Review article

Complex genetics of familial exudative vitreoretinopathy and related pediatric retinal detachments

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A B S T R A C T
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.

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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 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. The pathogenesis of the retinal detachments in eyes with FEVR is poor vascularization in the peripheral retina.

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), LRPS (low-density lipoprotein receptor-like...
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 secreted proteins that regulate signaling in cellular processes throughout the animal kingdom. 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.15 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.22 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).20–31

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/LRP5 signaling by recruiting norrin to the cell surface, thereby facilitating norrin internalization.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

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

FEVR = familial exudative vitreoretinopathy.
ZNF408 gene is a transcription factor of 720 amino acids that belongs to the class of C2H2 zinc finger proteins consisting of five exons. The ZNF408 gene is predicted to contain an SET domain, which is thought to be involved in protein–protein interactions in the regulation of chromatin-mediated gene expression. The ZNF408 gene was suggested to be a transcription factor that plays an important role in retinal vasculogenesis. A mutant zebrafish model with a morpholino-induced knockdown of znf408 had a deficient development of retinal vasculature. The frequency of the ZNF408 gene in cases of FEVR is very low according to Collin et al. Sequence analysis of the ZNF408 gene in 132 individuals with FEVR in whom mutations were excluded revealed only one potentially pathogenic missense variant, p.S126N.

2.6. Functional assays

The effects of FEVR-associated mutations in the FZD4, LRP5, TSPAN12, and NDP genes have been determined in vitro with the luciferase reporter assay and binding ability assays of norrin. Qin et al. reported that the norrin/beta-catenin signal transduction was completely stopped by a nonsense mutation in the FZD4 gene, and the transduction was moderately reduced by 26–48% by nonsynonymous variants (missense mutations) of the FZD4, NDP, or LRP5 genes. In addition, some known polymorphisms of FZD4 and LRP, including p.T1540M in LRP5, were shown to lead to milder but significant reductions in signal transduction. The results of these assays provided evidence that the functional impairments were caused by these variants, and the data were concordant with the milder phenotypes of patients who carry them.

2.7. Genotype–phenotype correlation of FEVR

The penetrance of FEVR is considered to be 100% but it can exhibit various phenotypes in members from the same family, or even between the two eyes of one individual. The majority of patients with FEVR have only asymptomatic deficiency of vasculature in the peripheral retina as a consistent feature detected with certainty by fluorescein angiography. This is in contrast to the severity of homogeneous conditions in Norrie disease and OPPG.

The various phenotypes of FEVR can partly be attributed to the different degrees of the norrin/beta-catenin signal transduction that had been shown by functional assays. Loss-of-function mutations in the FZD4, LRP5, or TSPAN12 genes can be the cause of both autosomal dominant and autosomal recessive forms of FEVR. Patients with homozygous mutations in these genes tend to show more severe phenotypes than patients with heterozygous mutations. Practically, families with dominant heterozygous FEVR mutations led to the identification of homozygous mutations in severely affected family members and vice versa. Furthermore, although X-linked FEVR is caused by hemizygous mutations in the NDP gene, heterozygous female members in a family were reported to have an exceptionally mild phenotype of FEVR. A digenic inheritance of FEVR is known as a combination of mutations in p.R444C in LRP5 and p.R417Q in FZD4. These observations suggest that it is difficult to determine whether the responsible mutations are clearly distinct in different forms of autosomal dominant and recessive inheritance. FEVR is not a disease that strictly follows Mendelian inheritance although it is sensitive to gene dosage.

In vitro assays demonstrated that a combination of two mutations displayed a more severe reduction of the norrin/beta-catenin signal activity than a single mutation. Moreover, a dosage sensitivity was consistently observed in mutant mouse models in which the FZD4 gene was disrupted.

