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Review article

Complex genetics of familial exudative vitreoretinopathy and related pediatric retinal detachments

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ABSTRACT

Familial exudative vitreoretinopathy (FEVR) is a hereditary vitreoretinal disorder that can cause various types of retinal detachments. The abnormalities in eyes with FEVR are caused by poor vascularization in the peripheral retina. The genetics of FEVR is highly heterogeneous, and mutations in the genes for Wnt signaling and a transcription factor have been reported to be responsible for FEVR. These factors have been shown to be the regulators of the pathophysiological pathways of retinal vascular development. Studies conducted to identify the causative genes of FEVR have uncovered a diverse and complex relationship between FEVR and other diseases; for example, Norrie disease, a Mendelian-inherited disease; retinopathy of prematurity, a multifactorial genetic disease; and Coats disease, a nongenetic disease, associated with pediatric retinal detachments.

1. Introduction

A pediatric retinal detachment is a highly heterogeneous condition. Compared with adult retinal detachments in which the rhegmatogenous form is most common, pediatric retinal detachments can be of various types, and a genetic involvement is highly likely. The diagnosis and referral of pediatric retinal detachments are generally delayed, and the presence of other congenital anomalies makes the management difficult. However, understanding the etiology of pediatric retinal detachments can lead to better management. Moreover, understanding the genotype–phenotype relationship can provide additional information that can lead to more accurate genetic counseling.

One of the most frequent causes of pediatric retinal detachments is found in cases of familial exudative vitreoretinopathy (FEVR; MIM number 133780). FEVR was first described by Criswick and Schepens[1] in 1969 as a hereditary vitreoretinal disorder. FEVR was reported to cause a reduction of vision due to various types of retinal detachments such as congenital retinal detachment with leukocoria, falciform retinal folds, exudative retinal detachment, and rhegmatogenous retinal detachment. The retinal detachments develop during the first three decades of life.[2,3] The pathogenesis of the retinal detachments in eyes with FEVR is poor vascularization in the peripheral retina.[4]

During the past decade, several genes have been identified as the cause of FEVR, and as the regulators of a new signaling pathway involved in retinal vascular development. Identification of the causative genes has uncovered a diverse and complex relationship of FEVR with other types of pediatric retinal detachments.

The aim of this review is to characterize FEVR and related pediatric ocular diseases with retinal detachments in regard to the genes and heredity. These retinal detachments have been categorized into the following three groups: Mendelian-inherited diseases, multifactorial genetic diseases, and nongenetic diseases (Table 1).

2. Genetics of FEVR and related inherited diseases

FEVR is genetically heterogeneous, and its inheritance patterns can be autosomal dominant, autosomal recessive, or X-linked recessive. The autosomal dominant form is the most common, and the sporadic form is frequently detected with a prevalence of up to 50% in all the FEVR cases. To date, four genes are known to be responsible for FEVR, namely, *FZD4* (frizzled-4), *NDP* (Norrie disease pseudoglioma), *LRP5* (low-density lipoprotein receptor-like

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Table 1
Categories of diseases involving familial exudative vitreoretinopathy and related genes.

Class	Heredity	Bilaterality	Diseases	Genes
1	Monogenic	Bilateral	FEVR, Norrie disease, osteoporosis–pseudoglioma syndrome Persistent fetal vasculature syndrome	*FZD4, LRP5, TSPAN12, NDP, ZNF408* *ATOH7*
2	Multigenic	Bilateral	Retinopathy of prematurity	*FZD4, LRP5, NDP*
3	Nongenic	Unilateral	Coats disease	*NDP*

FEVR = familial exudative vitreoretinopathy.

protein 5), and *TSPAN12* (tetraspanin 12). These genes are responsible for nearly 50% of the FEVR cases.[5–7]

2.1. Frizzled 4 (FZD4) gene

FZD4 is a gene encoding the Wnt receptor. Wnt is a member of a family of secreting proteins that regulate signaling in cellular systems throughout the animal kingdom.[4] The Wnt proteins are cysteine-rich glycoproteins that play a pivotal role in various cellular processes, including determination of cell fate, control of cell polarity, and control of malignant transformation.[8] Thus far, 20 Wnt ligands and 10 frizzled receptors have been identified in mammals.[9] The human *FZD4* gene codes for a 537-amino-acid protein. *FZD4* is expressed in the retina, and is considered to function during the normal development of retinal vessels by activating the canonical Wnt/β-catenin pathway and targeted genes.[10–12] An absence of *FZD4* leads to defective vascular development with subsequent retinal neovascularization and exudation.

