Human Genomics

Sven Cichon

Department of Biomedicine
and Institute of Medical
Genetics and Pathology
University Hospital Basel

Group Members

Michèle Attenhofer* (Technician)
Dr. Robert Blatter* (Postdoc)
Dr. Bettina Burger (Project Leader)
Madina Burkhart* (MSc Student)
Amanda Susanna Dirnberger* (MSc Student)
PD Dr. Isabel Filges (Project Leader)
Sascha Fischer (PhD Student)
Prof. Dr. Karl Heinimann (Project Leader)
Dipl.-Biol. Stefan Herms (Bioinformatician)
Dr. Per Hoffmann (Project Leader)
Dr. Silvia Kalantari (Postdoc)
Nicole Meier* (PhD Student)
Dr. Thomas Mühleisen (Visiting Scientist)
Céline Reinbold* (PhD Student)
Meret Rohner (MSc Student)
Carmela Schumacher (MSc Student)
Dr. Luana Sella Motta Maia (Postdoc)
Benjamin Tschupp (MD Student)
Agnieszka Tupalska (PhD Student)
Anna Vettiger (MSc Student)

*left during report period

Human Genomics: investigating the molecular basis of human genetic disesases

The research group "Human Genomics" aims to identify the molecular (genetic) basis of human diseases and the underlying molecular mechanisms and pathomechanisms by combining human genetics knowledge with new genomics technologies (project leader: Per Hoffmann), bioinformatics and biostatistical approaches and in-depth phenotyping. We focus on genetically complex neuropsychiatric disorders (project leader: Sven Cichon, DMB's Focal Area Neurobiology), congenital developmental disorders (project leader: Isabel Filges), and hereditary cancer syndromes (project leader: Karl Heinimann, DBM's Focal Area Oncology). We closely interact with the research group Skin Biology and have a strong interest in the molecular basis of genodermatoses (project leader: Bettina Burger) and hereditary angioedema (project leader: Sven Cichon).

Neuropsychiatric disorders

One strong focus of the research group is the genetic analysis of neuropsychiatric disorders, in particular bipolar disorder. In the context of the Psychiatric Genomics Consortium (PGC), we performed the so far largest genome-wide association study (GWAS) including 20,352 cases and 31,358 controls of European descent (Stahl *et al.,* 2019). 30 loci were genome-wide significant, including 20 newly identified loci (Fig. 1). The significant loci contain genes encoding ion channels, neurotransmitter transporters and synaptic components. Pathway analysis revealed nine significantly enriched gene sets, including regulation of insulin secretion and endocannabinoid signaling. The study also showed that the clinical subgroup Bipolar I disorder is strongly genetically correlated with schizophrenia, driven by psychosis, whereas bipolar II disorder is more strongly correlated with major depressive disorder. These findings address key clinical questions and provide potential biological mechanisms for bipolar disorder.
In parallel we performed exome sequencing studies in large and multiply affected bipolar disorder families (e. g. Maaser *et al.,* 2018). Current and future projects aim at a mechanistic understanding of common and rare genetic risk variants for bipolar disorder. This will include sequencing in further large families with bipolar disorder as well as the study of sets of common risk variants in induced pluripotent stem cell (iPSC) models.

Congenital developmental disorders

Our specific interest relates to birth defects and multiple congenital anomaly syndromes which present early during pregnancy, since the monogenic aetiology of most severe fetal anomalies is poorly understood. In addition, the clinical description of most genetic conditions relates to paediatric and adult patients, and we are trying to understand how those same conditions may present in the prenatal period.
We systematically investigate families with one or more fetuses presenting with distinctive anomaly patterns and identified novel disease genes, new fetal phenotypes and phenotypes as a variable of developmental timing (Meier *et al.,* 2017; Meier *et al.,* 2019; Meier *et al.,* 2020). We further characterized the function of KIF14 in humans and zebrafish (Reilly *et al.,* 2019) and reviewed the emerging role of kinesin family member genes in birth defects, which we proposed to term "kinesinopathies" as a recognizable entity (Kalantari&Filges, 2020; Fig. 2).
Our group also studies Arthrogryposis multiplex congenita (AMC), a heterogeneous group of conditions with multiple contractures (Filges *et al.,* 2019). In an international consortium we work towards a standardized interdisciplinary approach to diagnose and care for patients with AMC.

