Human Genomics

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Molecular genetic analysis of neuropsychiatric disorders, hereditary colorectal cancer syndromes, and congenital developmental disorders

Our research group aims to identify the molecular (genetic) basis of human diseases by combining human genetics knowledge, new genomics technologies, bioinformatics/-statistical approaches, and in-depth phenotyping. We work on complex neuropsychiatric disorders (Sven Cichon and Per Hoffmann), congenital developmental disorders (Isabel Filges, primarily linked to the DKF), and hereditary colorectal cancer syndromes (Karl Heinimann).

Neuropsychiatric disorders

We recently published the so far largest genome-wide association study (GWAS) of bipolar disorder (BD) (Mühleisen *et al.*, 2014), a common neuropsychiatric disorder and implicated novel risk loci at the ADCY2 gene and between the genes MIR2113 and POU3F2. In particular the gene for ADCY2 (encoding adenylate cyclase 2) is biologically interesting, it plays a key role in cAMP-dependent G-protein coupled receptor pathways. Disturbed neurotransmission at these pathways is a long-standing hypothesis in psychiatric research.
We contributed to the largest GWAS of schizophrenia to date (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) in which 128 independent single nucleotide polymorphisms (SNPs) were identified. Using these GWAS data, we performed several follow-up analyses, including an analysis of the contribution of microRNA coding genes to BD (Forstner *et al.,* 2015).
A current project aims at the identification of risk genes for BD in large, multiply affected BD and major depression families, by analyzing whole-exome sequencing data in up to 10 genetically distant patients selected from each family.

Congenital developmental disorders

Our goal is to understand the genomic basis of congenital developmental disorders and improve patient care. We identified several genes causing developmental delay and intellectual disabilities (ID) through the systematic study of individuals with unexplained congenital anomaly syndromes and syndromic and non-syndromic ID (e.g. PTCHD1, SETBP1, SMARCA2). Recent research expands to using next generation sequencing technologies to discover genes in which mutations cause early fetal mal-development, since improved ultrasound technology and its use by maternal fetal medicine specialists fetal diagnosis clinics worldwide deal with an increasing number of cases with serious or lethal anomalies of unknown cause. Most important findings so far were the delineation of the first human lethal phenotype caused by mutations in KIF14 (Filges *et al.,* 2014), and the identification of mutations in CENPF, causing a variable phenotypic presentation ranging from a fetal lethal ciliary phenotype to the postnatal Stømme syndrome (Filges *et al.,* 2016).

Fig. 1a

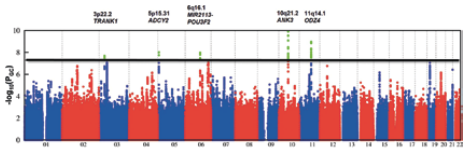

Fig. 1b

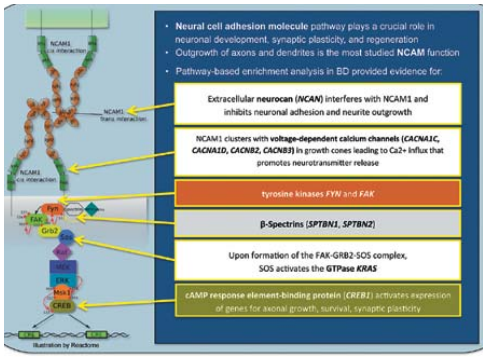

Fig. 1: Refers to our research on neuropsychiatric disorders. In **Fig. 1a,** results of our most recent (and so far largest) GWAS for bipolar disorder (BD) are shown (Mühleisen *et al.*, 2014). The Manhattan plot gives a genome-wide overview of association results for SNPs. The x-axis depicts all the whole genome from chromosome 1 to X. The y-axis shows the negative decadic logarithm of the p-value for each tested SNP. 56 SNPs exceeded the threshold for genome-wide significance ($p<5 \times e-08$), they clustered in 5 genomic loci: chr. 3 containing the TRANK1 gene, chr. 5 covering the ADCY2 gene, chr. 6 in an intergenic region between genes MIR2113 and POU3F2, chr. 10 covering the ANK3 gene, and chr. 11 including the gene ODZ4. **Fig. 1b** shows results of a biological pathway analysis using the program INRICH, using the complete GWAS results as input. Our analysis shows that association signals in SNPs located in genes coding for proteins of the NCAM1 signaling pathway are significantly clustered. This provides evidence that the NCAM1 signaling pathway is disturbed in BD. Future studies will have to show the exact functional consequences (pathophysiology) of such SNP risk alleles on the pathway in BD (Manuscript in preparation).

