Genomics and proteomics

Genomics and proteomics of retinopathy of prematurity: DNA-based prevention and treatment

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Genetic factors play a role in causing retinopathy of prematurity: genetic evaluation could eventually lead to earlier identification of infants in need of screening and treatment

With the advent of new treatments and improved precision in the timing of treatment, retinopathy of prematurity (ROP) is slowly morphing into a chronic illness. To be sure, blindness in infancy from ROP remains a possible outcome, even with the best surgical management. Nevertheless, problems of reduced visual acuity, high myopia, nystagmus, strabismus, late retinal detachments, and glaucoma, occur in children who had severe ROP. These problems last a lifetime, even though they do not cause blindness in infancy.

What causes these chronic problems, and what causes the disease in the first place? We know a lot about some of the risk factors for ROP, such as low birth weight and gestational age. Is it simply peradventure that two similar infants, side by side in the same nursery, with the same general hospital course, could have highly discrepant outcomes? Why does one child with advanced ROP develop myopia, and another not? What are the factors that result in retinal detachment in one child and not the other?

The answer to these questions is that genetic factors surely play a role in causing ROP and its complications. In this month's *British Journal of Ophthalmology*, Holmström and colleagues describe their *perspective* on evidence favouring genetic causation in ROP ***(see page 1704)***.[1] From mice to humans, there is abundant evidence that genetic factors are important to the development and progression of the disease. The authors' conclusion, that genetic evaluation could eventually lead to earlier identification of infants in need of screening and treatment is particularly exciting. We can only hope that in the future, screening guidelines will be dictated by factors other than gestational age and birth weight of the infant.

To the clinician, there are at least three compelling reasons to suspect genetic factors in ROP. The first of these is that ROP development is timed to the gestational age of the infant, and not to the infant's chronological age. This suggests that inherent factors at least partially promote a timely progression of disease development. Second, as noted by the authors, pigmentation plays a significant role in who develops severe disease. Caucasian children in the US are more likely to suffer the effects of ROP than are African-American infants. Third, twins are more likely to develop concordant disease.

Research into identification of genes involved in ROP should include a proteomics approach. The authors note that the protein, insulin-like growth factor-1, is a plausible culprit in ROP, for example. For the initiate in this field, and in simple terms, a proteomics approach involves screening all or nearly all proteins in an individual's blood at a given point in time. The use of mass spectroscopy tools, and complex bioinformatics algorithms, allows comparison of one individual's protein constituency to another's. Also possible is a comparison of protein distribution in the same individual, but at different times in the course of a disease. Differences in protein expression can be evaluated. Once differences are identified, the possibility that expression of a given protein during active disease plays a role in the disease can be evaluated. The protein can be sequenced, and its gene identified.

Proteomics and genomics are not immiscible. Proteins regulate and affect diseases and homeostasis at given times. Genes, even though they may be responsible for the proteins that contribute to a disease, are not necessarily "switched on" during the disease process. It is not enough to identify genetic mutations and polymorphisms statistically associated with ROP. The next step should include confirmation that the presence, absence or alteration of an *expressed* protein is linked to ROP. Furthemore, protein expression can occur as a result of environmental effects (eg, perinatal events, oxygen exposure, sepsis and so on), and thus proteomics considers effects that we know also contribute to the disease. It is also likely that ROP will be found to be a disease characterised by changes in the expression and functional patterns of the products of several or many genes. As we learn more about the specific genes and proteins mediating ROP, "proteomes" reflecting the ROP disease state and the stages through which ROP progresses might eventually be measurable in sera of individuals and might serve as useful diagnostic and prognostic indicators. These approaches will no doubt rely heavily on the technological advances being made in mass spectrometry and bioinformatics.

This brings us back to our original thought, that ROP has become a chronic disease. Most children in a paediatric ophthalmology clinic suffer the effects of severe ROP after the acute phase regresses. Thankfully, only a few are blinded by the disease. A genomic/proteomic approach to these complications of ROP will be important to the identification of risk factors and, ultimately, causes of myopia, reduced visual acuity, glaucoma, and so on.

The rate of unfavourable structural outcome in high-risk prethreshold ROP is probably now less than 10% in Western countries. New strategies to reduce rates of blindness and eliminate chronic complications are going to be medical, and should target prevention of the disease and all of its various complications. Holmström and colleagues offer an excellent guide for how to begin searching for non-surgical approaches to prevention and management of ROP.

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REFERENCE

1 **Holmström G**, van Wijngaarden P, Coster DJ, *et al.* Genetic susceptibility to retinopathy of prematurity—the evidence from clinical and experimental animal studies. *Br J Ophthalmol* 2007;**91**:1704–8.