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Familial exudative vitreoretinopathy and related retinopathies

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Abstract

Familial exudative vitreoretinopathy (FEVR) is a rare inherited disorder of retinal angiogenesis. Cases can be autosomal dominant, autosomal recessive, or X-linked. FEVR patients have an avascular peripheral retina which, depending on the degree of ischaemia, causes the secondary complications of the disease. Expressivity may be asymmetric and is highly variable. Five genes have been identified that when mutated, cause FEVR; *NDP* (X-linked), *FZD4* (autosomal dominant and recessive), *LRP5* (autosomal dominant and recessive), *TSPAN12* (autosomal dominant and recessive), and *ZNF408* (autosomal dominant). Four of these genes have been shown to have a central role in Norrin/Frizzled4 signalling, suggesting a critical role for this pathway in retinal angiogenesis. In addition to the ocular features, *LRP5* mutations can cause osteopenia and osteoporosis. All FEVR patients in whom molecular testing is not easily accessible should have dual energy X-ray absorptiometry (DEXA) scans to assess bone mineral density, as treatment can be initiated to reduce the risk of bone fractures.
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Introduction

Familial exudative vitreoretinopathy (FEVR) was first described by Criswick and Schepens.[1] It is a rare disorder of retinal blood vessel development principally affecting retinal angiogenesis, leading to incomplete vascularisation of the peripheral retina and poor vascular differentiation. Cases can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner, or can affect individuals with no family history. Most FEVR patients have an avascular peripheral retina but expressivity may be asymmetric and is highly variable, ranging from asymptomatic to severe

within the same family. If there is a significant degree of retinal ischaemia, then secondary neovascularisation can occur leading to fibrosis, traction of the posterior pole structures, retinal detachment (RD), retinal folds, or complete retinal dysplasia in the most severe cases. A diagnosis of FEVR can be made if there is evidence of peripheral retinal avascularity in ≥1 eye in patients of any age who were born at full term, or preterm with a disease tempo not consistent with retinopathy of prematurity (ROP).

Five genes have so far been identified that when mutated, cause FEVR; *NDP* (MIM 300658), *FZD4* (MIM 604579), *LRP5* (MIM 603506), *TSPAN12* (MIM 613138), and *ZNF408*.[2–7] Mutations in these genes account for around 50% of FEVR cases.[2,3,6,8] Four of the genes identified to date have been shown to have a role in a variant of the Wnt signalling pathway, termed as Norrin/Frizzled4 signalling,[9] suggesting a crucial role for this pathway in retinal vascular development.

FEVR: a disorder of retinal angiogenesis

Vasculogenesis vs angiogenesis

Vascularisation of the retina begins at around 18 weeks gestation (WG) and is complete by 38–40 WG. The vessels are organised into a network of vascular plexuses, which form by a combination of vasculogenesis and angiogenesis.[10] Vasculogenesis is the process of vessel development *de novo* from endothelial precursor cells that coalesce into cords and then form a lumen. In angiogenesis, blood vessels form by sprouting from pre-existing vessels. Although not proven, it is believed that vasculogenesis forms most of the primary retinal vascular plexus of the developing human retina, while angiogenesis forms the remaining capillary layers around the fovea and in the deeper and peripheral retina.[10]

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Formation of the vascular layers in the retina

Spindle-shaped mesodermal vascular precursor cells first enter the developing retina from the optic disc at around 15 WG.[10] These precursor cells aggregate to form solid cords, which subsequently become patent to form early retinal vessels. This event is preceded by the entry of neural ectodermal astrocytes into the retina from the optic nerve head, which then migrate across the retinal surface towards the periphery to provide a framework for growth of the primary (inner) vascular plexus.[10] At this stage in retinal development astrocytes have a critical role in vessel patterning and guidance. They respond to hypoxia in the developing retina by releasing VEGF-A, which promotes endothelial cell growth and differentiation.[11–13] Angiogenic sprouts made up of specialised endothelial cells are guided by varying concentrations of VEGF-A in the extracellular matrix.[14] Astrocytes also provide the structural framework for blood vessel growth and release factors that increase the integrity of the blood retinal barrier.[15] The primary vascular plexus forms at the interface between the nerve fibre layer (NFL) and the ganglion cell layer (GCL) and is complete by 25–26 WG.[16] The perifoveal and peripheral vasculature are not formed at this time.[10]

At 25–26 WG, angiogenic sprouting into the retina from the primary retinal plexus, in response to extracellular VEGF-A, leads to the formation of the deeper retinal plexuses; and unlike the primary plexus these vessels develop independently of astrocytes.[10,16,17] The vessels migrate into the retina along Müller cell processes then turn perpendicularly to form two further parallel layers at the inner and outer borders of the inner nuclear layer (INL) in the macula.[17] In the mid-peripheral retina, only one further plexus grows at the outer border of the INL; and towards the far periphery, where the retina is thinner, the two vascular layers become less distinct and eventually form one layer (Figure 1).[18–20] A fourth capillary layer is present within the thick NFL around the optic disc and along the temporal vascular arcades. These peripapillary capillaries run radially, in parallel with the retinal nerve fibres, and have few anastamoses.[18]

Throughout retinal vascular development the immature vascular tree undergoes extensive pruning and remodelling. Both endothelial cell migration and leukocyte-mediated apoptosis take place to fashion the vasculature into an ordered pattern of different sized arteries, capillaries, and veins.[21,22] Pericytes (sometimes referred to as mural cells) are embedded in the basement membrane of the vascular endothelium. The interaction between pericytes and endothelial cells is critical for the maturation and maintenance of the microvasculature in the retina.[23]

The deeper retinal vessels are thought to grow along Müller cell processes into the retina but do not rely on VEGF-A released from Müller cells or astrocytes to develop.[24] These vessels may be guided by VEGF-A released from pre-existing vascular endothelial cells.[25] Interestingly, the knockout mouse models of four of the known FEVR genes ($Ndp-/-$, $Fzd4-/-$, $Lrp5-/-$, and $Tspan12-/-$) all show the absence of the deeper retinal plexuses in the presence of a formed primary retinal plexus (Figure 2).[26–29] At present, there is no clinical data that demonstrate disturbance of the deeper retinal vascular layers in patients with FEVR. However, most patients with FEVR have a peripheral avascular retina and in mild cases the primary (inner) vascular layer appears to be normal. This suggests that FEVR may be a disorder of angiogenesis in which the primary vascular plexus develops normally but the secondary capillary layers in the deep and peripheral retina are absent or abnormal. This avascularity then causes the clinical features of the disease. This has not been described in patients as yet, perhaps because patients who present with visually significant FEVR invariably have distortion of the macular anatomy. Nevertheless, the murine models of FEVR support this hypothesis.

The hyaloid vasculature

Before blood vessels enter the retina the developing eye is supported metabolically by the hyaloid vasculature. This is a network of arterial vessels that branch off from the central hyaloid artery into the vitreous, around the developing lens and drain into the choroidal veins.[30] The hyaloid vasculature begins to regress at 13 WG and is completely gone by 40 WG when development of the retinal vasculature is complete.[31] Failure of the hyaloid vasculature to regress causes a range of pathology from non-sight threatening conditions (Bergmeister's papillae) to blindness (persistent fetal vasculature (PFV)) and can be a feature of FEVR.[32–35]

