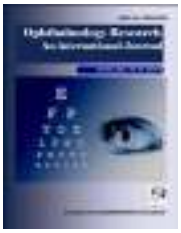

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Genetic Predisposition to Advanced Retinopathy of Prematurity (ROP) Gains Support

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Author's contribution

This work was carried out by the author BSS. Author BSS read and approved the final manuscript.

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ABSTRACT

Aims: The purpose of this short review is to summarize the recent developments in the genetics of retinopathy of prematurity.
Background: Retinopathy of prematurity is a well known blinding disorder in children in both developed and developing countries. It is characterized by the hypovascularization of the peripheral retina in children with a short gestational age and low birth-weight. Morphologically it is similar to familial exudative vitreoretinopathy (FEVR) but FEVR patients do not have the history of oxygen therapy and prematurity. ROP is a life time disease and patients can still have long-term effect even after timely treatment. Although many causative factors have been suggested, the pathogenesis of ROP is not understood. Some of the unpredictability of ROP could be due to genetic factors.
Methodology: Using the key words or phrases such as ROP, genetics, animal models and pediatric retinal disorders, the literature search was carried out.
Results: Molecular genetic analysis has identified mutations in three of the four FEVR causing genes in patients with advanced ROP in different ethnic backgrounds. These three genes are involved in a highly regulated Wnt signaling pathway that controls the development of the retinal vasculature. The genetic association of ROP was further supported by the higher concordance rate of the disorder in monozygotic twins, racial variation, strain dependent difference in oxygen-induced ROP in inbred rats and the existence of quantitative loci on chromosome 7 and 9 that modify susceptibility to oxygen-induced ROP.

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Conclusion: Although much remains to be done in the field of ROP, the above finding supports a role for the Wnt signaling pathway in the development of severe ROP. The availability of animal models may provide opportunities for the development of novel therapeutic approaches to prevent or treat this pediatric blinding disorder.

Keywords: Blindness; gene; mutation; polymorphism; retina.

1. INTRODUCTION

Retinopathy of prematurity (ROP) is a major cause of childhood blindness that predominantly occurs in infants with short gestational age and low birth-weight. It is a vasoproliferative eye disorder that affects both the retina and the vitreous body. The disorder is characterized by the abnormal vascularization of the peripheral retina that may lead to retinal fold and retinal detachment resulting in blindness. ROP occurs in two phases. In phase I, hyperoxia (because of supplemental oxygen) causes cessation of normal retinal vascularization and in phase II, hypoxia renews vascularization. In both of these cases vascular endothelial growth factor (VEGF) plays a major role [1-2] and depending on the local retinal responses, the effect can be normal or abnormal vascularization. The disorder is clinically similar to genetically heterogeneous inherited eye disorder called familial exudative vitreoretinopathy (FEVR). However, the affected individuals of FEVR have a normal gestational period and do not have the history of oxygen therapy. Both of these disorders carry a high financial cost for the community and the individual by affecting the normal motor, language, conceptual and social development of the child. Of the four thousand children affected by ROP each year, approximately 10% of them develop severe form of the disease even after timely medical intervention and become blind. ROP is a life time disease. In some children, the disorder may regress and they may not need any treatment. However, these same children may later develop visual impairment from retinal detachment [3]. Although many causative factors such as excessive light exposure, length of time exposed to supplemental oxygen and hypoxia have been suggested, the pathogenesis of advanced ROP is not understood [4]. However, low birth-weight and short gestational age have been consistently shown to be associated with ROP. It is unclear why ROP in a subset of infants with low birth-weight progresses to a severe stage despite timely intervention whereas in other infants with similar clinical characteristics, ROP regresses spontaneously. It is possible that in addition to prematurity and environmental factors, there may be a strong genetic predisposition to ROP [5].

