Institute of Human Genetics

Chair of Human Genetics

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Research focus
- Neurodevelopmental disorders
- Growth disorders
- Psoriasis
- Ophthalmogenetics
- Familial cancer
- Developmental genetics

Structure of the Chair

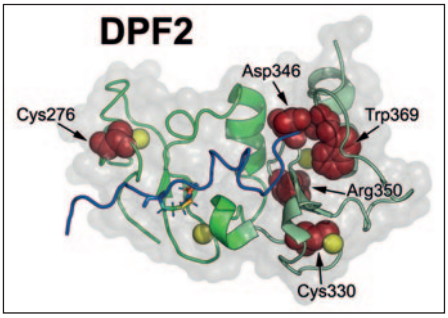
Professorships: 2
Personnel: 49
- Doctors (of Medicine): 9
- Scientists: 9 (thereof funded externally: 3)
- Graduate students: 10

Clinical focus areas
- Genetic outpatient clinic for all aspects of genetic diseases
- Participation in different B-centers for rare diseases within the Erlangen Center for Rare 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 genome sequencing technologies 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 are used.
The Institute cooperates with numerous departments and institutes within the Faculty and operates the core unit „Next Generation Sequencing".

Neurodevelopmental disorders
PI: Prof. Dr. C. Zweier, Prof. Dr. A. Reis
Intellectual disability can occur independently, but also in a syndromic presentation with additional symptoms and malformations. These are summarized as neurodevelopmental disorders (NDDs) and genetic factors are the main cause. Over the years the working groups at the Institute identified numerous single gene defects causing NDDs. Genetic defects of members of the BAF complex, including ARID1B, are particularly frequent in patients with intellectual disability and Coffin-Siris syndrome. In the latter, mutations in DPF2, another subunit of the BAF complex, were newly identified. Furthermore, de novo variants in the F-box protein FBXO11 were implicated in variable NDDs, and a clustering of missense variants in RHOBTB2 was identified as causative for a severe developmental and epileptic encephalopathy. Drosophila was used as a model to further characterize the role of RhoBTB.

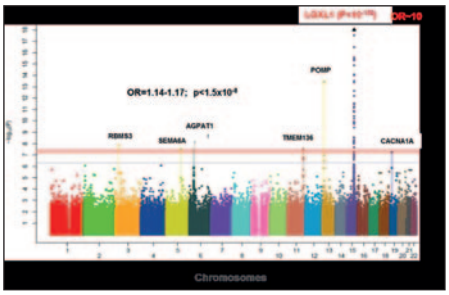


Computer-based modelling of mutations in PHD2 domain of DPF2 found in patients with Coffin-Siris syndrome

Growth disorders
PI: PD Dr. C. Thiel
The elucidation of genetic causes of growth disturbances allows insights into the regulation of fundamental cellular processes. The group focuses on the identification and functional characterization of genes involved in idiopathic short stature and ciliary growth disorders. In a genome-wide approach using exome sequencing in large study groups, the group could both expand the molecular and clinical spectrum of known entities as well as identify novel causes of idiopathic short stature.

Psoriasis
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. At the Institute, both, the more frequent forms of plaque and psoriatic arthritis as well as the rarer manifestations of pustular psoriasis, are studied. Using large patient groups, recruited genetic and functional analysis of candidate genes were continued. In generalized pustular psoriasis evidence was found for a rather oligogenic inheritance while no association of the palmoplantar form with variants in the genes IL36RN and CARD14 could be identified.

Ophthalmogenetics
PI: PD Dr. F. Pasutto, Prof. Dr. A. Reis
Glaucoma represents a heterogeneous group of eye disorders characterized by irreversible damage of the optic nerve and usually elevated intraocular pressure, leading to vision loss and ultimately, if untreated, to blindness. Genetic factors are considered to play a key role in all major forms of glaucoma. In recent years, the working group in collaboration with the Department of Ophthalmology and international consortia has made important contributions to elucidate the genetic causes of pseudoexfoliation syndrome, the most common form of secondary glaucoma. Current work focuses on the mechanisms of disease development at the main predisposition locus LOXL1.



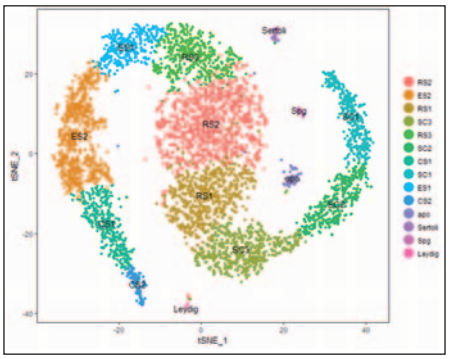
Results of the international meta-analysis of several genome-wide association studies (GWAS) for exfoliation syndrome (modified from Aung T et al. Nat Genet 2017)

Familial cancer
PI: Dr. A. Ekici, Prof. Dr. A. Reis
Some 5 -10% of cancer patients are affected by a familiar cancer syndrome. These are often caused by mutations in cancer susceptibility genes, either inherited or occurring de novo. The Institute closely collaborates with several oncology departments on campus to identify mutations in both, highly penetrant and low-penetrant genes, and to correlate genetic findings with patients' symptoms. In particular, in cooperation with working groups at the Department of Obstetrics and Gynecology, we carried out several such systematic mutation screens in large patient groups with familial breast and ovarian cancer.

Developmental genetics

PI: Prof. Dr. A. Winterpacht

This group is interested in the molecular basis of developmental processes and their individual variability, including epigenetic mechanisms and regulatory networks of organogenesis and cell differentiation. 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. Using novel single-cell transcriptomic analyses the group investigates its role in mitosis and in epigenetic regulation of meiosis as well as spermatogonial stem cell maintenance and differentiation.



Pseudotime analysis of single-cell RNA-seq data of testis cells shows continuous cell development of spermatogenesis (labeled for cell types; adapted from Lukassen et al. Sci Data 2018)

Teaching

The Institute of Human Genetics is involved in curricular teaching activities in Medicine and in the B.Sc. and M.Sc. degree programs Molecular Medicine as well as Cellular and Molecular Biology (M.Sc.), respectively.

Bachelor's and Master's theses as well as MD and PhD theses are supervised.

Selected publications

Aung T et al. Genetic association study of exfoliation syndrome identifies a protective rare variant at LOXL1 and five new susceptibility loci. Nat Genet 2017, 49: 993-1004

Pasutto F et al. Pseudoexfoliation syndrome-associated genetic variants affect transcription factor binding and alternative splicing of LOXL1. Nat Commun 2017, 8: 15466

Kraus C, Hoyer J, Vasileiou G, Wunderle M, Lux MP, Fasching PA, Krumbiegel M, Uebe S, Reuter M, Beckmann MW, Reis A. Gene panel sequencing in familial breast/ovarian cancer patients identifies multiple novel mutations also in genes others than BRCA1/2. Int J Cancer 2017, 140: 95-102

Vasileiou G et al. Mutations in the BAF-Complex Subunit DPF2 Are Associated with Coffin-Siris Syndrome. Am J Hum Genet 2018, 102: 468-479

Hauer NN et al. Clinical relevance of systematic phenotyping and exome sequencing in patients with short stature. Genet Med 2018, 20: 630-638

Gregor A et al. De Novo Variants in the F-Box Protein FBXO11 in 20 Individuals with a Variable Neurodevelopmental Disorder. Am J Hum Genet 2018, 103: 305-316

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