Phenotypic characteristics in FEVR

Clinical features

The hallmark of FEVR is peripheral retinal avascularity, which often has a V-shaped pattern in the temporal periphery.[36,37] In mild cases, these peripheral retinal changes do not cause any symptoms.[38] In moderate to severe cases, pre-retinal neovascularisation and fibrosis at the junction between vascular and avascular retina can occur that causes traction of the macula and retinal vessels (Figure 3). This can cause varying degrees of macular ectopia and visual dysfunction. In severe cases, the traction can lead to RD and retinal folds resulting in
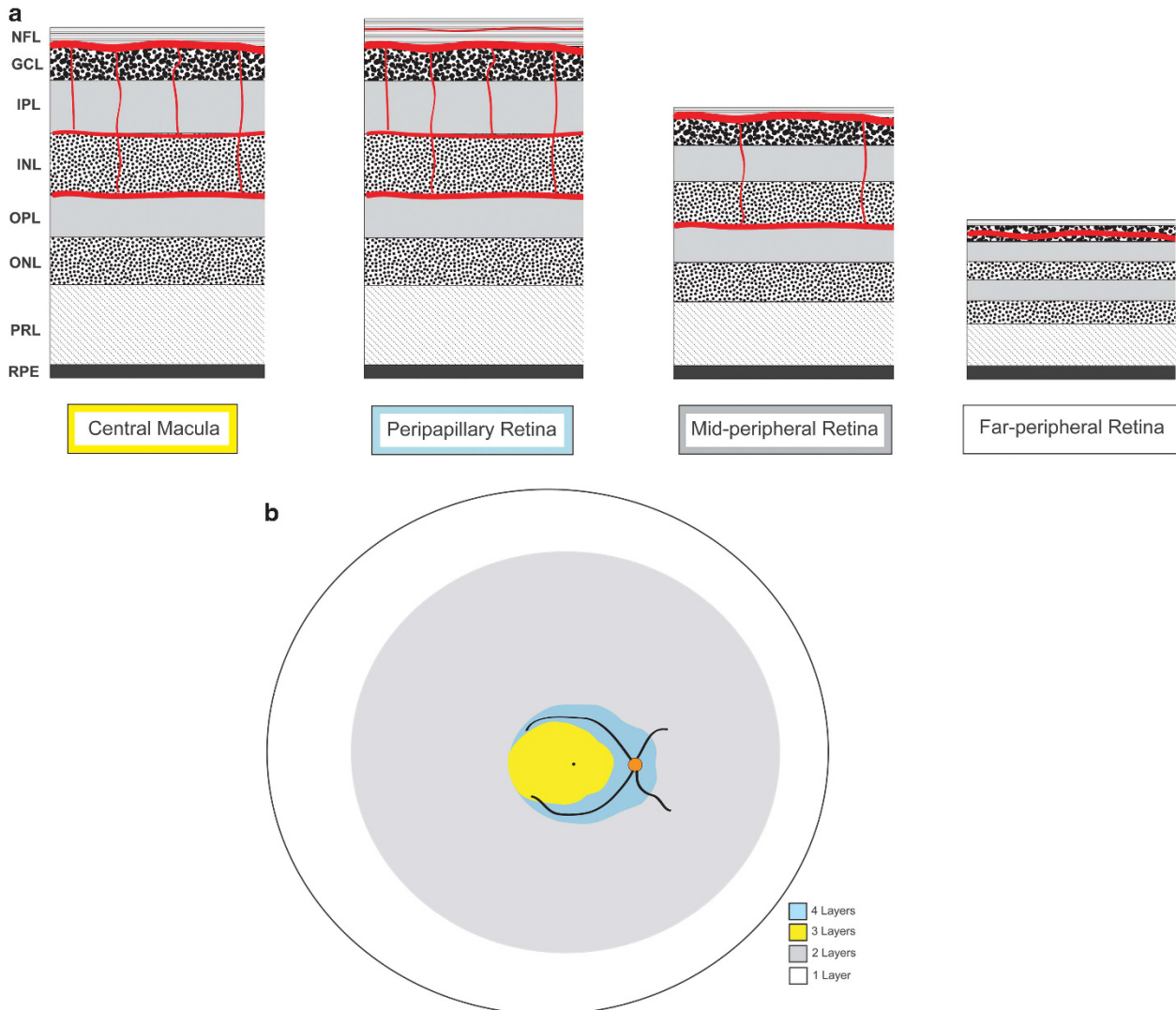
Figure 1 Vascular layers in the adult human retina with respect to (a) retinal depth and (b) retinal location. These figures were based on histopathology studies by Michealson and Campbell, Wise et al, and Bek and Jensen.[18–20] IPL, inner plexiform layer; OPL, outer plexiform layer; ONL, outer nuclear layer; PRL, photoreceptor layer; RPE, retinal pigment epithelium.

very poor vision. Patients can present at any age depending on the severity of the disease. An important clinical feature in FEVR is the lack of prematurity. The vitreoretinal signs seen in ROP are almost identical to those seen in FEVR.[39]

RDs are a common finding in FEVR and occur in 21–64% of affected individuals.[36–38,40,41] They can be rhegmatogenous, tractional, or serous in nature. Advanced tractional RDs can progress to form radial folds in the retina, sometimes described as 'falciform'. These folds represent one of the classic features of severe FEVR (Figure 4),[42] and are similar to the fundal appearance seen in Norrie disease and osteoporosis pseudoglioma (OPPG). Often patients can have very mild or no disease in one eye, with severe disease in the fellow eye, and disease asymmetry is another common

feature in FEVR.[40,41] Less common findings are retinal exudation, secondary epiretinal membrane formation (Figure 5), peripheral retinoschisis, neovascularisation, vitreous haemorrhage, secondary glaucoma (neovascular or phacomorphic), phacolytic uveitis, retinal capillary angioma, retained hyaloid vascular remnants, and PFV.[33,36–38,40,41,43,44] The fundus fluorescein angiography (FFA) features in FEVR were published by Canny and Oliver.[45] In the current clinical management of the disorder this test is only used when the diagnosis is in doubt in very mild cases.

FEVR patients with *LRP5* mutations have reduced bone mass, and those with severe *NDP* mutations are more likely to have progressive deafness and mental retardation. The spectrum of allelic FEVR disorders and the genotype–phenotype correlation in FEVR are

discussed later in this review. Extra-ocular associations in FEVR are otherwise extremely rare. Nevertheless, both DiGeorge syndrome and congenital microcephaly have been described.[46,47] Table 1 summarises the published data on the prevalence of the more common clinical features in FEVR. The table illustrates how variable the phenotype can be.

Phenotypic variability

In FEVR, there can be a range of disease severity in the individual, and within families. First-degree relatives of patients with severe FEVR often have mild asymptomatic disease despite having the same FEVR mutation.[48]
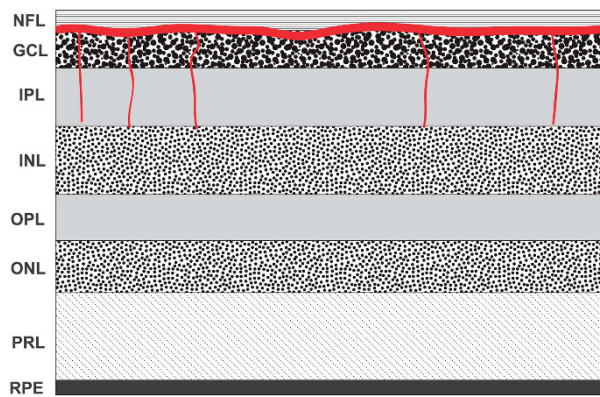

Figure 2 Absence of the deeper retinal plexuses in animal models of FEVR. Schematic representation of the retinal vascular phenotype seen in mouse models of FEVR.[26–29] IPL, inner plexiform layer; OPL, outer plexiform layer; ONL, outer nuclear layer; PRL, photoreceptor layer; RPE, retinal pigment epithelium.

This could be explained by the presence of genetic modifiers, which may have a protective or predisposing effect. Environmental influences, either systemic or local, could also have a role in the aetiology. In ROP, abnormally high and variable arterial oxygen levels (PaO_2) in premature infants have a profound effect on retinal vascular development.[49] FEVR patients are not premature and are not subjected to the extremely abnormal physiological conditions that premature infants are, but smaller changes in the intrauterine environment, like PaO_2 or exposure to certain drugs, may have greater influence in patients carrying FEVR mutations. Another common feature of FEVR is disease asymmetry. This asymmetry can be marked with some patients having an RD in one eye and no observable signs of disease in the other. These findings could suggest a local environmental difference between the two eyes during ocular development or, more plausibly, a somatic genetic variant in one eye having an influence on retinal vascular embryogenesis.

