Exploring the combined role of genetic and non-genetic factors for developing Age-Related Macular Degeneration: A systems level analysis of disease subgroups, risk factors, and pathways

Reporting

Project Information

EYE-RISK

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Periodic Reporting for period 3 - EYE-RISK (Exploring the combined role of genetic and non-genetic factors for developing Age-Related Macular Degeneration: A systems

level analysis of disease subgroups, risk factors, and pathways)

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Summary of the context and overall objectives of the project

Age-related macular degeneration (AMD) is a chronic and progressive disease of the retina and is the most frequent cause of legal blindness in the EU. Patients progressing to late AMD, gradually lose the central field of vision - making it impossible to read, write, drive and recognize faces. This loss of vision greatly impedes an independent and active life. AMD is also causing increasing costs on the ageing European society as it reaches a frequency of up to 25% in those aged 85 years and older.

AMD is a complex disease caused by a combination of non-genetic as well as genetic factors. The most powerful factor influencing the risk for AMD is the factor “being over the age of 60”. AMD can affect the retina either as wet form (also called neovascular) or as dry form (also called atrophic). Neither form can be cured. There is a therapy for the slowing of progression to choroidal neovascularization; unfortunately, a therapy for the dry form is still lacking.

Research to understand AMD is aiming to predict, prevent and treat AMD. So far, genetic and epidemiologic studies have been able to pinpoint a number of genetic variants as well as environmental and lifestyle factors that define the individual risk for AMD. Turning this knowledge into prediction, prevention and treatment is difficult because disease progression varies widely between individuals and more than one cellular pathway contributes to the retinal degeneration in AMD.

The EYE-RISK consortium has been using a systems medicine approach to overcome the difficulties in understanding the causes of AMD and its development. The project analyses data from large European cohorts and biobanks, combining the expertise of people from multiple disciplines and 14 organizations from all over Europe. This approach has an increased power to extract relevant information from existing databases and to validate new findings.

EYE-RISK is funded by the EU’s Horizon 2020 research and innovation programme within its personalising health and care challenge PHC-01 “Understanding health, ageing and disease: determinants, risk factors and pathways”. The planned output in EYE-RISK comprises i) an algorithm for predicting AMD risk; ii) predicting progression and conversion; iii) an array of proteins that confer risk; iv) identification of molecular drivers for disease progression; v) a web-based prediction programme to be used by patients and clinicians for patients at risk.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

For in-depth analysis of multimodal data, an EYE-RISK database was set up and continuously supplied with data. This database includes epidemiological and genetic data from pre-existing cohorts of the European Eye Epidemiology (E3) consortium, which collaborates with EYE-RISK.
To our knowledge, it has grown to be the largest data repository on AMD worldwide. By in-depth analysis of these data we determined the prevalence and incidence of AMD in Europe and made projections for the future. The number of patients within the E.U. is predicted to rise by 50% in 2040 as the population is growing and more people live longer.

Since genetic predispositi on is a major risk factor for AMD, we have designed and optimized an AMD genotyping assay, including published loci strongly associated to AMD risk (International Age-related Macular Degeneration Genomics Consortium; Nature Genetics 2016 with contributions from EYE-RISK partners). This test was used to genotype AMD patients within the EYE-RISK database and correlations between genotypes, AMD phenotpyes as well as lifestyle factors were investigated. For data analysis, statistical and algorithmic software tools have been used.

Results showed that diet influences the risk to develop AMD and that a Mediterranean diet can be protective. Further, we identified a correlation of serum lipid levels with AMD and studied the phenotypic features that correlate to the defined disease states. In addition, we have been creating a network model of genes and their corresponding proteins, built a computational simulation of disease pathways that centres on the genetic risk loci and in-depth investigated candidate markers and network components for their role in AMD pathogenesis. This knowledge was used to characterise several of these proteins by protein chemistry, cellular assays, organotypic cultures and patient derived induced pluripotent stem cells (iPSC) differentiated into RPE.

EYE-RISK partners have extensively analysed primary human blood and tissue as well as iPSC derived cultures of non-risk and genetic risk affected individuals on the level of their RNA and protein expression, metabolism and higher order pathological features including drusen and deposit formation and inflammatory activity. The output of this analysis has been subjected to patient versus control biomaterial for significance. The focus here was on the alternative complement pathway, one of the main drivers for AMD, and on the analysis of lipid and protein deposits in the choreocapillaris-Bruch's membrane-retinal pigment interface. Two protein arrays of proteins that confer risk have been produced and commercialized and are now under clinical validation.

Integrating the obtained knowledge, EYE-RISK researchers have developed a tool for AMD risk prediction. From information on age, genetic predisposition, physiology, clinical features and lifestyle the model can predict an individual person's risk to develop AMD. The model shows excellent discriminative performances and has been integrated into a website, which will be made available soon. This will make the provision of personalised health care easier in the future.

Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the project so far)

Analysing and integrating heterogeneous data qualities, EYE-RISK has determined the interrelationship between non-genetic as well as genetic risk factors for AMD. Specific emphasis has been put on the question, how a combination of risks jointly increases the risk for AMD by perturbing homeostasis in the choreocapillaris/Bruchs-Membrane/RPE interface towards a diseased state. Targeted laboratory approaches are currently generating high content datasets to validate two comprehensive in-silico models created by EYE-RISK researchers that are integrating genetic and environmental risks, pathophysiological drivers and mechanisms. Additionally, a risk-prediction algorithm, which will be incorporated in a web-tool available for patients and ophthalmologists is under way. This will allow professional caretakers and patients to gain insight into individual lifestyle-associated parameters that influence disease risk and manifestation. This will provide options and incentives to patients to alter their lifestyle towards influencing their course of AMD.

EYE-RISK logo

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