Marie Curie Innovative Training Network

Training researchers to Diagnose, Understand and Treat Stargardt Disease, a Frequent Inherited Blinding Disorder

(StarT project)

Eye diseases are among the most common inherited human disorders. Around one third of the known genetic defects or syndromes involve the eye. Vision research has often blazed a trail for many disciplines to follow, giving a lead in omics, genome editing, stem cell biology, animal models of disease, and the development of novel therapeutic approaches such as gene therapy.

StarT will create an interdisciplinary and intersectorial European training network focusing on different aspects of autosomal recessive Stargardt disease (STGD1), a frequent inherited blinding disorder that affects an estimated 925,000 persons worldwide, representing more than one-third of all inherited retinal disorders. StarT research aims to uncover the regulation of its disease gene ABCA4 and its missing heritability, in order to develop novel treatments.

STGD1 is due to ABCA4 mutations, however up to 35% of STGD1 cases carries one or no ABCA4 coding mutation. New unconventional classes of ABCA4 mutations were recently discovered by us, the significance of which largely remains elusive. In order to understand the mechanisms triggered by these missing ABCA4 mutations and to design new therapies for STGD1 cases, challenging research questions will be addressed by the integration of unique skills from this network.

Early-Stage Researchers will perform cutting edge research using innovative and interdisciplinary approaches: (functional) genomics and transcriptomics, bio-informatics, CRISPR/Cas9 genome editing, generation of stem cell and animal disease models and design of new treatments.

Individual project descriptions

ESR5 Partner 2 (RUMC): Identification and splice assays of deep-intronic ABCA4 variants in mono-allelic STGD1
Approximately 25% of STGD1 cases show one or no coding ABCA4 variant. Using ABCA4 locus sequencing, we and others identified deep-intronic variants. We focused on the identification of RNA splice defects and generated a complete set of Gateway-based splice vectors, denoted midigenes, that contain wild-type (WT) ABCA4 multi-exon segments of 4.7 to 11.7 kb. Using a mutagenesis protocol, we rapidly introduced new variants into these vectors and performed in vitro splice assays in HEK293T cells. We assessed the effect of all reported 47 non-canonical ABCA4 splice variants and tested 10 deep-intronic variants identified in 40 mono-allelic Dutch STGD1 cases. Splice defects were visualised by RT-PCR using primers annealing to flanking ABCA4 exons. For selected variants, we also confirmed their effect on patient-derived photoreceptor progenitor cells (PPCs). ESR5 will develop a cost-effective sequencing method for the ABCA4 locus using single molecule Molecular Inversion Probes (smMIPs), and sequence 400 mono-allelic STGD1 cases that have been recruited by P2-RUMC. Sequence data (variants) of ESR5, ESR6 and ESR7 will be compiled. Hundred variants predicted to affect splicing will be introduced into WT midigenes. The effect of selected variants will be analysed in patient-derived PPCs and retinal pigment epithelium (RPE) cells. Supervisor: Prof. Dr. F. Cremers. url: https://www.ru.nl/donders/research/theme-2-perception-action-control/research-groups-theme-2/blindness-genetics/

EUROPEAN CURRICULUM VITAE FORMAT

PERSONAL INFORMATION

Name	[SURNAME, other name(s)]
Address	[House number, street name, postcode, city, country]
Telephone	
Fax	
E-mail	
Nationality	
Gender	Male / Female
Date of birth	[Day, month, year]

WORK EXPERIENCE

• Dates (from – to)	[Add separate entries for each relevant post occupied, starting with the most recent.]
• Name and address of employer	
• Type of business or sector	
• Occupation or position held	
• Main activities and responsibilities	

EDUCATION AND TRAINING

• Dates (from – to)	[Add separate entries for each relevant course you have completed, starting with the most recent.]
• Name and type of organisation providing education and training	
• Principal subjects/occupational skills covered	
• Title of qualification awarded	
• Level in national classification (if appropriate)	

PERSONAL SKILLS AND COMPETENCES *Acquired in the course of life and career but not necessarily covered by formal certificates and diplomas*.	
MOTHER TONGUE	[Specify mother tongue]
OTHER LANGUAGES	
	[Specify language]
• Reading skills	[Indicate level: excellent, good, basic.]
• Writing skills	[Indicate level: excellent, good, basic.]
• Verbal skills	[Indicate level: excellent, good, basic.]
SOCIAL SKILLS AND COMPETENCES *Living and working with other people, in multicultural environments, in positions where communication is important and situations where teamwork is essential (for example culture and sports), etc.*	[Describe these competences and indicate where they were acquired.]
ORGANISATIONAL SKILLS AND COMPETENCES *Coordination and administration of people, projects and budgets; at work, in voluntary work (for example culture and sports) and at home, etc.*	[Describe these competences and indicate where they were acquired.]
AVAILABILITY	[Please indicate what would be the earliest date that you can start a new job]
ADDITIONAL INFORMATION	[Include here any other information that may be relevant, for example contact persons, references, etc.]
ANNEXES	[List any attached annexes.]