Staging

There have been three different grading systems devised in an attempt to classify FEVR. Laqua proposed a three-stage system that was modified from one of the earliest descriptions of FEVR by Gow and Oliver.[50,51] In stage 1, the patient is asymptomatic and all the pathology is confined to the peripheral retina. Stage 2 describes a peripheral fibrovascular mass with dragging of the posterior pole structures causing reduced visual acuity. In stage 3, complications that cause severe visual loss are
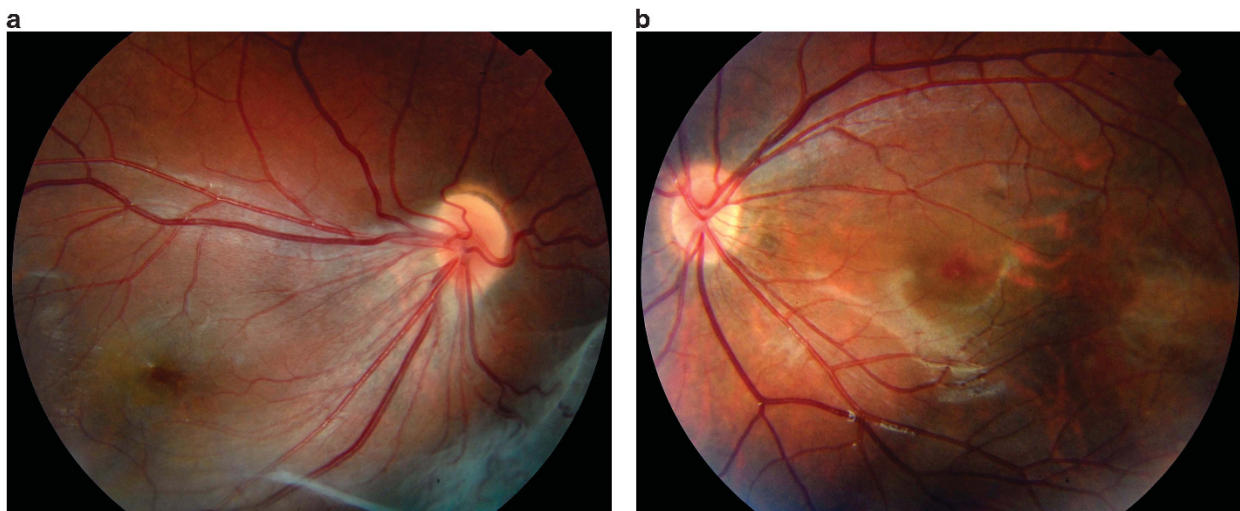

Figure 3 Retinal traction in FEVR. Fundus images of a 13-year-old female with mild FEVR and no family history. (a) The right eye has moderate dragging of the optic disc along with the macula and temporal vessels. Some retained hyaloid vascular remnants are present inferiorly. Snellen visual acuity is 6/12 in this eye. (b) The left eye has normal vision and has only mild straightening of the retinal vessels. A peripheral area of temporal retinal avascularity was seen in this eye (not imaged).
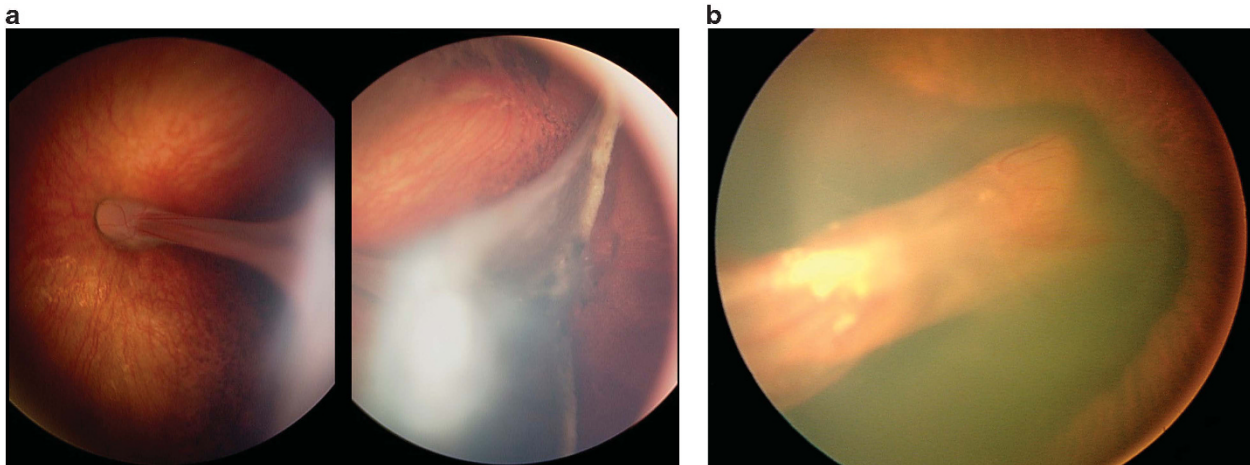
Figure 4 Radial retinal folds in FEVR. (a) Fundus image of the left eye of 1-year-old baby girl with FEVR showing a radial retinal fold towards an area of fibrosis and temporal avascularity. (b) Fundus image of the right eye of a neonate with recessive FEVR showing a severe retinal fold. This appearance is clinically identical to the ocular features seen in Norrie disease, and has previously been termed pseudoglioma.

present (eg, total RD, neovascular glaucoma, and PFV). Miyakubo et al[37] suggested a slightly more complicated five-stage system ranging from type 1 (peripheral avascularity of less than two disc diameters with straightening of the temporal retinal vessels) to type 5 (cicatricial mass in the periphery). More recently, Pendergast et al[52] proposed the most comprehensive system described to date (Table 2). FEVR occurs due to a congenital failure of retinal vascular development and the disease rarely progresses. Therefore, these staging systems do not represent stages through which the disease advances.

Genetics and molecular mechanisms for pathogenicity

Genes

FZD4   FEVR was first described by Criswick and Schepens[1] in two families; one with an autosomal dominant inheritance pattern and one which suggested X-linked recessive inheritance. The EVR1 locus was initially mapped to the chromosomal region 11q13-q23 by Li et al[53] using traditional genetic linkage studies in two families with autosomal dominant FEVR. This region was later refined to 1.55 Mb by Robitaille et al[4] who then went on to discover mutations in *FZD4* in two autosomal dominant pedigrees.

Since the first disease causing *FZD4* mutations were identified, several different mutations have been described in autosomal dominant pedigrees and more recently it has been shown that *FZD4* mutations can also cause recessive FEVR.[5,35,48,54,55] Kaykas et al[56] demonstrated that oligomerisation of mutant and wild-type FZD4 in the endoplasmic reticulum reduces *FZD4*

function by preventing sufficient wild-type protein from reaching the cell membrane. This dominant-negative effect may be the pathological mechanism causing the disease phenotype in patients with heterozygous *FZD4* mutations. Alternatively, nonsense-mediated decay and subsequent haploinsufficiency of the protein may have a role. Missense mutations predicted to disrupt the expressed protein in the extracellular cysteine-rich domain (CRD), intracellular loops 1 and 3, the transmembrane and the cytoplasmic domains cause FEVR. This suggests that these protein domains have a significant role in FZD4 protein function.

NDP   In the 1920s Leopold Heine and Gordon Norrie described 'congenital pseudotumours' of the retina in two large families with an X-linked recessive inheritance pattern.[57] Warburg[58] later described progressive deafness and mental retardation associated with the disorder and named the syndrome Norrie disease. Genetic linkage to chromosome Xp11.4 was noted by Warburg and others and defined as EVR2. The gene involved, *NDP*, was finally identified in 1992 by positional cloning.[59–62] The protein encoded by the *NDP* gene was subsequently named Norrin. Fullwood et al[63] studied a family with X-linked FEVR and found a suggestion of linkage to the Xp11 region. They proposed the hypothesis that Norrie disease and X-linked FEVR could be allelic, and this was later validated when mutations were identified in *NDP* in X-linked FEVR families.[7]