Interestingly, there are some variants that cause milder phenotypes as found in patients with FEVR. A p.H69Y change in FZD4 that is found in the Asian population was reported to be responsible for FEVR. In vitro assays showed that p.H69Y has moderately reduced the binding abilities of norrin but exhibited a very mild reduction of the norrin/beta-catenin signal activity. FEVR patients with p.H69Y often have mild or no retinal changes, which have been considered to be due to low penetrance. In addition, p.H69Y was found in several patients as a second mutation accompanying other FEVR mutations, suggesting its role as a phenotype modifier. Thus, it is suggested that variants of intermediate severity underlie the phenotypes of some patients with FEVR, and they are manifested as complex genetic traits rather than a simple mono- genic inheritance.

2.8. Persistent hyperplastic primary vitreous (persistent fetal vasculature) syndrome and ATOH7 gene

The persistent hyperplastic primary vitreous (PHPV) syndrome, also referred to as “persistent fetal vasculature (PFV)”, is a congenital malformation characterized by intraocular vascular anomalies due to the persistence of the hyaloid artery and intraocular mass. The disease is a nonhereditary condition and 90% of the cases are unilateral with the exception of a few familial cases. The persistence of the hyaloid vessels, retrolental mass with falciform retinal folds, and pseudoglioma (retinal dysplasia) conditions more or less overlap between the FEVR and PHPV/PFV syndromes. Astrocytes have been shown to play a crucial role in the pathogenesis of both diseases. Unilateral or bilateral PHPV/ PFV-like retinal detachment is reported to be associated with mutations in the FZD4 and NDP genes. Therefore, the norrin/beta-catenin signaling pathway has been suggested to play a role in the development of the PHPV phenotype.

The ATOH7 gene is a transcription factor gene, which has been identified to be responsible for the PHPV/PFV phenotype in both humans and mice. It is an ortholog of mouse Math5, a gene that is crucial for retinal cell fate. Homozygous mutations in the ATOH7 gene are known to cause pseudoglioma (retinal dysplasia) conditions, which include the familial PHPV/PFV syndrome. These ocular features were also found in severe FEVR and related pseudoglioma (retinal dysplasia) syndrome as Norrie disease although mutations in the ATOH7 gene have yet to be shown to be associated with FEVR.

3. Retinopathy of prematurity

Retinopathy of prematurity (ROP) is a disorder affecting the development of the retinal vasculature in premature infants. ROP is a multifactorial disease, and many factors have been suggested to cause ROP including low birth weight, young gestational age, and prolonged oxygen supplementation. Genetic variations of genes related to retinal angiogenesis have also been considered to be associated with the development of advanced ROP. However, little is known about the exact genetic mechanisms. According to Bizzarro et al., who used a complex statistical model of mixed-effects logistic regression analysis, the genetic factors of ROP accounts for 70% of the cases.

ROP can be considered a second class of disease involved in the FEVR-causing genes (i.e., multifactorial diseases). The fundus characteristics of eyes with ROP are similar to those of FEVR. Because of the phenotypic resemblance, genetic changes in the norrin/beta-catenin signaling pathway are considered to be risk factors for advanced ROP. Several studies have addressed this possibility, and the results showed that variants in the FZD4, LRP5,
and NDP genes can account for 3–12% of eyes with ROP. The incidence of these variants may be related to ethnicity (Table 2). These are common or rare changes, and the variants were located in the untranslated regions (UTRs) or coding regions. These variants are highly heterogeneous, and therefore, their relevance to biological significance needs to be evaluated carefully. No functionally important sequence changes have been identified in the TSPAN12, ZNF408, or ATOH7 genes in cases of ROP.

### 3.1. Common variants

Common variants can be tested for their significance by association studies under the assumption of the disease-common variant hypothesis. A previous study reported that the common variants are associated with ROP. Haider et al identified a polymorphism in 5’ UTR of the NDP gene (C597A) that was associated with severe ROP in a Kuwaiti population. However, the pathogenicity of the substitution is unclear, and no other study has addressed its association in different ethnic populations.

