Introduction

We study large patient cohorts to identify gene defects underlying different forms of inherited retinal diseases and develop gene-based innovative therapies

Presentation

Inherited retinal diseases (IRDs) represent a major cause of blindness or visual defects in adults. They affect approximately 1 in 2000 individuals worldwide. Symptoms and associated phenotypes are variable. In some groups the disease can be stationary such as in congenital stationary night blindness (CSNB), whereas other disorders are progressive, leading to severe visual impairment, such as in rod-cone dystrophies, also known as retinitis pigmentosa (RP). There is currently no treatment to restore vision for these diseases. Our group is interested in two aspects of IRDs, one is deciphering underlying genetic defects and the other one is developing gene-based innovative therapies.

The heterogeneity of IRDs is reflected by the number of underlying gene defects with all modes of inheritance reported. More than 180 genes have been implicated in different forms of retinal diseases accounting for about 60% of the cases. This suggests that a large proportion of patients do not have mutations in the known genes with a significant number of novel genes still remaining to be discovered. Mutation detection by Sanger sequencing and microarray analysis are frequently used to identify known and novel gene defects but these methods are time consuming and expensive. To overcome these, new technologies such as next generation sequencing (NGS) are used to rapidly identify the genetic defect.

Our group has established a comprehensive panel of targeted NGS, analyzing coding sequences of genes involved in IRDs. This tool is continuously updated to improve genomic coverage and fit the current knowledge.

Our goal is to genetically characterize a large cohort of patients with various IRDs, the majority of whom have been clinically well phenotyped and followed up at the Quinze-Vingts hospital (Paris), to further perform phenotype/genotype correlations. Patients' DNA is extracted and banked through the DNA extraction platform. Our strategy is to apply the comprehensive NGS panel to identify the causative gene defect and perform whole exome sequencing on cases with no mutation on known genes therefore giving us a chance to identify new genes implicated in IRDs. The Sanger sequencing validations are performed on our sequencing platform. In addition, we are interested to better understand the function and pathophysiology of these novel genes by performing in vitro and in vivo studies on various platforms

available at the Institute (e.g. histology, imaging, phenotyping of rodent models). This comprehensive study leads to a better understanding of retinal physiopathology, delivers epidemiological data on mutations involved in IRD in Europe and may also identify novel targets for therapies. It also allows a better patient characterization and counseling and helps prepare future clinical trials such as those on gene therapy by identifying suitable candidates.

The second axis of our work is engineering gene-based innovative therapies. These projects are developed for two distinct diseases CSNB, with a strategy of gene augmentation therapy, and autosomal dominant RP with a strategy of genome surgery. Both projects are validated in vitro (iPSCs or retinal explants) and in vivo on the rodent phenotyping platform of the animal facility.