Mutations in the *NDP* gene cause Norrie disease and X-linked FEVR.[7,64] In addition, *NDP* mutations have been identified in PFV, Coats disease, and ROP.[32,65,66] The majority of known mutations in *NDP* involve its cysteine knot domain. The cysteine knot domain binds
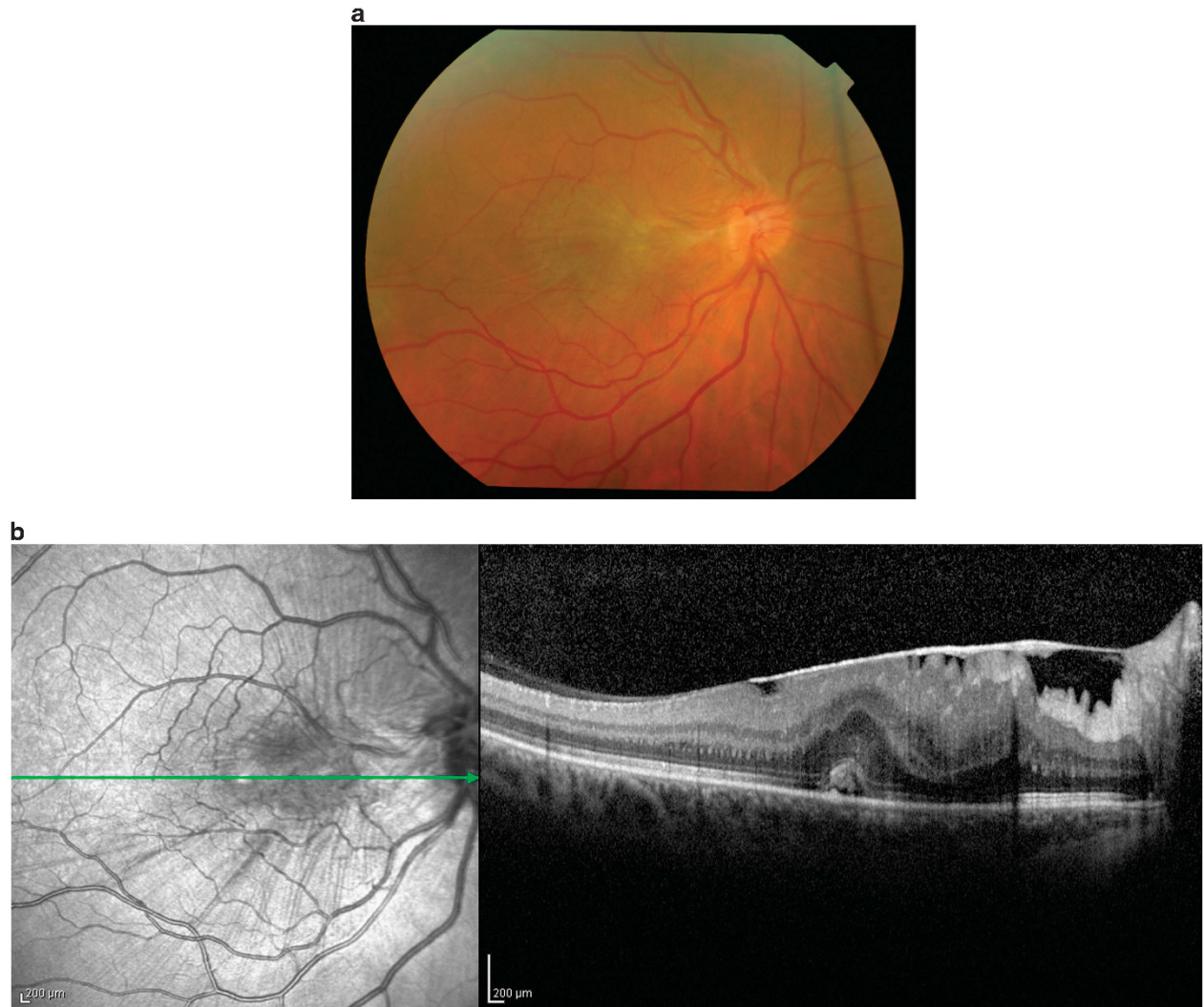
Figure 5 Epiretinal membrane formation in FEVR. (a) Fundus image and (b) optical coherence tomography image of a patient with FEVR who had peripheral retinal exudation and avascularity resulting in secondary epiretinal membrane formation.

Table 1 Ocular features of FEVR patients

	Ranchod et al[40] (n = 273[a]) (%)	Van Nouhuys[36] (n = 176[a]) (%)	Miyakubo et al[37] (n = 133[a]) (%)	Shukla et al[41] (n = 116[a]) (%)	Benson[38] (n = 78[a]) (%)
Peripheral avascularity	97	79		100	100
Macular ectopia		49	18	10	
Avascular zone only	16			41	44
Retinal detachment	64	21	43	30	28
Radial retinal fold	28	8			26
Retinal exudates	19	9			22
Neovascularisation	12	11	20	7	18

Blank = not specified in the study.
[a]Number of eyes.

to the CRD of FZD4 to initiate intracellular signalling so it is not surprising that mutations in this domain cause disease. Several missense mutations are predicted to change one of the highly conserved cysteine residues within this domain. This highlights the importance of the cysteine knot domain to the function of Norrin in humans.

LRP5 Toomes and co-workers failed to identify an *FZD4* mutation in an Asian family with autosomal

Table 2 Staging system for FEVR

Stage	Description
1	Avascular periphery
2	Retinal neovascularisation
	A Without exudate
	B With exudate
3	Extramacular retinal detachment
	A Without exudate
	B With exudate
4	Subtotal macula-involving retinal detachment
	A Without exudate
	B With exudates
5	Total retinal detachment

dominant FEVR, which had previously been mapped to the EVR1 locus described by Li et al.[53,67,68] Genotyping in this family around the FZD4 gene revealed that the mutation in this family lay in an ~15-cM region 10 cM centromeric to FZD4, providing evidence for a separate locus termed EVR4.[67] By identifying heterozygous mutations in this family and several other patients with FEVR, Toomes et al[5] demonstrated that the disease gene in this region was LRP5. Following the identification of dominant mutations in LRP5, Jiao et al[69] found homozygous mutations in three families with recessive FEVR, thus identifying LRP5 as the first recessive FEVR gene.

LRP5 mutations were initially identified in patients with the recessive disorder OPPG,[70] now known to be on the same disease spectrum as FEVR. The first LRP5 mutations found to cause FEVR were identified in 2004, and since then many mutations have been described in both autosomal dominant and recessive pedigrees.[5,54,69] When these patients are tested by bone dual energy X-ray absorptiometry (DEXA) scanning they are found to have reduced bone density.[54] Some LRP5 polymorphisms have also been found to be associated with idiopathic osteoporosis.[71,72] Hartikka et al[73] found heterozygous LRP5 mutations in three children with osteoporosis but did not detect an eye phenotype. As discussed earlier, FEVR patients are often asymptomatic so these patients may well have had undiagnosed FEVR. In addition, dominant missense mutations have been reported in patients with disorders characterised by high bone mass.[74] The bone mass phenotype was recently investigated by Yadav et al.[75] This group demonstrated that LRP5, in addition to its importance in retinal vascular development, has a separate role in duodenal enterochromaffin cells from where it controls osteoblast function and bone formation by inhibiting serotonin synthesis.

The range of types and locations of known LRP5 mutations suggest that no functional protein is present in the OPPG patients. FEVR is predominately caused by heterozygous mutations, though some recessive LRP5 mutations have been described. Missense mutations involving the four extracellular YWTD-EGF domains make up the majority of all known LRP5 missense mutations, highlighting this region of the protein as functionally important in humans.

TSPAN12   In 2010, TSPAN12 mutations causing FEVR were identified by two different groups.[3,6] Nikopoulos et al mapped a locus to chromosome 7q31.31 in a large Dutch family then used targeted sequence capture and next generation sequencing (NGS) to find the disease gene. Poulter and colleagues screened the gene in a panel of FEVR patients after Junge et al[29] published data linking TSPAN12 to retinal vascular development. In a further study, Poulter et al[76] identified TSPAN12 as a recessive FEVR gene by discovering homozygous mutations in patients with FEVR.

Mutations can be truncating, missense, or splice site in nature and there is no strong correlation between the severity of disease and type or location of mutation. Poulter et al[6] described this lack of genotype–phenotype correlation in patients with different TSPAN12 mutations and suggested that haploinsufficiency of TSPAN12 is the likely cause of FEVR in these patients.

ZNF408   The most recent gene to be implicated in the pathogenesis of FEVR is ZNF408. Collin et al[2] discovered disease causing mutations in three families with autosomal dominant FEVR. The group went on to carry out functional experiments to further establish the validity of their findings. These included immunolocalisation studies which demonstrated that protein expressed from mutated ZNF408 behaves abnormally in monkey cells, and a zebrafish model of retinal vascularisation that showed abnormal vascular differentiation when znf408 is absent. The immunolocalisation studies suggested that one of the missense mutations acted in a dominant-negative way and the group concluded that this may be the molecular mechanism causing the disease phenotype.[2]

Norrin/Frizzled4 signalling

The first four FEVR genes identified all encode proteins that function in Norrin/Frizzled4 signalling. This pathway is a unique variant of Wnt signalling and has a central role in retinal vascular development.[9] Wnt signalling is involved in multiple developmental events during embryogenesis and has a role in cell proliferation and regulation in adult tissues, including cancer.[77,78] When mutations in FZD4 and LRP5 were identified in FEVR patients, the function of the corresponding proteins as co-receptors in Wnt signalling was already

well established. However, the function of Norrin was unknown until 10 years after its identification as an FEVR gene. In 2004, Xu et al[27] demonstrated that Norrin binds with high specificity to Frizzled4 (the protein encoded by *FZD4*) at the cell membrane and, in the presence of the co-receptors LRP5 or LRP6, activates β-catenin signalling.[77,78] This finding was viewed as surprising at the time because Norrin is not a member of the Wnt family. Ye et al[25] went on to demonstrate that Norrin, derived from Müller cells, specifically controls capillary development in the eye by activating Norrin/Frizzled4 signalling in retinal capillary endothelial cells. Further characterisation of the proteins involved in Norrin/Frizzled4 signalling was provided by Junge et al.[29] The authors demonstrated with a series of *in vivo* and *in vitro* experiments that Tspan12 has a pivotal role in the Norrin/Frizzled4 pathway. The findings of Junge et al and Ye et al highlight the specificity of Norrin/Frizzled4 signalling.

