Institute of Human Genetics

Chair of Human Genetics

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

Structure of the Chair

Professorships: 2
Personnel: 45
- Doctors (of Medicine): 9
- Scientists: 9 (thereof funded externally: 4)
- Graduate students: 10

Clinical focus areas
- genetic outpatient clinic for all aspects of genetic diseases
- Participation in different specialized centers for rare diseases within the Erlangen Center for Rare Diseases
- various interdisciplinary outpatient clinics
- 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, Dr. G. Vasileiou
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. In the last reporting season, we discovered that genetic variants in the SCAF4 gene cause a variable neurodevelopmental disorder due to impaired processing of messenger RNA (mRNA). In a study on Borjeson-Forssman-Lehman syndrome, we were able to demonstrate in cell culture models that PHF6 is necessary for proper development of the central nervous system (neuron proliferation, neurite outgrowth and migration). Furthermore, the first international consensus statement for the diagnosis and management of Pitt-Hopkins syndrome was established. Finally, as part of an international cooperation, we were able to significantly broaden the spectrum of the CTCF-associated neurodevelopmental disorder and better characterize its pathophysiology using transcriptome analyses and animal models.

Growth disorders
PI: Prof. 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 large study group of previously unsolved cases, new candidate genes for idiopathic short stature were identified using a combination of exome sequencing and clustering of evolutionary conserved functional networks.

Psoriasis
PI: Prof. 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 are studied. In recent years we have expanded our focus to rarer manifestations of pustular psoriasis, for which oligogenic inheritance with stronger allelic effects is suspected. Using exome sequencing, we identified the myeloperoxidase (MPO) gene as a cause of generalized pustular psoriasis. MPO is the main enzyme of neutrophil granulocytes and regulates inflammation by oxidative processes and at the cellular level. Genetic variants impairing the protein lead to partial or complete MPO deficiency. Pharmacological modulation of MPO signaling may thus represent a treatment option for this and other chronic inflammatory diseases.

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. Recently, our work focused on targeted deep sequencing of the main PEX predisposition locus (LOXL1) in more than eleven thousand individuals worldwide. We were able to identify a single genetic variant, located adjacent on the same chromosome, modulating the expression of key components of the retinoic acid signaling pathway including STRA6. *In vitro* inhibition of the retinoic acid signaling pathway in PEX-relevant cell types and tissues induced upregulation of PEX-associated matrix genes. Our results indicate that dysregulation of STRA6 and impaired retinoid metabolism are involved in the pathophysiology of PEX syndrome.

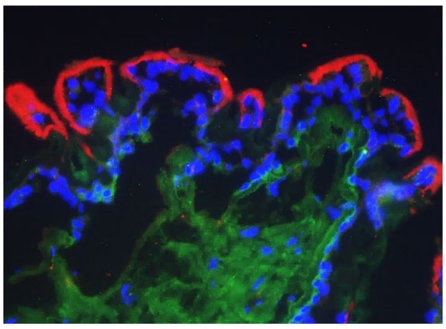

Fig. 1: Reduced expression levels of STRA6 in eye tissues (ciliary body and iris) of PEX patients associated with LOXL1-positive PEX material deposits

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. Furthermore, together with the Radiology and Gynecoloy Departments and Siemens Healthineers we explored magnetic resonance imaging methods for early detection of women with genetic predisposition to familial breast cancer. In collaboration with the Institute of Pathology, we characterised biallelic somatic variants of fumarate hydratase in hormone-dependent benign uterine leiomyomas using massive parallel sequencing. Finally, in collaboration with the Childrens´s Hospital, we identified TRIM28 as a predisposing gene for Wilms tumor (nephroblastoma), acting as a tumor suppressor gene.

