IDENTIFICATION OF NOVEL DISEASE GENE FOR PRIMARY CONGENITAL GLAUCOMA (PCG) THROUGH HOMOZYGOSITY MAPPING AND NEXT-GENERATION SEQUENCING

VERDIN H., DE BAERE E., KESTELYN P.

Affiliation Institution: Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium

Promotors of the Project: DE BAERE E., MD, PhD, KESTELYN P.H., MD, PhD

BACKGROUND AND AIM OF THE PROJECT

Glaucoma is known to be a leading cause of blindness worldwide. One of the types is primary congenital glaucoma (PCG) which displays symptoms from birth or early infancy. PCG is caused by developmental anomalies of the trabecular meshwork and the anterior chamber angle resulting in an increased ocular pressure (IOP) and optic nerve damage. The prevalence of PCG is population-dependent, estimated to be 1:10.000 in Western populations with higher prevalences in inbred populations. In general PCG displays an autosomal recessive inheritance pattern and is genetically heterogeneous. To date, three PCG loci are known and two causal genes have been identified, *CYP1B1* (1) and *LTPB2* (2).
The aim of the current study is to identify the causal disease gene in a large consanguineous family with PCG, originating from Jordany.

DEVELOPMENT OF THE PROJECT

In a first step, DNA from members of the consanguineous family will be genotyped by 250K GeneChip Mapping Affymetrix arrays containing more than 250 000 SNPs. Using this technique, the entire genome can be searched for regions identical on both chromosomes, which originated from a common ancestor. These homozygous or identical- by-descent regions are very likely to contain the disease gene in a consanguineous family. The results of the homozygosity mapping will be analyzed using a homemade Perl script. Next, microsatellite analysis will be performed in all family members in order to confirm findings of the SNP chip analysis and to narrow down candidate regions. However, these candidate regions still contain hundreds of genes which complicates the search for the disease gene. Therefore a very recent technique will be applied, namely next-generation sequencing. This approach has the advantage that large stretches of DNA can be analyzed simultaneously. To this end, candidate regions of interest first need to be captured.

Next, sequencing will be performed on a genome analyzer. Gene and variant prioritization will be done using appropriate software, followed by segregation analysis and screening in control individuals. At last, a cohort of 30 molecularly unsolved PCG patients which are mainly recruited in Belgium and do not have an established molecular diagnosis, will be screened for mutations in the newly identified disease

gene using Sanger sequencing. Sequence variants will be analyzed for a potential pathogenic effect based on their evolutionary conservation, their location in the protein, and the outcome of several prediction programs. In addition, segregation analysis of identified variations will be performed in available family members.

REFERENCES

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