ZNF408 is a transcription factor from the zinc finger family of proteins. Collin et al[2] have established that mutations in the gene which encodes this protein cause FEVR. The precise role of ZNF408 within the process of retinal vascular development remains unclear. Nevertheless, the discoveries of Collin et al have opened up a new area of experimentation for those studying retinal vascular development. Identifying new FEVR genes is an excellent way to discover and characterise new members of molecular pathways that are central to retinal angiogenesis.

Genetically related disorders

Norrie disease

Norrie disease is a severe X-linked retinal dysplasia with non-existent or near non-existent vision at birth caused by mutations in the *NDP* gene.[79] About 30–50% of Norrie disease patients have developmental delay and most have progressive hearing loss from early childhood. Female cases have been reported but are extremely rare.[80] The classic ocular feature of Norrie disease is a glistening white elevated mass seen through a clear lens, historically referred to as a pseudotumour or pseudoglioma. These are non-specific terms and refer to anything that looks similar to a tumour in the retina. As with severe FEVR the disease can involve the anterior segment structures and cause secondary complications.[79] The posterior disease is not treatable, but management of the secondary complications is indicated to prevent loss of the globe.

Osteoporosis pseudoglioma

OPPG is characterised by osteoporosis and ocular features similar to severe FEVR, and in the majority

of cases is caused by mutations in the *LRP5* gene.[71] While the majority of OPPG patients are congenitally blind with a severe bilateral retinal dysplasia similar to that seen in Norrie disease, some have less severe ocular findings more common in FEVR.[71] Markedly reduced bone mineral density means that affected individuals often suffer from childhood fractures secondary to relatively mild trauma. Growth retardation, muscle hypotonia, and developmental delay may also be present. The bone disease is managed with bisphosphonate treatment and eye complications are treated in a similar manner to FEVR and Norrie disease.[72]

Spectrum of FEVR-related retinopathies

Both Norrie disease and OPPG were given names and classifications before the pathogenic gene mutations were discovered. It is now clear that these diseases are part of the same disease spectrum as FEVR. Patients at the severe end of the spectrum are more likely to have the extra-ocular features described above which aid the clinician in making the diagnosis of either Norrie disease, if mental retardation and deafness are present, or OPPG, if childhood fractures or reduced bone density are an associated feature.

Genotype–phenotype correlations

There is no genotype–phenotype correlation for the ocular features observed in FEVR. Mutations in *FZD4*, *NDP*, *LRP5*, *TSPAN12*, and *ZNF408* can cause varying degrees of disease severity within the same family and between eyes of the same individual.[2,5,40,48,81] If a patient has the low bone mass phenotype, then a dominant or recessive LRP5 mutation is the likely cause. No patients with *FZD4*, *NDP*, *TSPAN12*, or *ZNF408* mutations have been reported to have reduced bone mass, but it is often the case that bone density scanning is not carried out.[54] However, given that the bone phenotype has been shown to be independent of the Norrin/Frizzled4 signalling pathway, a bone phenotype is not expected in these patients.[75] If a patient is male, has a severe ocular phenotype and hearing loss with or without developmental delay, then a mutation in the *NDP* gene is likely.

In FEVR, there does not appear to be a clear correlation between the severity of the mutation and the severity of the phenotype, with the exception that recessive mutations usually result in a more severe phenotype. Many severely affected patients have only been shown to harbour a single mutation in an FEVR gene. This raises the possibility that a second unidentified gene mutation and/or a combination of pathogenic polymorphisms in

genes important in retinal vascular development are present in these individuals.

Visual function and long-term visual outcomes

Most patients with FEVR retain good visual acuity with 64–74% of affected patients having vision of 6/12 or better.[36,41] In a comprehensive review, Benson[38] estimated that around 50% of patients are asymptomatic. Children and adolescents diagnosed with the disease have a poorer visual prognosis when compared with adults; with macular ectopia, RDs, and retinal folds being the main causes of reduced vision. Progression is uncommon in adults but has been described.[38,41]

Management

It is generally agreed that only patients that show signs of significant progression, or are at high risk of progression, should be treated.[36,38,41] All FEVR patients in whom molecular testing is not easily accessible, adults or children, should have DEXA scans to assess bone mineral density. If positive, then the patient should be referred to a rheumatologist for bisphosphonate therapy.[72]

Due to the low prevalence of the disease, there is an absence of robust data to guide clinicians in managing FEVR patients. Shukla et al[41] treated 17 patients (20 eyes) prophylactically with either laser or cryotherapy. The patients all had peripheral abnormalities that included retinal breaks, exudative RD, neovascularisation, and/or vitreous haemorrhage. The final visual acuity was stable in all patients at a mean follow-up of 16.4 months (range 2–40). In contrast, Pendergast and Trese[52] treated 15 eyes with retinal laser and 7 progressed to RD requiring surgical repair. In the same study, 32 eyes in total required RD surgery. Twenty-nine of these eyes were followed up over 6 months and eighteen (62%) had a successful surgical (anatomical) outcome with just over half gaining visual acuity. Ikeda et al[82] found an 86% reattachment rate in 28 FEVR eyes that needed surgery, with 71% gaining visual acuity. Published RD surgery outcomes are summarised in Table 3. The surgery performed in these studies was an even mixture of pars plana vitrectomy, scleral buckling, or a combination of both. Poor surgical outcome is more common in patients under the age of 19.[36,41,52,83,84]

The use of intravitreal anti-VEGF injections to reduce the exudative and neovascular components of FEVR and other inherited retinal vasculopathies has been reviewed.[85] Anti-VEGF therapy reduces retinal exudation and neovascularisation in FEVR patients but the rapid resolution of exudation can stimulate worsening vitreoretinal traction that often requires surgery. This treatment may have a role as an adjunctive therapy before surgery.

Vitreoretinopathies with similarities to FEVR

Coats disease

Coats disease is a sporadic retinal vasculopathy characterised by retinal telangiectasias, intraretinal exudation, and exudative RD that is not associated with any systemic disease. The disease is unilateral in 95% of cases, and mostly affects young males.[86] Patients usually present in early childhood, but cases can often go unnoticed due to the fellow eye being normal.[86] The exudation most commonly involves the macular region, and often spreads diffusely to the whole retina. If left untreated then the exudation can penetrate the external limiting membrane to cause an exudative RD, which eventually will slowly progress to a total RD and secondary neovascular glaucoma. Mild cases can be treated successfully with retinal laser or cryotherapy, but the prognosis deteriorates and intervention becomes less successful as the disease progresses. Advanced cases sometimes require enucleation.[87]

The aetiology of Coats disease is not clear. The disease appears to spare the larger retinal vessels, so the disorder somehow disrupts the normal development of the smaller retinal vessels and capillaries. Black et al[65] described a family in which the mother of a Norrie disease patient had Coats disease and both patients carried a missense *NDP* mutation. They suggested that the cause of the unilateral disease in the mother may have been a second somatic mutation in the developing retina of the affected eye and postulated that a similar mechanism may contribute to Coats disease. Prompted by this finding the authors screened RNA extracted from the enucleated eyes of nine male Coats patients and found a somatic *NDP* mutation in the retinal tissue of one of these patients.[65] *NDP* is situated on the X chromosome and this theory could explain why the disease almost exclusively affects males.

