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Age-related macular degeneration and genomics

Age-related macular degeneration (AMD) is an eye disease in which a person's sight gets progressively worse over time. It is a complex disease with multiple environmental and biological risk factors. Age is the prominent biological risk factor for AMD development and smoking is one of the most strongly associated environmental risk factors. A person's risk is also based on their specific genetic makeup.

Genetic studies have implicated multiple genes and variants in the development and progression of AMD. While there is still information to uncover, potential applications for genetic testing and novel treatment options, including gene therapy, are emerging.

Summary

- AMD is the most common cause of vision impairment in the developed world. Around 5% of those aged 65 and over and around 12% aged 80 and over are estimated to have advanced AMD
- Potential applications of genomic technologies for AMD include genetic testing, the development of polygenic risk scores (PRS) and the development of gene therapies
- More evidence to demonstrate the utility of PRS applications for AMD, further research on the role of genetics in AMD, and the development of personalised treatments and preventative options is required
- Results from early phase clinical trials of gene therapies targeting underlying disease mechanisms look promising but multiple technical and practical difficulties remain

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AMD is a disease characterised by the degeneration of cells within the macula, a small spot in the retina located at the rear of the eye. The retina contains the light sensitive cells, called rods and cones, which are essential for night vision and colour vision, respectively. The macula contains a high density of cone cells. Degeneration in the macula causes blurring and/or dark spots in central vision which can eventually lead to a complete loss of central vision, whereas the peripheral vision stays intact.

AMD can be divided into dry and wet AMD, though the two are not mutually exclusive. In the early stage, both display the accumulation of protein and lipid deposits called drusen. Advanced dry AMD is characterised by atrophy of multiple layers of the retina, referred to as geographic atrophy.

Around 10% of patients develop wet AMD, which is more severe and progresses rapidly. Degeneration is caused by new blood vessel formation in the choroid layer underlying the retina that leak and lead to scarring.

Treatment for wet AMD requires repeated injections of anti-vascular endothelial growth factor (anti-VEGF) into the eye and there is currently no treatment available for dry AMD aside from support with visionary aids. This has stimulated the development of new therapies including the delivery of genes that can ameliorate the disease.

In addition to age, smoking, obesity, and hypertension, risk of AMD is also associated with ethnicity. For example, research found that AMD prevalence was highest in people with European (12.3 %) and Hispanic (10.4 %) ancestry compared to Asian (7.4 %) and African (7.5 %) ancestry. Statistical modelling based on the UN World Population Prospects data, estimates the global prevalence will reach 288 million cases by 2040. Asia is predicted to have the highest number of cases as well as increasing more rapidly than other regions in the coming years. This is largely due to differences in population structure (i.e. an ageing population)[1].

Genetics of AMD

Genetics plays an important role in AMD – its heritability is estimated to be 46% for the development and 71% for severity of AMD, respectively[2]. Sequencing candidate genes in case-control studies and in families with high prevalence of AMD have revealed multiple genetic variants associated with the disease. The largest genome-wide association study for AMD was published in 2016 by the International AMD Genomics Consortium and identified 52 common and rare genetic variants associated with the disease across 34 loci[3]. These associated variants are estimated to account for approximately half of the genomic heritability of AMD[3]. Further large scale studies with different populations are needed to uncover the sources of the missing heritability.

The genes and variants implicated in the development of AMD reveal several potential pathways. The most consistently associated genes/variants are involved in:

- The complement system, the part of the immune system that regulates inflammation, e.g. *CFH* and *CFI*
- The development of new blood vessels, e.g. *HTRA1*
- Transport and metabolism of high-density lipoproteins, e.g. *ABCA1*
- Modulation of oxidative stress, e.g. *ARMS2*

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Genetic testing

Routine genetic testing for AMD is not currently recommended. However, several rare genetic variants that confer a high risk of developing the disease have been identified. Genetic testing of these variants may be valuable, particularly in patients with a strong family history or early onset AMD.

Evidence suggests that some patients with late onset macular dystrophies (i.e. that are caused by single mutations in specific genes) are misdiagnosed with AMD. These diseases[4], which usually present before the fourth decade of life, can be misdiagnosed as AMD if they manifest later than expected since they display similar symptoms to AMD. Obtaining an accurate genetic diagnosis is therefore essential for patients, to decide appropriate treatment options, and for patients' relatives who might have an increased risk of AMD. A genetic diagnosis is also important in preventing the accidental inclusion of patients who do not have AMD in AMD clinical trials.

Risk prediction

Risk prediction models and tools can be based on genetic, clinical and/or environmental risk factors. An area of increasing interest is polygenic risk scores (PRS) and their potential use in prediction models for a multitude of diseases. PRS estimate risk based on the cumulative impact of multiple genetic variants linked to a disease. These are typically common variants that individually confer very small amounts of risk, but when combined can be used to create a meaningful risk score. PRS can be used alone or with other risk factors to predict a person's risk of disease, prognosis and response to treatment. There are several promising areas for the use of PRS that can help to predict those with high risk of AMD or progression to more severe forms.

Public health

AMD is a good example of a complex disease where there is a known strong genetic risk for the development of the disease and the environmental factors are well characterised. Modifiable factors such as smoking, and to a lesser extent obesity, increase the risk of developing AMD and, in people with high genetic risk for the disease, further increases their risk. In the future, risk prediction could be used to identify people with high risk of developing AMD, enabling early preventative action.

Patient care

Risk prediction models for AMD that include PRS have been developed to predict which individuals are at higher risk of developing AMD, progressing to more severe forms and how they respond to treatment. These are yet to reach clinical practice, however there have been some promising results in recent years particularly on predicting severe disease in those with early AMD[5].

Research

PRS could also be useful for selecting participants for clinical trials. For example, choosing those at high risk for progressing to severe AMD for treatment trials aimed at arresting progression, or grouping participants for analyses to determine if PRS or genotype has an influence on treatment response.

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Before we can use PRS for public health activity, patient care or even in research, there needs to be more evidence that these risk scores can be applied across diverse populations. Better understanding of how how genetic and environmental factors interact to cause the disease is also needed. In addition, the utility of using PRS in risk prediction remains uncertain. In particular, whether they add sufficient value to risk prediction and how available interventions can reduce risk and slow progression of the disease. Health economic analysis of this type of intervention is also necessary.

Gene therapy

There are several promising gene therapies undergoing early phase clinical trials for both wet and dry AMD. Typically, they enable the continuous expression of anti-complement (to inhibit inflammation) and/or anti-angiogenic proteins (to reduce new blood vessel formation). A potential benefit of gene therapy is that one dose may be effective for life, reducing the burden on patients and the healthcare system.

Determining the optimum therapeutic gene(s) to deliver and the route of administration, remains challenging. There are also safety concerns to resolve. Effectiveness will depend on disease stage since irreversible loss of photoreceptors in later stages limits the benefits of the therapy. Long term effectiveness remains to be demonstrated, and the effect of chronic, constant suppression of VEGF and complement proteins is a concern. In addition, the difficulties associated with the manufacturing of gene therapies mean the costs associated with the treatment remain high.

Conclusions

Science is revealing important insights into the role of genetic variants on individual AMD risk, and developing novel therapies, including gene therapies, to treat the disease. Improved understanding of the role of genetic variation in AMD is expected to aid the development of validated and useful PRS applications.

The clinical and public health utility of PRS applications remain to be proven but genetic testing is beginning to be used to determine who is eligible to take part in clinical trials. Genetic testing for AMD is expected to become more useful as personalised preventative and treatment options become available.

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