2. GENETIC ANALYSIS

The relationship between the genotype and phenotype is complex and is not straightforward. However, it is possible that in several distinct disorders that have clinical similarities, different phenotypes could be due to allelic heterogeneity at a single locus. This idea has prompted several investigators from around the world to analyze DNA from ROP babies. Many studies have employed stage 4 to 5 ROP patients with an average gestational age 22 to 29 weeks and birth weight of 422 to 1244 g using the International Classification system of ROP. These studies have also used different types of controls but many of them used controls with same gestation age without ROP or regressed ROP. As a result of genetic analysis, it was found that in a small percentage (5-12%) of ROP patients from several different ethnic backgrounds three of the four FEVR causing genes encoding Norrin (NDP), frizzled 4 (FZD4) and low density lipoprotein receptor protein 5 (LRP5) are mutated [6-10]. Mutations

were not reported to date in the fourth FEVR causing gene (TSPAN 12) encoding a member of the tetraspanin family (Table 1). Most of the mutations identified in NDP gene are either insertions (large and small) or deletions or single nucleotide polymorphisms (SNPs) in 5'- and 3' untranslated regions (UTR). These changes may not affect the protein structure but they may have an effect on the gene expression at the levels of transcription and translation. On the other hand, mutations in FZD4 and LRP5 genes are missense changes that may affect the protein functions. Affected individuals with different mutations exhibited variable phenotypes such as aggressive posterior ROP and retinal detachment. The NDP gene encodes a protein called norrin that acts as a ligand for FZD4. The binding of ligand to the receptor activates the specific branch of the Wnt signaling pathway. Similarly, Wnt requires interaction with another single transmembrane receptor LRP5 [6-8]. The genetic association of ROP was further supported by the higher concordance rate of the disorder in monozygotic twins, racial variation and strain dependent difference in oxygen-induced ROP in inbred rats. The prevalence of mutations in three FEVR causing genes in ROP may be correlated with ethnic differences. All studies were conducted using a small number of patients and hence their statistical significance cannot be addressed at present. It is also relevant to add that the NDP, FZD4 and LRP5 genes are not the major genes independently accounting for a significant portion of ROP patients. Interestingly, in a limited number of cases of clinically similar diseases such as persistent fetal vasculature (PFV) and Coats' disease, two of the four FEVR genes (NDP and FZD4) are also mutated [6] suggesting allelic heterogeneity at a single locus.

All of the above four proteins are involved in a specific branch of the beta-catenin mediated Wnt signaling pathway and are expressed in several tissues including retina. This pathway is highly conserved in several species and controls the development of retinal vasculature [11-12]. It was also reported that Wnt signaling mediates pathological vascular growth in proliferative retinopathy [11]. Norrin also promotes vascular regrowth in oxygen-induced retinopathy in mice [13-14] and has neuro- and vasculo-protective effects on retinal ganglion cells [15]. In genetically engineered mice, abnormal norrin production leads to either premature retinal vascular invasion or defects in intraretinal vascular architecture [16]. These results demonstrate the importance of Wnt signaling pathway in inner retinal vascular development. Mutations in the three genes of Wnt pathway produce deficit in the signaling that may lead to abnormalities in the vascularization of the peripheral retina. This has been further confirmed by the development of knockout mice for all of the above four FEVR genes [6]. Although these mice models did not exactly replicate the human phenotype (FEVR) such as avascular peripheral retina and severe sight threatening complications, some of them exhibited degeneration of the outer retina, delayed hayloid vessel regression, disorganization and loss of ganglion cell layer and malformation of the retinal vasculature. It will be interesting to see if these mice models when exposed to hyperoxia will be more susceptible to develop ROP like pathology.

Table 1. Mutations in NDP, FZD4 and LRP5 genes identified in patients with severe ROP

Gene	cDNA sequence change	Amino acid Sequence change	Frequency	Population	Reference*
NDP	Mostly ins, del, and SNP in 5' and 3'UTR	----------	----------	African-American, Caucasian, Japanese, Kuwaiti	[6]
FZD4	c. C205T	H69Y	1/53	Japanese	[9]
	c. G380A	R127H	1/53	Japanese	[9]
	c. G609T	K203N	1/71	Caucasian	[6]
	c. T631C	Y211H	2/53	Japanese	[9]
	c. A766G	I256V	1/20	Caucasian	[6]
	c. C1109G	A370G	1/71	Caucasian	[6]
LRP5	c. G3656A	A1219H	1/53	Japanese	[9]
	c. A4148C	H1383P	1/53	Japanese	[9]
	c. C4619T	T1540M	1/53	Japanese	[9]
	CTG ins in exon 1	Ins Leu in signal peptide	1/17	Japanese	[6]
	CTGCTG ins in exon 1	Ins LeuLeu in signal peptide	2/53	Japanese	[9]