Persistent fetal vasculature

PFV is a congenital disorder in which the hyaloid vasculature and primary vitreous have failed to regress. The disorder is normally sporadic, has no sex predilection, and is almost always unilateral.[88] Inherited forms of this disease have been reported, but are extremely rare. These familial cases are always bilateral and can be inherited in a recessive or dominant pattern.[89,90] Some cases are mild and do not have significant ocular morbidity but most are severe resulting

Table 3 Retinal detachment (RD) surgery outcomes in FEVR

	Eyes requiring RD repair	No. of requiring further surgery	Final reattachment rate (%)	Improved visual acuity (%)	No change (%)	Worse visual acuity (%)	Mean follow-up (months)
Ikeda et al[83]	28	6	86	71	14	14	25.8
Pendergast et al[52]	32	7	62	55	38	7	38.3
Chen et al[84]	7	5	57				
Van Nouhuys[36]	14	6	50				
Shukla et al[41]	14	4	83				23.8

Blank = not specified in the study.

in secondary cataract and glaucoma.[88] Surgery is advocated only in selected cases with anterior PFV.[91]

The phenotypic overlap of PFV and FEVR was highlighted by Robitaille et al[34] who showed that *FZD4* mutations can cause features identical to PFV. The first gene mutation to directly be implicated in PFV was identified by Prasov et al[92] who found a homozygous *ATOH7* mutation in a family with PFV. The close relationship of PFV and FEVR makes *ATOH7* an excellent candidate gene for screening in FEVR. The cause of sporadic unilateral PFV is not known. It is interesting to speculate that patients with unilateral PFV may have undergone a somatic mutation in the affected eye during the early stages of ocular development. There is no experimental evidence to support this hypothesis at present, but a study of enucleated PFV eyes looking for somatic mutations in candidate genes, similar to the Coats disease study conducted by Black et al,[65] would be of interest.

Incontinentia pigmenti

Incontinentia pigmenti (IP) is an X-linked dominant disorder of the skin, which is associated with ocular features very similar to FEVR in about one-third of cases.[93] The disease is a form of ectodermal dysplasia and may also cause abnormalities of the teeth, nails, hair (alopecia), and neurological system (developmental delay and epilepsy). In the majority of cases a vesicular rash is present at birth, predominately on the extremities and the trunk, which then becomes verrucous in the first few months of life. The skin subsequently develops hyperpigmented lesions, which slowly become hypopigmented over a period of several years. The disorder is normally lethal prenatally in males and in surviving females there is significant phenotypic variability. Patients can have any of the features with varying degrees of severity.

The majority of cases are caused by mutations in the *IKBKG* gene on chromosome Xq28.[94] *IKBKG* encodes a protein (NEMO) that forms a regulatory subunit of the IκB kinase complex, which is required for the activation of the transcription factor NF-κB.[95] NF-κB has an

important role in many inflammatory, immune, and apoptotic pathways.[96] Cells expressing the mutated X chromosome have reduced levels of NF-κB and are not able to prevent apoptosis in the presence of inflammatory cytokines. The variable expressivity of the disorder is thought to be due to skewed X inactivation.

Retinopathy of prematurity

Although environmental factors represent the major determinant in the pathogenesis of ROP, there is increasing evidence that the genetic background of the individual may also have a role.[97] FEVR genes are excellent candidates for screening in ROP due to the phenotypic similarities between the disorders. *NDP*, *FZD4*, and *LRP5* genetic variants have all been identified in patients with ROP.[98,99–101] These findings suggest that FEVR genes may be implicated in ROP disease; however, several small gene association studies have been carried out which have not supported this hypothesis.[102–105] Further larger studies are required before any definitive conclusions can be made regarding the association of specific genetic variants and severity of ROP.

Conclusions

Mutations in *NDP*, *FZD4*, *LRP5*, *TSPAN12*, and *ZN408* account for ~50% cases of FEVR.[2,3,6,8] It is clear that there are still a large proportion of FEVR patients in whom the pathogenic genetic variants remain unidentified and therefore there is huge potential for novel scientific discovery within this field. Four of the known FEVR genes encode proteins known to have a major role in Norrin/Frizzled4 signalling, a variant of Wnt signalling. There are several Wnt signalling pathways, and each pathway is turned on in a highly specific manner. The Norrin/Frizzled4 pathway has a specialised function in helping to build small blood vessels in the developing retina. The detection of more novel FEVR genes may either help to further characterise this pathway, or uncover a completely new molecular pathway.

There is increasing evidence, from both human and animal studies, that Wnt signalling has an important role in the pathogenesis of diabetic retinopathy.[106,107] It is thought that Wnt signalling becomes aberrantly upregulated due to oxidative stress, and several groups have investigated whether blocking this pathway could have a therapeutic benefit. Both Lee *et al* and Liu *et al* have recently published experiments using the mouse oxygen-induced retinopathy model in which they showed that antagonising Wnt signalling reduces retinal vascular leakage, inflammation, and ischaemia.[106–109] Current treatments for diabetic retinopathy are aimed at reducing sight loss after the sight-threatening pathology has developed. These findings demonstrate the potential for a drug to be developed that prevents the ischaemic and exudative complications of diabetic retinopathy by inhibiting the Wnt pathway. The highly specific function of Norrin/Frizzled4 signalling in the eye makes this variant of Wnt signalling a very attractive target for drug development.

FEVR is a clinically and genetically heterogeneous disorder affecting the development of the retinal vasculature. Though it is a rare disease, studying families with FEVR is of considerable clinical and scientific interest as each new FEVR gene that is identified increases our understanding of the molecular mechanisms controlling angiogenesis in the retina. In diseases such as diabetic retinopathy and ROP, pathological angiogenesis driven by retinal ischaemia is the principal pathology. The study of FEVR may therefore support the development of therapies that control or prevent the sight-threatening complications of these far more common diseases.

Conflict of interest

The author declares no conflict of interest.

Acknowledgements

References

1 Criswick VG, Schepens CL. Familial exudative vitreoretinopathy. *Am J Ophthalmol* 1969; **68**: 578–594.

2 Collin RW, Nikopoulos K, Dona M, Gilissen C, Hoischen A, Boonstra FN *et al.* ZNF408 is mutated in familial exudative vitreoretinopathy and is crucial for the development of zebrafish retinal vasculature. *Proc Natl Acad Sci USA* 2013; **110**: 9856–9861.

3 Nikopoulos K, Gilissen C, Hoischen A, CEv Nouhuys, Boonstra FN, Blokland EA *et al.* Next-generation sequencing of a 40 Mb linkage interval reveals TSPAN12 mutations in patients with familial exudative vitreoretinopathy. *Am J Hum Genet* 2010; **86**: 240–247.

4 Robitaille J, MacDonald ML, Kaykas A, Sheldahl LC, Zeisler J, Dubé M *et al.* Mutant frizzled-4 disrupts retinal angiogenesis in familial exudative vitreoretinopathy. *Nat Genet* 2002; **32**: 326–330.

5 Toomes C, Bottomley HM, Jackson RM, Towns KV, Scott S, Mackey DA *et al.* Mutations in LRP5 or FZD4 underlie the common familial exudative vitreoretinopathy locus on chromosome 11q. *Am J Hum Genet* 2004; **74**: 721–730.

6 Poulter JA, Ali M, Gilmour DF, Rice A, Kondo H, Hayashi K *et al.* Mutations in TSPAN12 cause autosomal-dominant familial exudative vitreoretinopathy. *Am J Hum Genet* 2010; **86**: 248–253.

7 Chen ZY, Battinelli EM, Fielder A, Bundey S, Sims K, Breakefield XO *et al.* A mutation in the Norrie disease gene (NDP) associated with X-linked familial exudative vitreoretinopathy. *Nat Genet* 1993; **5**: 180–183.

8 Nikopoulos K, Venselaar H, Collin RW, Riveiro-Alvarez R, Boonstra FN, Hooymans JM *et al.* Overview of the mutation spectrum in familial exudative vitreoretinopathy and Norrie disease with identification of 21 novel variants in FZD4, LRP5, and NDP. *Hum Mutat* 2010; **31**: 656–666.

9 Wang Y, Rattner A, Zhou Y, Williams J, Smallwood PM, Nathans J. Norrin/Frizzled4 signaling in retinal vascular development and blood brain barrier plasticity. *Cell* 2012; **151**: 1332–1344.

10 Hughes S, Yang H, Chan-Ling T. Vascularization of the human fetal retina: roles of vasculogenesis and angiogenesis. *Invest Ophthalmol Vis Sci* 2000; **41**: 1217–1228.

11 Dorrell MI, Aguilar E, Friedlander M. Retinal vascular development is mediated by endothelial filopodia, a preexisting astrocytic template and specific R-cadherin adhesion. *Invest Ophthalmol Vis Sci* 2002; **43**: 3500–3510.

