Genetics of aHUS and other thrombotic microangiopathies:
Who will benefit from Eculizumab?

Atypical HUS (aHUS) is a severe and frequently relapsing disorder that is known to be caused by mutations in complement genes. Incomplete penetrance suggests that additional factors are necessary for the disease to manifest. Secondary triggers (e. g., hypertension, pregnancy, transplantation, infection) and predisposing polymorphisms are known to lower the threshold for disease onset. In this clinically and genetically heterogeneous disorder, genetic testing becomes increasingly important for proper clinical management and therapeutic and prognostic issues.

We established an NGS-based panel for parallel analysis of genes involved in complement regulation and coagulation including all known genes described for aHUS and related disorders (DDD, C3-GN and other glomerulopathies) to enable a comprehensive time- and cost-efficient diagnostic approach for these heterogeneous disorders with huge clinical and genetic overlap.

We present comprehensive data of our cohort of patients with aHUS. We were able to detect the disease causing mutation in more than 50% of patients including point mutations, deletions and structural rearrangements causing hybrid genes. Furthermore, we evaluated frequencies of risk haplotypes known as potential disease modifiers in our cohort.

Our study represents the largest cohort of patients that have been analysed by comprehensive NGS-based genetic testing so far. Detailed information on the underlying genotype is of major advantage for discussions regarding transplantation, recurrence risk and treatment options and should be determined in any patient with clinical suspicion of aHUS.

Genomic medicine for our children?

Over the past decade, the field of molecular diagnostics has evolved rapidly with the advent of high-throughput next generation sequencing (NGS). Genetics is increasingly being used to direct clinical decision-making. NGS will continue to simplify diagnostic testing while technical capabilities have been enhanced. Many clinical laboratories are now offering an ever-increasing catalogue of genetic tests including single genes, multi-gene panels, exomes, genomes, transcriptomes, and epigenetic assays. Substantial challenges and increasing complexity arise from data storage and bioinformatic and interpretative issues. In future years, genome sequencing (WGS) may eventually serve as a universal first line test for any disorder with a suspected genetic origin. However, for the time being, a one-size-fits-all approach might not be the best solution and many arguments in favour of a more differentiated approach dependent on the patient's phenotype can be provided. Thus, initial targeted testing is currently still the gold standard for a number of indications. In contrast, for some disorders such as non-specific global mental retardation unbiased, hypothesis-free approaches (WES/WGS) are already used routinely early in the diagnostic work-up of these patients. Given obvious advantages particularly of WGS, it probably won't take long before those assays will be used in greater volume for diagnostic purposes. Currently, the interpretation of intronic and regulatory variants is still challenging and of limited clinical value, but this may change soon when more genomic data is available in public databases. In my talk, I will try to supply a balanced discussion of the opportunities, challenges and shortcomings of various approaches in different clinical settings.

**Polycystic kidney disease, nephronophthisis and related ciliopathies-
An emerging field of interest in pediatric nephrology**

Carsten Bergmann

Early and severe forms of polycystic kidney disease (PKD) do already manifest during childhood or adolescence. They are characterized by enlarged kidneys and diminished renal function that prenatally may result in Potter's oligohydramnios sequence. Genetically, various defects can mimic this phenotype. Most common are *PKHD1* mutations that lead to autosomal recessive polycystic kidney disease (ARPKD). About the same number of children do carry mutations in the dominant ADPKD genes, *PKD1* and less frequent *PKD2,* that often arise *de novo* or may affect both disease alleles in a recessive mode. Mutations in *DZIP1L* have been recently described to result in an ARPKD-like phenotype. Likewise, mutations in several other cystogenes can phenocopy early and severe PKD. Early and reliable prenatal diagnosis for which there is a strong demand in ARPKD and related diseases is only feasible by genetics. A comprehensive knowledge of disease-causing genes is essential for the correct diagnosis and parental counselling. The increasing number of genes that need to be considered benefit from the advances of next generation sequencing (NGS) and allows the simultaneous analysis of all genes of interest in a single test which is now the mainstay for genetic diagnosis. Interpretation of data is challenging and requires expert knowledge in data handling, bioinformatics and clinical genetics.