 2015, 47: 387-92

Vasileiou G, Ekici AB, Uebe S, Zweier C, Hoyer J, Engels H, Behrens J, Reis A, Hadjihannas MV. Chromatin-Remodeling-Factor ARID1B Represses Wnt/ß-Catenin Signaling. Am J Hum Genet. 2015, 97: 445-56

Boycott KM et al. Autosomal-Recessive Intellectual Disability with Cerebellar Atrophy Syndrome Caused by Mutation of the Manganese and Zinc Transporter Gene SLC39A8. Am J Hum Genet. 2015, 97: 886-93

Mössner R, Frambach Y, Wilsmann-Theis D, Löhr S, Jacobi A, Weyergraf A, Müller M, Philipp S, Renner R, Traupe H, Burkhardt H, Kingo K, Kõks S, Uebe S, Sticherling M, Sticht H, Oji V, Hüffmeier U. Palmoplantar Pustular Psoriasis Is Associated with Missense Variants in CARD14, but Not with Loss-of-Function Mutations in IL36RN in European Patients. J Invest Dermatol. 2015, 135: 2538-41

Kessler K, Wunderlich I, Uebe S, Falk NS, Gießl A, Brandstätter JH, Popp B, Klinger P, Ekici AB, Sticht H, Dörr HG, Reis A, Roepman R, Seemanová E, Thiel CT. DYNC2LI1 mutations broaden the clinical spectrum of dynein-2 defects. Sci Rep. 2015, 5: 11649

Kochinke K, Zweier C, Nijhof B, Fenckova M, Cizek P, Honti F, Keerthikumar S, Oortveld MA, Kleefstra T, Kramer JM, Webber C, Huynen MA, Schenck A. Systematic Phenomics Analysis Deconvolutes Genes Mutated in Intellectual Disability into Biologically Coherent Modules. Am J Hum Genet. 2016, 98: 149-64

International Cooperations

Prof. A. Schenk, Donders Centre for Neuroscience, Nijmegen: The Netherlands

Prof. A. Barton, University of Manchester, Manchester: UK

Prof. R. Roepman, University of Nijmegen, Nijmegen: The Netherlands

Prof. Tin Aung, Singapore National Eye Centre, Singapore: Singapore

Prof. T. Arnesen, University of Bergen, Bergen: Norway