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The Genetics of Retinopathy of Prematurity: A Model for Neovascular Retinal Disease

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Topic: Retinopathy of prematurity (ROP) is a proliferative retinal vascular disease in premature infants and is a major cause of childhood blindness worldwide. In addition to known clinical risk factors such as low birth weight and gestational age, there is a growing body of evidence supporting a genetic basis for ROP.

Clinical Relevance: Although comorbidities and environmental factors—most notably gestational age and oxygen—have been identified as contributing to ROP outcomes in premature infants, some infants progress to severe disease despite absence of these clinical risk factors. The contribution of genetic factors may explain these differences and allow better detection and treatment of infants at risk for severe ROP.

Methods: To comprehensively review genetic factors that potentially contribute to the development and severity of ROP, we conducted a literature search focusing on the genetic basis for ROP. Terms related to other heritable retinal vascular diseases such as "familial exudative vitreoretinopathy," as well as to genes implicated in animal models of ROP, were also used to capture research in diseases with similar pathogenesis to ROP in humans with known genetic components.

Results: Contributions across several genetic domains are described, including vascular endothelial growth factor, the Wnt signaling pathway, insulin-like growth factor 1, inflammatory mediators, and brain-derived neurotrophic factor.

Conclusions: Most candidate gene studies of ROP have limitations such as inability to replicate results, conflicting results from various studies, small sample size, and differences in clinical characterization. Additional difficulty arises in separating the contribution of genetic factors such as Wnt signaling to ROP and prematurity. Although studies have implicated involvement of multiple signaling pathways in ROP, the genetics of ROP have not been clearly elucidated. Next-generation sequencing and genome-wide association studies have potential to expand future understanding of underlying genetic risk factors and pathophysiology of ROP. *Ophthalmology Retina 2018;■:1–14 © 2018 by the American Academy of Ophthalmology*

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Retinopathy of prematurity (ROP) is a retinal vascular disorder affecting premature low-birth-weight infants and is a major cause of childhood blindness in the United States and internationally. Beyond its clinical impact, infancy-acquired visual loss from ROP represents an enormous social and economic burden.[1–4] Furthermore, as the incidence of premature births worldwide increases and as medical technology becomes better able to treat the complications of premature birth, the number of infants at risk for ROP is increasing rapidly.[5–8]

Oxygen plays a central role in ROP.[9–13] The oxygen environment and a key transcription factor that oxygen regulates (e.g., hypoxia-inducible factor [HIF]) are thought to modulate ROP. In terms of ROP pathogenesis, a 2-phase hypothesis has been proposed and has become widely accepted.[14,15] In phase 1, there is delayed physiologic retinal vascular development and vasoattenuation, which is aggravated by hyperoxia and loss of nutrients and growth factors. In phase 2, vasoproliferation occurs at the junction of vascularized and avascular retina. The mouse oxygen-induced retinopathy (OIR) model (exposure to 75% oxygen for 5 days followed by room air), a widely used animal model of ROP, best represents the 2-phase hypothesis.[16,17] During the vasoproliferative phase, the avascular retina releases proangiogenic growth factors such as vascular endothelial growth factor (VEGF), which are induced by hypoxia and may cause aberrant vessel growth and neovascularization. Oxygen fluctuations with intermittent hypoxia are also implicated in development of ROP in clinical studies[18–20] and OIR animal model studies, especially in rats (e.g., cycling between 50 and 10% oxygen).[21,22] Growing neovascular vessels lead to fibrovascular membranes that may pull on the retina, causing tractional retinal detachment and eventual blindness. The phenotype of ROP is classified based on location, extent, and severity of these pathologic changes.[23] Some infants show a rapidly progressing, severe form of ROP, known as aggressive posterior ROP.[23–27]

Early investigations into ROP risk factors focused primarily on prematurity itself, as well as environmental factors, including oxygen exposure after birth.[10,11] Various

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studies focusing on oxygen exposure have proven its importance as a primary predictor of ROP outcomes.[9–11] However, in some high-risk infants with extremely low birth weight and gestational age, ROP does not develop, whereas severe ROP does develop in some low-risk infants. In these infants at phenotypic extremes, a study showed that known clinical risk factors were not significantly associated with development of ROP.[28] In addition, it is not understood why certain infants are predisposed to aggressive posterior ROP with very high likelihood of blindness. This heterogeneity of ROP risk suggests that other factors such as genetics may be involved in creating a predisposition to ROP. Before specific genetic variations were investigated in ROP, epidemiologic studies suggested racial and ethnic differences in ROP incidence.[29–31] The Cryotherapy for Retinopathy of Prematurity study of 4099 premature infants found 7.4% of white infants reached threshold disease, whereas only 3.2% of black infants achieved a similar level of disease.[31] Also, twin and sibling studies have supported the involvement of a genetic component of disease. Two studies of monozygotic and dizygotic twins found that the heritability of ROP was 0.70 and 0.73, respectively.[32,33] Evidence of genetic effects is also supported by data from the OIR phenotype in rodent models, in which studies of different rat strains have found differences in the retinal avascular area and VEGF expression between strains.[34–36] Investigations into this genetic component in humans and animal models have implicated the involvement of multiple genes, but they have not discovered a genetic component of large effect. It is likely that knowledge of such a genetic component could be used to identify possible targets to improve outcomes of screening and treatment.