Hiraoka et al identified a CTG (leucine: Leu) insertion in putative nine Leu repeats of the signal peptide of the LRP5 gene in one of 17 samples. Kondo et al found an identical variant and two Leu insertions in the same position of the LRP5 gene in each of the 53 samples studied. These changes were thought to be common polymorphisms, and the frequency of the (Leu)X10 and (Leu)X11 was reported to be 10% and <1%, respectively, in a German population. Chung et al reported that these changes led to a significant reduction in the norrin/β-catenin signaling by a luciferase assay, which suggests a pathogenic character. Furthermore, the (Leu)X11 change leads to an approximately 40% reduction of the activity that is comparable with the p.A29T mutation in the same gene, which is known to cause osteoporosis but no retinal phenotype. Association studies are yet to be performed especially for variants as the Leu repeat of LRP5.

### 3.2. Rare or novel variants

The other types of variants are rare or novel variants. These variants are likely to be of fairly recent origin and are not suitable for association studies because their rarity makes it difficult to obtain sufficient samples to achieve statistical significance. As an alternative to the disease-common variant hypothesis, the mutation-selection hypothesis proposes that much of the susceptibility is due to rare variants. Such rare variants account for only a small fraction of patients with ROP, and thus, it is not surprising that different screening studies have identified different variants even in the same ethnic population. Some known rare variants are as important as novel mutations for the pathogenesis, and these should be evaluated together for ROP. The single nucleotide polymorphism database (build 135) contains > 53 × 10⁶ human variations, consisting of not only common benign polymorphisms but also clinically associated variants. In addition, some rare variants are newly identified to be the cause of Mendelian diseases. Nonetheless, a possibility that cannot be fully discarded is that ROP infants with some of these variants include patients with FEVR who were premature.

There are two different types of rare variants: variants in the UTRs and missense variants (nonsynonymous) in the coding regions. The putative disease-associated variants located in the UTRs are only found in the NDP gene. These are insertions, deletions, and single-base substitutions either in the 5’ or 3’ UTR. These regions play a role in gene regulation, and variants in the 5’

### Table 2

| Gene | DNA change | Protein change | dbSNP rsID | Frequency | Ethnicity-matched control | Refs |
|------|------------|----------------|------------|----------|--------------------------|------|
| **FZD4** | c.205C>T | p.H69Y | rs80358282 | 0.28% | 1/53 Stages 4B–5 | 2/300 | JP | 50 |
| | c.380G>A | p.R127H | rs184709254 | 0.05% | 1/53 Stages 4B–5 | 0/300 | JP | 50 |
| | c.1109G>C | p.A360G |  |  | 1/71 advanced ROP | 0/33 no ROP | WH | 69 |
| | c.609G>C | p.K203N |  |  | 1/71 advanced ROP | 0/33 no ROP | WH | 69 |
| | c.611T>C | p.Y211H |  |  | 2/53 Stages 4B–5 | 0/300 | JP | 50 |
| | c.1396G>T | p.R466W |  |  | 1/71 advanced ROP | 0/33 no ROP | WH | 69 |
| | c.597C>T/c.502C | T/c.502C |  |  |  |  |  |  |
| | c.597C>T/c.502C | T/c.502C |  |  | 6/71 advanced ROP | 1/33 no ROP | WH | 69 |
| | c.766A>C | p.I256V | rs104894223 | 0.18% | 1/53 Stages 4B | 0/28 | JP | 68 |
| | c.97C>G | p.T1540M | rs141407040 | 0.06% | 1/53 Stages 4B | 1/386 | JP | 50 |
| | c.97C>G | p.T1540M | rs141407040 | 0.06% | 1/53 Stages 4B | 4/386 | JP | 50 |
| | c.4148A>C | p.I256V | rs104894223 | 0.18% | 1/53 Stages 4B | 1/386 | JP | 50 |
| | c.4148A>C | p.I256V | rs104894223 | 0.18% | 1/53 Stages 4B | 4/386 | JP | 50 |

AA = African American; dbSNP = single nucleotide polymorphism database; JP = Japanese; ROP = retinopathy of prematurity; WH = white; WH = predominantly white and included other ethnicities.