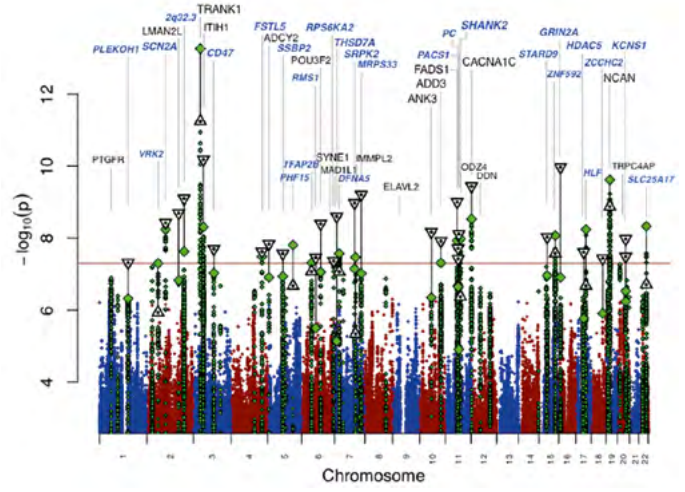

Fig. 1: Results of a large GWAS of bipolar disorder (Stahl *et al.,* 2019, Nat. Genet.): Manhattan plot for our primary genomewide association analysis of 20,352 cases and 31,358 controls. GWAS -log^{10}P-values are plotted for all SNPs across chromosomes 1-22 (diamonds, green for loci with lead SNP GWAS $P < 10^{-6}$). Combined GWAS+followup -log^{10}Pvalues for lead SNPs reaching genome-wide significance in either GWAS or combined analysis (triangles, inverted if GWAS+followup -log^{10}P > GWAS -log^{10}P). Labels correspond to gene symbols previously reported for published loci for bipolar disorder (black) and the nearest genes for novel loci (blue), at top if GWAS+followup $P < 5x10^{-8}$.

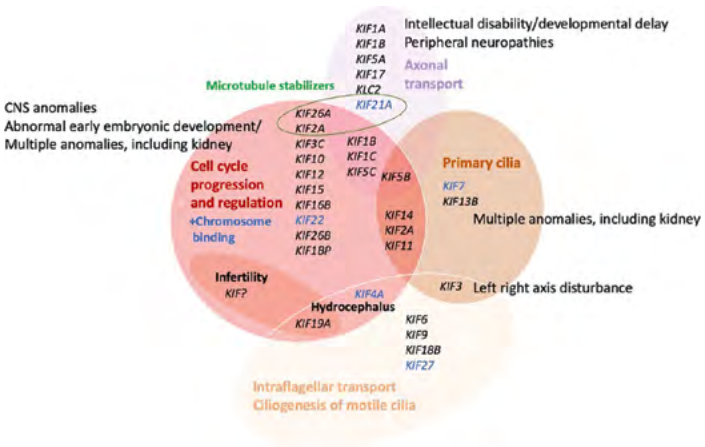

Fig. 2: Congenital developmental disorders: Assignment and clustering of *KIF* genes to various functions and relation to birth defect or monogenic phenotype groups. Detailed phenotypes are shown in tables 1 and 3. Cancer and multifactorial conditions are not included. CNS, central nervous system (from Kalantari, S. & Filges, I. (2020) J. Med. Genetics).

Hereditary cancer syndromes

In a collaborative study on autosomal dominant Juvenile Polyposis Syndrome (JPS), we analysed data on almost 700 JPS patients. Compared with BMPR1A carriers, SMAD4 carriers displayed anaemia twice as often, exclusively showed overlap symptoms with haemorrhagic telangiectasia and an increased prevalence of gastric juvenile polyps. Cancer, reported in 15 % of JPS patients, mainly occurred in the colorectum and the stomach. Our results facilitate recommendations for clinical management, and contribute to SMAD4 and BMPR1A databases (Blatter *et al.,* 2020).

In addition, we collated prospective clinical data on 80 Lynch syndrome patients harbouring pathogenic DNA mismatch repair (MMR) gene variants. Integration into the Prospective Lynch Syndrome Database (PLSD) resulted in studies assessing cancer incidence, prognosis, gene-specific cancer risks and the effect of current surveillance measures on mortality (Seppala *et al.,* 2019; Dominguez-Valentin *et al.,* 2020). Research collaborations on RET germline alterations in osteosarcoma patients and on colorectal carcinogenesis, particularly MMR deficient cancers, were successfully published (Kovac *et al.,* 2020; Cross *et al.,* 2018).

Selected Publications

Stahl EA, Breen G, Forstner JF, Cichon S, Ophoff RA, Scott LJ, Andreassen OA, Kelsoe J, Sklar P. Bipolar Disorder Working Group of the Psychiatric Genomics Consortium (2019) Genome-wide association study indentifies 30 loci associated with bipolar disorder. Nat Genet 51, 793–803.

Maaser A, Forstner AJ, Strohmaier J, Cichon S, Marcheco-Teruel B, Mors O, Rietschel M, Nöthen MM (2018) Exome Sequencing in large, multiplex bipolar disorder families from Cuba. PLoS One 13, e0205895.

Meier N, Bruder E, Lapaire O, Hoesli I, Kang A, Hench J, Hoeller S, De Geyter J, Miny P, Heinimann K, Chaoui R, Tercanli S, Filges I (2019) Exome sequencing of fetal anomaly syndromes: novel phenotype-genotype discoveries. Eur J Hum Genet. 27, 730–737.

Filges I, Tercanli S, Hall JG (2019) Fetal arthrogryposis: Challenges and perspectives for prenatal detection and management. Am J Med Genet C Semin Med Genet. 181, 327–336.

Blatter R, Tschupp B, Aretz S, Bernstein I, Colas C, Evans DG, Genuardi M, Hes FJ, Hüneburg R, Järvinen H, Lalloo F, Moeslein G, Renkonen-Sinisalo L, Resta N, Spier I, Varvara D, Vasen H, Latchford AR, Heinimann K. (2020) Disease expression in juvenile polyposis syndrome: a retrospective survey on a cohort of 221 European patients and comparison with a literature-derived cohort of 473 SMAD4/BMPR1A pathogenic variant carriers. Genet Med. 2020 May 13.