Genetics of AMD

Complement System.

The link between the CFH gene and AMD has been studied intensively. The complement system is a part of the immune system that attacks invading bacteria. Although the liver is the major source of systemic complement, retinal cells make their own complement. As well as the genetic implication of CFH in AMD, raised systemic levels of complement have been reported in AMD patients. Complement proteins have also been detected in drusen, yellowish deposits of an extracellular lipoprotein, which are the earliest visible sign of AMD during an eye exam.

Genetic changes in and around several complement system genes are found to add to a person's risk of developing AMD. Among the known complement genes, it has been found that the complement factor H (CFH) confers the greatest AMD risk.[2,3,4]
CFH usually has the amino acid tyrosine at position 402, but sometimes it has the amino acid histidine instead. This Tyr402His polymorphism seems to be associated with an increased risk of AMD. People who carry a copy of this polymorphism have a 2.5- fold increased risk of developing AMD than people who do not. People who carry two copies of the polymorphism have a six-fold increase, however, most people with these variant never develop the disorder[4]. Although It is suspected that changes in the CFH gene alters the production of CFH protein, how this abnormal protein is linked to the build-up of drusen and progressive vision loss is not well understood.

Researchers in the UK have recently identified a new protein linked to AMD. They found significantly higher levels of a protein called factor H-related protein 4 (FHR-4), a regulator of complement (mentioned above), in the blood of AMD patients in comparison with age-matched control samples. The higher blood FHR-4 levels were associated with changes to genes that code for proteins that belong to the factor H family. These changes also overlapped with genetic variants first found to increase the risk of AMD[5].

This indicates FHR-4 as a key molecular player contributing to complement dysregulation in AMD and it demonstrate FHR-4's prominent role in AMD pathogenesis. It can be presumed that inherited changes can lead to higher blood FHR-4 causes uncontrolled activation of the complement system withing the eye and drive AMD[5].

Drugs that target the complement pathway

Since the discovery of the involvement of the complement system with AMD, pharmaceutical companies have developed therapies targeting the complement pathway to treat and prevent AMD.
A complement inhibitor, which inhibits the Complement 3 (C3) showed promising results in a phase two clinical trial and has now progressed into stage three trials[2].

ARMS2 and HRTA1

Changes in the long (q) arm of chromosome 10 in a region known as 10q26 are also associated with an increased risk of AMD. This region contains two genes ARMS2 and HRTA1, changes in these genes are possible risk factors for AMD.
However, because these genes are so close together, it is difficult to tell which gene is associated with AMD risk, or whether increased risk results from variation in both genes. However, new data indicate that the genetic variants at ARMS2, but not HTRA1 are responsible for AMD risk[6].

Genetic Testing

Routine genetic testing for AMD is not currently advised in clinical practice. However, as there is a list of known AMD-associated genetic variants, genetic testing will allow for the prediction of a person's risk of developing AMD, so that preventive measures can be taken in high risk individuals[6].

Genetic testing will also be an important step towards personalised medicine. Furthermore, it will help to identify which AMD patients are most likely to benefit from certain treatments. For example, it can be expected that therapies modulating the complement system may be most effective in patients harbouring complement-related risk alleles. Lastly, genetic testing may help with the selection of patients for clinical trials.

Rare Variants

Several rare genetic variants have been found to contribute to the development of AMD. Results from a large study of the complete set of human genes reveal possible rare variants associated with AMD. All variants found in this study were seen in/near the complement genes. One of the rare variants was in the CFH gene (Arg1210Cys)[1]. This highly penetrant rare variant is the strongest genetic risk factor for AMD identified to date. People with this mutation are 20 times higher risk of developing AMD compared with people without the mutation[7]. This

mutation is also associated with earlier onset of advanced AMD[6]. Carriers of rare CFH variants tend to have increased drusen load and are more likely to have extramacular drusen and crystalline or calcified drusen.

Other rare genetic variants in and near the complement gene were seen in the CFI, C9, and C3 genes. These variants were more frequently observed in patients with geographic atrophy (GA) than those with wet-AMD.

Other studies have shown rare variants associated with non-complement genes. These variants were seen on the TIMP3 and SLC16A8 genes[6].

The Action You Can Take Now.

In addition to avoiding smoking, and protecting your eyes from the sun, developing a healthy eating habit can help to maintain eye health. It is recommended to avoid artificial fats and processed food as much as possible. Adding foods that are rich in antioxidants such as lutein, zeaxanthin, omega-3 fatty acids, beta carotene, vitamin C/E and zinc to your diet, may help to reduce the risk of AMD, or slow down its progression.

Foods for Healthy Eyes include:

- Fruits and vegetables – most fruits and vegetables including strawberries, oranges, tomatoes, bell peppers and kale contain **vitamin C**

- Almonds, brazil nuts, pecans as well as from vegetable oils (corn oil and olive oil) are good sources of **vitamin E.**

- Dark green leafy vegetables such as spinach, kale, broccoli and asparagus are the primary sources of **lutein and zeaxanthin**.

- Leafy green vegetables, nuts, salmon, vegetable oils and flaxseeds are a good source of **omega3 fatty acid.**

- Deep orange or yellow fruits and vegetables such as carrots, sweet potatoes, peaches and apricots are good sources of **beta-carotene**.

- Beef, pork, lamb, eggs, milk, peanuts, wholegrain and wheat germ are good sources of **zinc** (However be aware that high meat intake is a risk factor for AMD)

- Avocados are one of the most nutrient-dense food that exists. They contain more **lutein** than any other fruit, which is important in the prevention of macular degeneration. They are also a great source **of vitamin A, vitamin C, vitamin B6 and vitamin E.**

AREDS/AREDS2 and Caution

Age-Related Eye Disease Study (AREDS) was a clinical trial that studied the benefits of a nutritional supplement containing high doses of antioxidants, vitamins and zinc in reducing the risk of developing late AMD. Results showed that the combination of antioxidant and zinc reduced the risk of developing advanced stages of AMD by about 25% and also it reduced the risk of central vision loss by 19%[8].

A second study called AREDS2 was carried out to determine if the AREDS could be improved. In this study, beta-carotene was substituted for lutein and zeaxanthin, as beta-carotene was found to be linked to an increased risk of lung cancer in smokers. Therefore, AREDS2 is a safer combination for those who are smokers or former smokers. Results from this study showed that AREDS2 reduced the risk of AMD progression by 19% and of vision loss by 25%[8, 9].

Some publications have recommended that the AREDS formula should be adjusted based on a patients' genetic variants in CFH and ARMS2/HTRA. It was found that patients with high-risk CFH allele and no ARMS2 risk alleles have an increased progression into wet-AMD if treated with the AREDS formulation compared with placebo. Whereas, for patients with low CFH risk allele and high ARMS2 risk alleles, there was a significant beneficial effect from the AREDS formulation treatment[10].

Genetic testing may be a useful method of showing of identifying who is likely to benefit from the AREDS formulation.