*UTR =untranslated region; ins = insertion; del = deletion; SNP = single nucleotide polymorphism; * = some of the original references are cited through the reviews to reduce the number of references.*

3. DISCUSSION

Recent research with candidate gene approach, higher concordance rate in monozygotic twins and other clinical and experimental animal studies suggest a strong genetic predisposition to ROP besides environmental factors such as prematurity. Three genes that are involved in the Wnt signaling pathway, are mutated in both FEVR and in a small percentage of ROP disorder implying that some of the Wnt signaling pathway genes (NDP, FZD4 and LRP5) play a role in the development of advanced ROP. The significance of mutations can be tested either by using the mutation selection hypothesis (for rare variants) or the disease common variant hypothesis (for common variants). However, there are many questions that need to be answered before any conclusion can be drawn. For instance, it is not clear whether these ROP patients that harbored mutations are indeed FEVR patients who have been born prematurely. This is because the number of patients harboring mutations is very low and they are only found in severe cases. However, the genetic association of ROP was further supported by the existence of quantitative loci on chromosome 7 and 9 that modify susceptibility to oxygen-induced ROP [17]. In addition, development of severe zone III ROP in an infant with birth-weight more than 1500g [18] suggests that birth-weight alone is not enough to cause severe ROP. Additionally, in non-black infants a significant association between assisted reproductive technology and severe ROP has been reported which may point to genetic predisposition to the disorder [19]. Unfortunately, we cannot address the functional significance of mutations because they are not available. However, many changes were in highly conserved amino acids and predicted to be pathogenic. Phenotypic severity may depend upon the functional effects of mutations. Missense mutations for instance, might moderately reduce the signal transduction and

produce milder phenotypes. However, there is no correlation between sequence changes and the phenotype. It may be the combination of genetic and environmental factors (prematurity) that causes severe ROP. It must also be noticed that ROP is most likely a non-familial disease and only a small fraction of patients harbor mutations in Wnt signaling pathway genes. Many times it is difficult to explain sporadic diseases. For instance, in some cases of hereditary colorectal cancer, no mutations have been found in several mismatch repair genes. However, an epimutation (epigenetic modification linked with disease) of the MLH1 gene that silences its expression has been reported [20-21]. Therefore, sporadic diseases can be associated with somatic epimutation that converts normal allele to epiallele that associates with disease risk. This could be the case of ROP.

Therefore, it is possible that many other members of the Wnt signaling pathway or other genes could contribute to severe ROP similar to other retinal disorders. ROP being multifactorial disease it might require contribution from more than one gene in concert with an environmental insult and sum of the genetic contribution would make the child more sensitive to the disease. In accordance with this notion, some studies have reported an association between ROP and VEGF, angiotensin converting enzyme gene polymorphism and cholesterole ester transfer protein gene. However, these studies are either controversial or need to be confirmed in a larger independent population. Similarly, insulin-like growth factor-1 (IGF-1) receptor polymorphism was not found to be associated with the development of ROP [22-23]. Therefore, these genes are not the major risk factors contributing to the risk and severity of ROP [24]. Only the study that is replicated at least twice is the association of the endothelial nitric oxide synthase (eNOS) gene promoter polymorphism (T-786C) with ROP [25-26]. The validity of this result however, depends upon a large-scale study of a mixed population. Although much remains to be done in the field of ROP, the above finding supports a role for the Wnt signaling pathway in the development of severe ROP. Future studies must address the functional significance of each mutation and large-scale analysis using a mixed population of ROP patients to understand the true roles of genetic and epigenetic impact on the progression of ROP. The availability of animal models may provide opportunities for the development of novel therapeutic approaches to prevent or treat this pediatric blinding disorder.

4. CONCLUSION

Recent research with candidate gene approach, higher concordance rate in monozygotic twins and other clinical and experimental animal studies suggest a strong genetic predisposition to ROP besides environmental factors such as prematurity. Three genes which are involved in the Wnt signaling pathway, are mutated in both FEVR and in a small percentage of ROP disorder. However, none of the genetic factors identified thus far in ROP account for a substantial number of patient population. Future studeis involving genomics, bioinformatics and proteomics may provide a better understanding of the pathophysiology and management of ROP.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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