12 Zhang Y, Stone J. Role of astrocytes in the control of developing retinal vessels. *Invest Ophthalmol Vis Sci* 1997; **38**: 1653–1666.

13 Stone J, Itin A, Alon T, Pe'er J, Gnessin H, Chan-Ling T *et al.* Development of retinal vasculature is mediated by hypoxia-induced vascular endothelial growth factor (VEGF) expression by neuroglia. *J Neurosci* 1995; **15**: 4738–4747.

14 Gerhardt H, Golding M, Fruttiger M, Ruhrberg C, Lundkvist A, Abramsson A *et al.* VEGF guides angiogenic sprouting utilizing endothelial tip cell filopodia. *J Cell Biol* 2003; **161**: 1163–1177.

15 Gardner TW, Lieth E, Khin SA, Barber AJ, Bonsall DJ, Lesher T *et al.* Astrocytes increase barrier properties and ZO-1 expression in retinal vascular endothelial cells. *Invest Ophthalmol Vis Sci* 1997; **38**: 2423–2427.

16 Provis JM. Development of the primate retinal vasculature. *Prog Retin Eye Res* 2001; **20**: 799–821.

17 Fruttiger M. Development of the retinal vasculature. *Angiogenesis* 2007; **10**: 77–88.

18 Bek T, Jensen PK. Three-dimensional structure of human retinal vessels studied by vascular casting. *Acta Ophthalmol* 1993; **71**: 506–513.

19 Michaelson IC, Campbell AC. The anatomy of the finer vessels. *Trans Ophthalmol Soc UK* 1940; **60**: 71–111.

20 Wise GN, Dollery CT, Henhind P. *The Retinal Circulation*. Harper and Row: New York, 1971.

21 Hughes S, Chang-Ling T. Roles of endothelial cell migration and apoptosis in vascular remodeling during development of the central nervous system. *Microcirculation* 2000; **7**: 317–333.

22 Ishida S, Yamashiro K, Usui T, Kaji Y, Ogura Y, Hida T *et al*. Leukocytes mediate retinal vascular remodeling during development and vaso-obliteration in disease. *Nat Med* 2003; **9**: 781–788.

23 Armulik A, Abramsson A, Betsholtz C. Endothelial/pericyte interactions. *Circ Res* 2005; **97**: 512–523.

24 Bai Y, Ma J, Guo J, Wang J, Zhu M, Chen Y *et al*. Müller cell-derived VEGF is a significant contributor to retinal neovascularization. *J Pathol* 2009; **219**: 446–454.

25 Ye X, Wang Y, Cahill H, Yu M, Badea TC, Smallwood PM *et al*. Norrin, frizzled-4, and Lrp5 signaling in endothelial cells controls a genetic program for retinal vascularization. *Cell* 2009; **139**: 285–298.

26 Xia C, Liu H, Cheung D, Wang M, Cheng C, Xin d *et al*. A model for familial exudative vitreoretinopathy caused by LPR5 mutations. *Hum Mol Genet* 2008; **17**: 1605–1612.

27 Xu Q, Wang Y, Dabdoub A, Smallwood PM, Williams J, Woods C *et al*. Vascular development in the retina and inner ear: control by Norrin and Frizzled-4, a high-affinity ligand-receptor pair. *Cell* 2004; **116**: 883–895.

28 Richter M, Gottanka J, May CA, Welge-Lüssen U, Berger W, Lütjen-Drecoll E. Retinal vasculature changes in Norrie disease mice. *Invest Ophthalmol Vis Sci* 1998; **39**: 2450–2457.

29 Junge HJ, Yang S, Burton JB, Paes K, Shu X, French DM *et al*. TSPAN12 regulates retinal vascular development by promoting Norrin- but not Wnt-induced FZD4/beta-catenin signaling. *Cell* 2009; **139**: 299–311.

30 Saint-Geniez M, D'Amore PA. Development and pathology of the hyaloid, choroidal and retinal vasculature. *Int J Dev Biol* 2004; **48**: 1045–1058.

31 Zhu M, Madigan MC, Dv Driel, Maslim J, Billson FA, Provis JM *et al*. The human hyaloid system: cell death and vascular regression. *Exp Eye Res* 2000; **70**: 767–776.

32 Aponte EP, Pulido JS, Ellison JW, Quiram PA, Mohney BG. A novel NDP mutation in an infant with unilateral persistent fetal vasculature and retinal vasculopathy. *Ophthalmic Genet* 2009; **30**: 99–102.

33 Chang-Godinich A, Paysse EA, Coats DK, Holz ER. Familial exudative vitreoretinopathy mimicking persistent hyperplastic primary vitreous. *Am J Ophthalmol* 1999; **127**: 469–471.

34 Robitaille JM, Wallace K, Zheng B, Beis MJ, Samuels M, Hoskin-Mott A *et al*. Phenotypic overlap of familial exudative vitreoretinopathy (FEVR) with persistent fetal vasculature (PFV) caused by FZD4 mutations in two distinct pedigrees. *Ophthalmic Genet* 2009; **30**: 23–30.

35 Omoto S, Hayashi T, Kitahara K, Takeuchi T, Ueoka Y. Autosomal dominant familial exudative vitreoretinopathy in two Japanese families with FZD4 mutations (H69Y and C181R). *Ophthalmic Genet* 2004; **25**: 81–90.

36 van Nouhuys CE. Signs, complications, and platelet aggregation in familial exudative vitreoretinopathy. *Am J Ophthalmol* 1991; **111**: 34–41.

37 Miyakubo H, Hashimoto K, Miyakubo S. Retinal vascular pattern in familial exudative vitreoretinopathy. *Ophthalmology* 1984; **91**: 1524–1530.

38 Benson WE. Familial exudative vitreoretinopathy. *Trans Am Ophthalmol Soc* 1995; **93**: 473–521.

39 Dickinson JL, Sale MM, Passmore A, FitzGerald LM, Wheatley CM, Burdon KP *et al*. Mutations in the NDP gene: contribution to Norrie disease, familial exudative vitreoretinopathy and retinopathy of prematurity. *Clin Experiment Ophthalmol* 2006; **34**: 682–688.

40 Ranchod TM, Ranchod TM, Ho LY, Drenser KA, Capone A, Trese MT *et al*. Clinical presentation of familial exudative vitreoretinopathy. *Ophthalmology* 2011; **118**: 2070–2075.

41 Shukla D, Singh J, Sudheer G, Soman M, John RK, Ramasamy K *et al*. Familial exudative vitreoretinopathy (FEVR). Clinical profile and management. *Indian J Ophthalmol* 2003; **51**: 323–328.

42 Nishimura M, Yamana T, Sugino M, Kohno T, Yamana Y, Minei M *et al*. Falciform retinal fold as sign of familial exudative vitreoretinopathy. *Jpn J Ophthalmol* 1983; **27**: 40–53.

43 Boldrey EE, Egbert P, Gass JD, Friberg T. The histopathology of familial exudative vitreoretinopathy. A report of two cases. *Arch Ophthalmol* 1985; **103**: 238–241.

44 Javellana JA, Drouilhet JH, Kokame GT, Chee PH, Wong BM. Retinal capillary angioma in familial exudative vitreoretinopathy treated with photodynamic therapy. *Am J Ophthalmol* 2004; **137**: 780–782.

45 Canny CL, Oliver GL. Fluorescein angiographic findings in familial exudative vitreoretinopathy. *Arch Ophthalmol* 1976; **94**: 1114–1120.

46 Gilmour DF, Downey LM, Sheridan E, Long V, Bradbury J, Inglehearn CF *et al*. Familial exudative vitreoretinopathy and DiGeorge syndrome: a new locus for familial exudative vitreoretinopathy on chromosome 22q11.2? *Ophthalmology* 2009; **116**: 1522–1524.

47 Young ID, Fielder AR, Simpson K. Microcephaly, microphthalmos, and retinal folds: report of a family. *J Med Genet* 1987; **24**: 172–174.

48 Toomes C, Bottomley HM, Scott S, Mackey DA, Craig JE, Appukuttan B *et al*. Spectrum and frequency of FZD4 mutations in familial exudative vitreoretinopathy. *Invest Ophthalmol Vis Sci* 2004; **45**: 2083–2090.

49 Sylvester CL. Retinopathy of prematurity. *Semin Ophthalmol* 2008; **23**: 318–323.

50 Gow J, Oliver GL. Familial exudative vitreoretinopathy. An expanded view. *Arch Ophthalmol* 1971; **86**: 150–155.

51 Laqua H. Familial exudative vitreoretinopathy. *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 1980; **213**: 121–133.