Hereditary colorectal cancer syndromes

We have assessed the mutational processes behind large, genomic deletions/insertions leading to colorectal cancer syndromes. Little is known about genomic rearrangements (GRs) in the germ line of cancer patients. We investigated DNA motifs and higher order structures of genome architecture, which may result in losses and gains of genetic material in the germ line, and created an algorithm to predict the propensity of rearrangements (Kovac *et al.,* 2015).
Another focus was on juvenile polyposis syndrome (JPS) with SMAD4 or BMPR1A germline mutations (1st-hit). Little is known about the nature of somatic alterations (2nd-hit) in SMAD4-/BMPR1A related juvenile polyps. We screened polyps from three patients with SMAD4-/BMPR1A germ line mutations for somatic alterations and SMAD4 protein expression. No somatic alterations were identified in 14 SMAD4-related polyps. SMAD4 protein expression, however, was lost in 57 % of the polyps (6 showing concomitant loss in both epithelial and stromal compartments). In BMPR1A-related polyps, five out of nine (56 %) displayed gene copy number neutral LOH, which had occurred in the epithelial compartment. The heterogeneity of genetic mutations and protein expression levels indicates that different modes of gene inactivation can be operational in SMAD4- and BMPR1A-related polyp formation. The observation that half of BMPR1A-related polyps displayed LOH suggests that BMPR1A acts as a tumour suppressor gene (Blatter *et al.,* 2015).

Selected Publications

Filges I, Bruder E, Brandal K, Meier S, Undlien DE, Waage TR, Hoesli I, Schubach M, de Beer T, Sheng Y, Hoeller S, Schulzke S, Røsby O, Miny P, Tercanli S, Oppedal T, Meyer P, Selmer KK, Strømme P. (2016) Strømme Syndrome Is a Ciliary Disorder Caused by Mutations in CENPF. Hum. Mutat. 37, 359–63

Blatter RH, Plasilova M, Wenzel F, Gokaslan ST, Terracciano L, Ashfaq R, Heinimann K. (2015) Somatic Alterations in Juvenile Polyps from BMPR1A and SMAD4 Mutation Carriers. Genes Chrom. Cancer 54, 575–582

Kovac MB, Kovacova M, Bachraty H, Bachrata K, Piscuoglio S, Hutter P, Ilencikova D, Bartosova Z, Tomlinson I, Roethlisberger B, Heinimann K. (2015) High-Resolution Breakpoint Analysis Provides Evidence for the Sequence-Directed Nature of Genome Rearrangements in Hereditary Disorders. Hum. Mutat. 36, 250–259

Forstner AJ, Hofmann A, Maaser A, Sumer S, Khudayberdiev S, Mühleisen TW, Cichon S, Nöthen MM. (2015) Genome-wide analysis implicates microRNAs and their target genes in the development of bipolar disorder. Transl. Psychiatry 5, e678

Mühleisen TW, Leber M, Schulze TG, Strohmaier J, Degenhardt F, Treutlein J, Cichon S. (2014) Genome-wide association study reveals two new risk loci for bipolar disorder. Nat. Commun. 5, 3339.

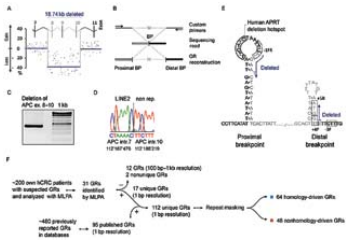

Fig. 2: Showing some of the work peformed in Hereditary colorectal cancer syndromes. In particular, this figure shows how Karl Heinimann investigated the mutational processes behind large, genomic deletions/insertions leading to colorectal cancer syndromes (Kovac *et al.* 2015). The figure gives an overview of the fine-mapping and the inclusion scheme for patients with genome rearrangements. Sections A–E exemplify fine-mapping of a 18.7 kb deletion encompassing APC exons 8–10 by custom-tiled array CGH, (A–C) allele-specific PCR followed by a GR reconstruction, (D) breakpoint sequencing, and (E) structural analysis and motif identification. Section F depicts selection and sub-classing of 112 nonrecurrent genomic rearrangements based on the repeat masking annotations. BP: breakpoint, GR: genome rearrangement.