DELIVERING THE ARVO/Alcon Keynote Lecture during the annual meeting of the Association for Research in Vision and Ophthalmology, Roderick R McInnes MD, PhD predicted major advances in understanding of the genetics of eye diseases are forthcoming within the next decade.

“Trying to predict the future can be hazardous. However, considering the extensive amount of exciting research underway in genetics and biology, I think it is safe to say that patients and physicians have a great deal to look forward to,” said Dr McInnes. Alva chair in human genetics, director, Lady Davis Research Institute, and Canada research chair in neurogenetics, at the Jewish General Hospital of McGill University, Montreal, Canada.

Interestingly, about 2,500 of the 7,000 known human single gene diseases involve the eye, and although all parts of the eye are represented among the monogenic diseases, it is also remarkable that the number of genes (190 loci, at which the gene has been identified in 155) in which mutations cause retinal degeneration is much greater than the number affecting any other part of the eye, noted Dr McInnes, who is also professor, departments of human genetics and biochemistry, McGill University, Montreal.

So far, the causative gene has been identified for fewer than half of known single gene diseases, and it is believed that another 4,500 to 7,000 more single gene diseases will eventually be identified. While these numbers suggest a monumental challenge, Dr McInnes predicted that the causative gene for virtually all presently known monogenic disease will be identified within the next five to 10 years, thanks to developments in sequencing technologies.

“Recently introduced sequencing technologies are very fast compared with the old tedious methods and relatively inexpensive. Consequently, whole genome sequencing can often find a mutation in a single affected individual without any family history pattern. As the cost per sample for this sequencing continues to fall and reaches $1000 per genome, which geneticists have considered a Holy Grail for maximising the potential of genomic medicine, the capabilities of this technique will have a huge impact on medicine,” said Dr McInnes.

The power of next-generation sequencing for identifying the causative gene is illustrated by recent research using high-throughput DNA sequencing to resolve the complex genetics of retinitis pigmentosa. As reported in a recent paper [J Med Genet 2011;48:145-51], application of this technology identified the involved gene in four of five unrelated patients with classical RP phenotypes. The same technology also led to identification of a new RP-associated gene, that for dehydrodolichol diphosphate synthase (DHDDS), in three siblings with RP. The disease gene in this family had not been identifiable using earlier techniques.

“This technology does not always find the mutant gene, but it is a great improvement over what has been done until now. In just two years since exome sequencing was introduced, to date it has been used to identify more than 30 diseases. This is remarkable progress...”

Roderick R McInnes MD, PhD

In just two years since exome sequencing was introduced, to date it has been used to identify more than 30 diseases. This is remarkable progress...

Roderick R McInnes MD, PhD

Although the discovery of genetic variant(s) in any individual may not be useful for predicting disease development, identification of these susceptibility genes is important as it can provide valuable insight into the pathophysiology of the disease. To this end, researchers worldwide are working to identify the cohorts of genes that confer risk to various common diseases and will be trying to weave this information together to construct a genetic and biologic network to explain the genetic risk for each disease.

“This will be hard and slow work for biologists in addition to geneticists, but the task will be facilitated by worldwide consortiums that are creating and bioinformatic mouse and yeast knockouts, to allow a systems approach to elucidating the biology of newly identified disease-related genes,” Dr McInnes said.