Many signaling molecules and related pathways have been suspected in the pathogenesis of ROP due to known biochemical and clinical associations: VEGF, insulin-like growth factor-1 (IGF-1), erythropoietin (EPO), and inflammatory mediators. In addition to ROP, the growth of abnormal, leaky blood vessels is a common pathologic component of other blinding neovascular eye diseases, such as diabetic retinopathy (DR) and neovascular age-related macular degeneration (AMD), both of which have strong evidence of a genetic predisposition to disease.[37–39] Moreover, because ROP progresses more rapidly and presents with relatively homogeneous clinical characteristics, the correlation of genotype and phenotype is easier than with a chronic disease such as DR or AMD.[15] Thus, the study of ROP genetics may provide important insights into the pathophysiology of other more prevalent adult and pediatric neovascular retinal diseases.

This review summarizes current research into genetic factors contributing to ROP risk in both human and animal models and recommends future directions for research into the underlying genetics of pathways that contribute to disease.

Methods

PubMed was queried from January 1980 to June 2017. The following search terms were used: *retinopathy of prematurity* AND *genetics, retinopathy of prematurity* AND *gene, retinopathy of prematurity* AND *single-nucleotide polymorphism (SNP), retinopathy of prematurity* AND *variant, and retinopathy of prematurity* AND *polymorphism*. Criteria for inclusion included the relevance, clinical importance, level of statistical evidence provided, and scientific importance of articles to the subject of this article. Articles cited in the reference lists of other articles were reviewed and included when considered appropriate. All articles with English abstracts were reviewed.

Candidate Genes in ROP

VEGF and Associated Receptors

VEGF plays a crucial role in ROP. Increased VEGF in avascular retina stimulates pathologic retinal neovascularization, which may result in blinding complications such as tractional retinal detachment. Moreover, VEGF is a proven therapeutic target, as intravitreal anti-VEGF therapy has shown efficacy in promoting regression of severe ROP.[40] There have been many genetic studies on associations between the VEGF gene and incidence or severity of ROP.

Table 1 summarizes results of SNP studies in the human VEGF gene (*VEGFA*). Among these results, rs2010963 (also known as −634G>C and +405G>C) is the most extensively studied SNP. In a British study on rs2010963 of 188 preterm infants in 2004, the G allele was found to have higher frequency among infants with ROP.[41] This result was supported by a 2015 study in 102 preterm infants from Egyptian hospitals showing that the G allele was significantly higher in infants with ROP.[42] However, 1 study in Hungary reported the opposite results—higher frequency of the C allele in severe ROP—and 5 other studies found no significant association between rs2010963 and ROP.

In addition, rs833061 (−460C>T) and *VEGFA* +13553C>T have been reported to be associated with ROP. However, replication has not been attempted for +13553C>T, and the association of rs833061 and ROP has not been replicated in 3 other studies. *VEGFA* haplotypes have also been reported to be associated with ROP. A study performed in an Italian population of 342 infants that focused on the distribution of polymorphisms in a handful of genes implicated in ROP showed evidence that the *VEGFA* haplotype (TCCT) decreases the risk of ROP.[43]

VEGF promotes angiogenesis and hyperpermeability by binding to the VEGF receptor 2 (VEGFR-2) on the vascular endothelium, whereas VEGFR-1 acts as a decoy receptor.[44] However, studies on the VEGFR-1 (*FLT1*) and -2 (*KDR*) genes found no associations with ROP (Table 2).

Familial Exudative Vitreoretinopathy, Norrie Disease, and the Wnt Pathway

Familial exudative vitreoretinopathy (FEVR) and Norrie disease are developmental diseases of the retina with known genetic causes with similar pathology to ROP. Both are hereditary disorders occurring primarily in full-term infants, characterized by abnormal retinal vascularization leading to retinal detachment.[45,46] Although patients with Norrie disease are blind from or shortly after birth and often have systemic pathologies such as deafness and mental retardation, the clinical manifestations of FEVR are variable but restricted to abnormalities in ocular development.[47] FEVR

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