What are the biggest impediments in translating genetic research to clinical applications?

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An achievable knowledge gap

Genetic research offers great potential to the eye, and we are very close to getting clinical applications from ocular genetics.


Kang Zhang

We already know a great deal about monogenic disorders in which there is a one-to-one correlation. For example, we know that the ABCA4 mutation will lead to Stargardt's disease. In complex disease, we know a majority of genetic loci of age-related macular degeneration and pseudoexfoliation syndrome. We know that patients who are homozygous for a LOXL1 allele have a 80- to 100-fold increased risk for pseudoexfoliation syndrome. Patients who are homozygous for CFH and HTRA1 risk alleles have a 60-fold increased risk for AMD.

Where we fall short is in validating genetic risk factors for these complex diseases in combination with other predictors such as clinical phenotypes. The goal is to make the genetic tests more predictive and better than the existing predictors based on clinical features. Therefore, genotype-phenotype correlations should be validated in ongoing longitudinal, long-term studies, and I believe we will learn a lot in the next 5 years.

The cost of genotyping is an impediment now too, but will rapidly get cheaper. As they do, through continued validation they will become more useful.

We may soon be able to predict precisely in a population of patients with drusen and know which ones will progress to geographic atrophy or choroidal neovascularization due to their underlying genotypes and their overlying ARDES classifications. We'll also be able to predict for patients who have one eye with advanced forms of macular degeneration, what is the chance the second eye will have macular degeneration due to genetic risks and in what period of time.

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Expanding the toolkit

The initial results of gene transfer in humans with the congenital blinding disease Leber's congenital amaurosis (LCA) have been greeted with excitement by scientists, clinicians and laymen alike. The safety and the proof-of-concept data will likely provide a stepping stone to developing gene therapy for other more common blinding conditions.


Jean Bennett

The challenges are similar to those facing gene therapy for other extra-ocular diseases. First, we need to expand the toolkit that allows efficient and stable delivery of the "therapeutic" DNA or RNA to the target cells. The vector that is being used in the LCA clinical trials, a recombinant adeno-associated virus, is ideal for carrying material up to a particular size (5 kb), but it is difficult to "over-stuff" this vector.

Secondly, while many of the genetic defects leading to blindness have been identified, this list is far from complete. We need to continue to identify these defects so that they can be targets for gene therapy.

Third, the LCA studies used a "gene augmentation" approach – one in which a correct version of the disease-causing gene is supplied to the appropriate cell type. While this strategy will be appropriate for many blinding diseases, others will require a different strategy – one in which a mutant gene is silenced. That strategy is more challenging because it will require high-efficiency gene transfer to the target cells.

There is concern about immune response to either the vector or new proteins formed in the target cell. Although the eye is an ideal target for gene therapy from an immunological perspective, further study must identify conditions that could lead to inflammation so that these can be avoided.

Finally, because there are so many different genes that have been implicated in eye disease, it will be difficult from an economic perspective to develop a drug for each one.

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