Thus far, 59 different mutations (41 missense, 8 nonsense, and 10 deletion/insertion mutations) in the *FZD4* gene are known to cause FEVR according to Human Gene Mutation Database (HGMD; accessed Jan 2015). Heterozygous mutations in the *FZD4* gene are known to cause autosomal dominant FEVR.[10]

The severity of retinopathy tends to vary considerably even with the same mutation, but a dosage sensitivity may exist. A homozygous state for the *FZD4* gene (p.R417Q) has been reported, and it caused a more severe retinopathy than that in the heterozygous parents.[13]

2.2. NDP gene

Norrie disease is a rare, X-linked recessive disorder characterized by congenital blindness due to retrolental masses referred to as “pseudogliomas” or “retinal dysplasia”.[14] Mental retardation and hearing loss are also observed in ~25% of the cases.[14] Norrie disease is genetically homogeneous and is caused by mutations in the *NDP* gene that codes for a 133-amino-acid protein called “norrin”.[15,16] This protein does not have sequence identities with other known proteins, but sequence comparisons and modeling studies have predicted that its tertiary structure has a strong resemblance to transforming growth factor-beta.[17,18] Despite no discernible sequence homology with the Wnt family, norrin encoded by the *NDP* gene has been recently identified as a specific ligand for FZD4.[11] Therefore, the Wnt/β-catenin pathway activated by the norrin ligand is called the “norrin/β-catenin signaling pathway” that is associated with the vascularization of the developing retina.[12]

A large number of mutations in the *NDP* gene have been described: 20 translocation and inversion mutations, 31 deletion/insertion mutations, and 95 point mutations (HGMD). The *NDP* gene is also responsible for X-linked recessive FEVR.[19] Different structural alterations in norrin may lead to different degrees of phenotypic severity.[20] Deletion and truncation mutations in the *NDP* gene cause Norrie disease, whereas missense mutations cause either FEVR or Norrie disease.[20] Missense mutations that do not disrupt any predicted disulfide bonds are more likely to express milder phenotypes of FEVR.[17,20,21]

2.3. LRP5 gene

The *LRP5* gene is a member of the low-density lipoprotein receptor family. It codes a 1615-amino-acid protein that consists of four domains, each composed of six YWTD repeats that form a beta-propeller structure and an epidermal growth factor-like repeat.[22] These domains are followed by three ligand-binding domains, a transmembrane domain, and a cytoplasmic domain. In the norrin/β-catenin signaling pathway, LRP5 acts as a functional receptor pair with FZD4.[22–25] Loss-of-function mutations in the *LRP5* gene are associated with the recessive osteoporosis–pseudoglioma syndrome (OPPG; MIM number 259770), which is characterized by osteoporosis and blindness.[23] Heterozygous mutations in the *LRP5* gene are known to cause autosomal dominant FEVR,[26,27] and homozygous mutations in *LRP5* are also known to cause autosomal recessive FEVR.[28] The spectrum of *LRP5*-related diseases indicates that FEVR is a milder form of OPPG in terms of the eye symptoms. Ninety-four mutations in the *LRP5* gene are known to cause either OPPG or FEVR (HGMD). FEVR patients with *LRP5* mutations are known to be associated with reduced bone density although the majority of the patients lack signs of bone fractures.[26,27]

By contrast, gain-of-function mutations in the *LRP5* gene have been reported to be responsible for high bone mass disorders but no retinal disorders are associated with these mutations (high bone mass, MIM number 601884; osteopetrosis, MIM number 607634; endosteal hyperostosis, MIM number 144750).[29–31]

2.4. TSPAN12 gene

The *TSPAN12* gene is a member of the tetraspanin superfamily, and codes for a 305-amino-acid protein. It consists of four transmembrane domains containing well-conserved residues, and the second extracellular loop has a cysteine–cysteine–glycine sequence and additional cysteines.[32] The tetraspanins are known to participate in a spectrum of membrane-associated activities involving cell adhesion, cell proliferation, and signaling pathway activation.[33] TSPAN12 is expressed in the endothelial cells of the retinal vessels, and it enhances the norrin/β-catenin signaling pathway through norrin and LRP5.[34] Two recent studies demonstrated that seven mutations in this gene were present in patients with autosomal dominant FEVR.[35,36] Homozygous mutations in the *TSPAN12* gene can also cause autosomal recessive FEVR.[37] Twenty mutations, 11 missense and nine truncation mutations, in the *TSPAN12* gene are known to cause FEVR (HGMD).

2.5. ZNF408 gene

The fifth FEVR-causing gene, *ZNF408*, was recently identified by Collin et al.[38] They found a missense mutation, p.H455Y, in a large Dutch family with an autosomal dominant inheritance pattern. The