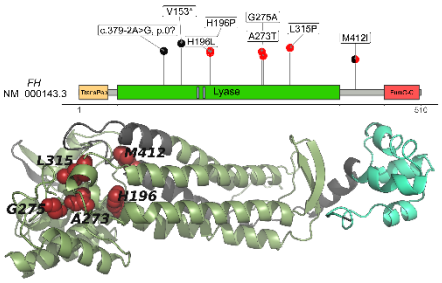

Fig.2: Schematic representation of the fumarate hydratase (FH) protein and its domains with localization of herein identified variants and depiction on the protein crystal structure

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

Berner D, Hoja U, Zenkel M, Ross JJ, Uebe S, Paoli D, Frezzotti P, Rautenbach RM, Ziskind A, Williams SE, Carmichael TR, Ramsay M, Topouzis F, Chatzikyriakidou A, Lambropoulos A, Sundaresan P, Ayub H, Akhtar F, Qamar R, Zenteno JC, Cruz-Aguilar M, Astakhov YS, Dubina M, Wiggs J, Ozaki M, Kruse FE, Aung T, Reis A, Khor CC, Pasutto F, Schlötzer-Schrehardt U. The protective variant rs7173049 at LOXL1 locus impacts on retinoic acid signaling pathway in pseudoexfoliation syndrome. Hum Mol Genet 2019 28:2531-2548

Diets IJ, Hoyer J, Ekici AB, Popp B, Hoogerbrugge N, van Reijmersdal SV, Bhaskaran R, Hadjihannas M, Vasileiou G, Thiel CT, Seven D, Uebe S, Ilencikova D, Waanders E, Mavinkurve-Groothuis AMC, Roeleveld N, de Krijger RR, Wegert J, Graf N, Vokuhl C, Agaimy A, Gessler M, Reis A, Kuiper RP, Jongmans MCJ, Metzler M. TRIM28 haploinsufficiency predisposes to Wilms tumor. Int J Cancer 2019 145:941-951

Hauer NN, Popp B, Taher L, Vogl C, Dhandapany PS, Büttner C, Uebe S, Sticht H, Ferrazzi F, Ekici AB, De Luca A, Klinger P, Kraus C, Zweier C, Wiesener A, Jamra RA, Kunstmann E, Rauch A, Wieczorek D, Jung AM, Rohrer TR, Zenker M, Doerr HG, Reis A, Thiel CT. Evolutionary conserved networks of human height identify multiple Mendelian causes of short stature. Eur J Hum Genet 2019 27:1061-1071

Fliedner A, Kirchner P, Wiesener A, van de Beek I, Waisfisz Q, van Haelst M, Scott DA, Lalani SR, Rosenfeld JA, Azamian M.S, Xia F, Dutra-Clarke M, Martinez-Agosto JA, Lee H, UCLA Clinical Genomics Center, Noh GJ, Lippa N, Alkelai A, Aggarwal V, Agre KE, Gavrilova R, Mirzaa GM, Straussberg R, Cohen R, Horist B, Krishnamurthy V, McWalter K, Juusola J, Davis-Keppen L, Ohden L, van Slegtenhorst M, de Man SA, Ekici AB, Gregor A, van de Laar I, Zweier C. Variants in SCAF4 Cause a Neurodevelopmental Disorder and Are Associated with Impaired mRNA Processing. Am J Hum Genet 2020 107: 544–554

Haskamp S, Bruns H, Hahn M, Hoffmann M, Gregor A, Löhr S, Hahn J, Schauer C, Ringer M, Flamann C, Frey B, Lesner A, Thiel CT, Ekici AB, von Hörsten S, Aßmann G, Riepe C, Euler M, Schäkel K, Philipp S, Prinz JC, Mößner R, Kersting F, Sticherling M, Sefiani A, Lyahyai J, Sondermann W, Oji V, Schulz P, Wilsmann-Theis D, Sticht H, Schett G, Reis A, Uebe S, Frey S, Hüffmeier U. Myeloperoxidase Modulates Inflammation in Generalized Pustular Psoriasis and Additional Rare Pustular Skin Diseases. Am J Hum Genet 2020 107:527-538

Popp B, Erber R, Kraus C, Vasileiou G, Hoyer J, Burghaus S, Hartmann A, Beckmann MW, Reis A, Agaimy A. Targeted sequencing of FH-deficient uterine leiomyomas reveals biallelic inactivating somatic fumarase variants and allows characterization of missense variants. Mod Pathol 2020 33:2341-2353

International cooperations

Nur Aydinli, Department of Pediatric Neurology, Istanbul University School of Medicine, Istanbul, Turkey

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Anita Rauch, Institute of Medical Genetics, University of Zurich, Zurich, Switzerland

Tin Aung, Singapore National Eye Centre, Singapur, Singapur