* Disease-associated single nucleotide polymorphism.
nucleotide substitutions or are located in less important
which suggests a somatic mutation in retinal progenitor cells
However, this mutation was not present in nonretinal tissues,
sporadic and noninherited condition and is generally unilateral.
due to exudative bullous retinal detachment. Eventually, the dis-
ported variants of
mains, and C-terminal tail).69 Contrary to FEVR, the previously re-
cysteine-rich domain, transmembrane domains, cytoplasmic do-
In support of this hypothesis, a distinct mutational spectrum has
inherited diseases. One of the other attractive candi-
nucleotide substitutions in the coding regions, which have been found as
non synonymous variants in the NDP, LRP5, or FZD4 genes
It is difficult to distinguish benign amino acid
substitutions from mutant amino acid substitutions that cause a disruption of the protein structure and/or an impairment of function.
Along with systemic abnormalities associated with prematurity, the retinopathy in patients carrying these genetic mutations may tend to be exacerbated. As mentioned, it is known that the severity of the mutations in the norrin/β-catenin signaling genes causes different phenotypes (e.g., FEVR, Norrie disease, and OPG). The phenotypic severities are related to the severity of the mutational effects.27,41 It is hypothesized that advanced ROP is related to milder functional impairments of the norrin/β-catenin signaling genes, whereas FEVR and Norrie disease are caused by more severe impairments of the genes.50
In support of this hypothesis, a distinct mutational spectrum has been proposed for FZD4 between FEVR and ROP.69 FEVR-causing mutations are located in important functional areas (e.g., the cysteine-rich domain, transmembrane domains, cytoplasmic domains, and C-terminal tail).69 Contrary to FEVR, the previously reported variants of FZD4 that are unique to ROP, namely, p.K203N, p.Y221H, p.I256V, p.A370G, and p.R466W, tend to be milder nucleotide substitutions or are located in less important regions.50,69–71 Similar distinct spectrums remain to be determined for the LRP5 gene.

4. Coats disease and sporadic unilateral diseases

Coats disease is an idiopathic condition that is characterized by retinal vascular telangiectasia and aneurysms and is associated with severe intraretinal and subretinal accumulation of yellowish exudates. The disease most often affects male patients during the first to second decade of life.81–83 Patients with Coats disease often have progressive retinal detachment and present with leukocoria due to exudative bullous retinal detachment. Eventually, the disease process leads to glaucoma and blindness. Coats disease is a sporadic and noninherited condition and is generally unilateral. The fundus appearance of some FEVR patients with severe exudation resembles that of Coats disease.47

Coats disease can be categorized into the third class of disease associated with the FEVR-causing genes, that is, a sporadic (noninherited) and generally unilateral disease. Black et al.84 analyzed the retinas from nine enucleated eyes from men with Coats disease. One of the samples had a mutation (p.C696W) in the NDP gene. However, this mutation was not present in nonretinal tissues, which suggests a somatic mutation in retinal progenitor cells causing Coats disease.84 The preponderance of male patients with the disease may be concordant with the hemizygous state of the pathogenicity. Therefore, Coats disease is the first example of a functional somatic mosaicism of a single gene causing a distinct retinal phenotype.84

4.1. Other possible candidate diseases

Thus far, no report has presented any evidence of somatic mutations in the retinal disorders. One of the other attractive candidate diseases for a somatic mutational effect of FEVR-related genes may be the PHPV/PPV syndrome.57

5. Conclusion

Identification of the genes responsible for FEVR has merged the key players involved in the pathogenesis of retinal vascular development. The involvement of mutations in these genes can lead to more complex phenotypes than previously believed. Unidentified genes for FEVR account for nearly 50% of the patients. Establishing a phenotype—genotype relationship can provide better understanding of the possible mechanisms for pediatric retinal detachments.

Clinically, identifying the underlying mutations in the causative gene can predict the prognosis of patients with FEVR. Patients with gene mutations tend to have more severe phenotypes with progression and recurring retinal detachments that are difficult to be reattached. In ROP cases, an acute progression to retinal detachment should be monitored more strictly. Patients with mutations in the FEVR-causing genes can be at a high risk of developing severe retinal detachments. The genetic diagnosis of the mutations can lead to more extensive follow-ups that can prevent the development of severe detachment by earlier surgical intervention.

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