52 Pendergast SD, Trese MT. Familial exudative vitreoretinopathy. Results of surgical management. *Ophthalmology* 1998; **105**: 1015–1023.

53 Li Y, Müller B, Fuhrmann C, Nouhuys CEv, Laqua H, Humphries P *et al*. The autosomal dominant familial exudative vitreoretinopathy locus maps on 11q and is closely linked to D11S533. *Am J Hum Genet* 1992; **51**: 749–754.

54 Qin M, Hayashi H, Oshima K, Tahira T, Hayashi K, Kondo H. Complexity of the genotype-phenotype correlation in familial exudative vitreoretinopathy with mutations in the LRP5 and/or FZD4 genes. *Hum Mutat* 2005; **26**: 104–112.

55 Kondo H, Hayashi H, Oshima K, Tahira T, Hayashi K. Frizzled 4 gene (FZD4) mutations in patients with familial exudative vitreoretinopathy with variable expressivity. *Br J Ophthalmol* 2003; **87**: 1291–1295.

56 Kaykas A, Yang-Snyder J, Héroux M, Shah KV, Bouvier M, Moon RT. Mutant Frizzled 4 associated with

vitreoretinopathy traps wild-type Frizzled in the endoplasmic reticulum by oligomerization. *Nat Cell Biol* 2004; **6**: 52–58.

57 Norrie G. Causes of blindness in children: twenty-five years' experience of Danish Institutes for the blind. *Acta Ophthalmol* 1927; **5**: 357–386.

58 Warburg M. Norrie's disease. A congenital progressive oculo-acoustico-cerebral degeneration. *Acta Ophthalmol* 1966; **89**(Supp): 1–47.

59 Berger W, Meindl A, TJvd Pol, Cremers FP, Ropers HH, Döerner C *et al.* Isolation of a candidate gene for Norrie disease by positional cloning. *Nat Genet* 1992; **2**: 84.

60 Kivlin JD, Sanborn GE, Wright E, Cannon L, Carey J. Further linkage data on Norrie disease. *Am J Med Genet* 1987; **26**: 733–736.

61 Gal A, Stolzenberger C, Wienker T, Wieacker P, Ropers HH, Friedrich U *et al.* Norrie's disease: close linkage with genetic markers from the proximal short arm of the X chromosome. *Clin Genet* 1985; **27**: 282–283.

62 Bleeker-Wagemakers LM, Friedrich U, Gal A, Wienker TF, Warburg M, Ropers HH. Close linkage between Norrie disease, a cloned DNA sequence from the proximal short arm, and the centromere of the X chromosome. *Hum Genet* 1985; **71**: 211–214.

63 Fullwood P, Jones J, Bundey S, Dudgeon J, Fielder AR, Kilpatrick MW. X linked exudative vitreoretinopathy: clinical features and genetic linkage analysis. *Br J Ophthalmol* 1993; **77**: 168–170.

64 Meindl A, Berger W, Meitinger T, van de Pol D, Achatz H, Dorner C *et al.* Norrie disease is caused by mutations in an extracellular protein resembling C-terminal globular domain of mucins. *Nat Genet* 1992; **2**: 139–143.

65 Black GC, Perveen R, Bonshek R, Cahill M, Clayton-Smith J, Lloyd IC *et al.* Coats' disease of the retina (unilateral retinal telangiectasis) caused by somatic mutation in the NDP gene: a role for norrin in retinal angiogenesis. *Hum Mol Genet* 1999; **8**: 2031–2035.

66 Wu W, Drenser K, Trese M, Capone Jr A, Dailey W. Retinal phenotype-genotype correlation of pediatric patients expressing mutations in the Norrie disease gene. *Arch Ophthalmol* 2007; **125**: 225–230.

67 Toomes C, Downey LM, Bottomley HM, Scott S, Woodruff G, Trembath RC *et al.* Identification of a fourth locus (EVR4) for familial exudative vitreoretinopathy (FEVR). *Mol Vis* 2004; **10**: 37–42.

68 Price SM, Periam N, Humphries A, Woodruff G, Trembath RC. Familial exudative vitreoretinopathy linked to D11S533 in a large Asian family with consanguinity. *Ophthalmic Genet* 1996; **17**: 53–57.

69 Jiao X, Ventruto V, Trese MT, Shastry BS, Hejtmancik JF. Autosomal recessive familial exudative vitreoretinopathy is associated with mutations in LRP5. *Am J Hum Genet* 2004; **75**: 878–884.

70 Gong Y, Slee RB, Fukai N, Rawadi G, Roman-Roman S, Reginato AM *et al.* LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. *Cell* 2001; **107**: 513–523.

71 Ai M, Heeger S, Bartels CF, Schelling DK. Clinical and molecular findings in osteoporosis-pseudoglioma syndrome. *Am J Hum Genet* 2005; **77**: 741–753.

72 Streeten EA, McBride D, Puffenberger E, Hoffman ME, Pollin TI, Donnelly P *et al.* Osteoporosis-pseudoglioma syndrome: description of 9 new cases and beneficial response to bisphosphonates. *Bone* 2008; **43**: 584–590.

73 Hartikka H, Mäkitie O, Männikkö M, Doria AS, Daneman A, Cole WG *et al.* Heterozygous mutations in the LDL receptor-related protein 5 (LRP5) gene are associated with primary osteoporosis in children. *J Bone Mineral Res* 2005; **20**: 783–789.

74 Boyden LM, Mao J, Belsky J, Mitzner L, Farhi A, Mitnick MA *et al.* High bone density due to a mutation in LDL-receptor-related protein 5. *N Engl J Med* 2002; **346**: 1513–1521.

75 Yadav VK, Ryu J, Suda N, Tanaka KF, Gingrich JA, Schütz G *et al.* Lrp5 controls bone formation by inhibiting serotonin synthesis in the duodenum. *Cell* 2008; **135**: 825–837.

76 Poulter JA, Davidson AE, Ali M, Gilmour DF, Parry DA, Mintz-Hittner HA *et al.* Recessive mutations in TSPAN12 cause retinal dysplasia and severe familial exudative vitreoretinopathy (FEVR). *Invest Ophthalmol Vis Sci* 2012; **53**: 2873–2879.

77 Clevers H. Wnt/beta-catenin signaling in development and disease. *Cell* 2006; **127**: 469–480.

78 Logan CY, Nusse R. The Wnt signaling pathway in development and disease. *Annu Rev Cell Dev Biol* 2004; **20**: 781–810.

79 Sims K. NDP-related retinopathies. *Gene Rev* 2009.

80 Chen ZY, Battinelli EM, Woodruff G, Young I, Breakefield XO, Craig IW. Characterization of a mutation within the NDP gene in a family with a manifesting female carrier. *Hum Mol Genet* 1993; **2**: 1727–1729.

81 Riveiro-Alvarez R, Trujillo-Tiebas MJ, Gimenez-Pardo A, Garcia-Hoyos M, Cantalapiedra D, Lorda-Sanchez I *et al.* Genotype-phenotype variations in five Spanish families with Norrie disease or X-linked FEVR. *Mol Vis* 2005; **11**: 705–712.

82 Ikeda T, Fujikado T, Tano Y, Tsujikawa K, Koizumi K, Sawa H *et al.* Vitrectomy for rhegmatogenous or tractional retinal detachment with familial exudative vitreoretinopathy. *Ophthalmology* 1999; **106**: 1081–1085.

83 Ikeda T, Fujikado T, Tano Y. Combined tractional rhegmatogenous retinal detachment in familial exudative vitreoretinopathy associated with posterior retinal holes: surgical therapy. *Retina* 1998; **18**: 566–568.

84 Chen S, Jiunn-Feng H, Te-Cheng Y. Pediatric rhegmatogenous retinal detachment in taiwan. *Retina* 2006; **26**: 410–414.

85 Lin KL, Hirose T, Kroll AJ, Lou PL, Ryan EA. Prospects for treatment of pediatric vitreoretinal diseases with vascular endothelial growth factor inhibition. *Semin Ophthalmol* 2009; **24**: 70–76.

86 Shields JA, Shields CL, Honavar SG, Demirci H. Clinical variations and complications of Coats disease in 150 cases: the 2000 Sanford Gifford Memorial Lecture. *Am J Ophthalmol* 2001; **131**: 561–571.

87 Shields JA, Shields CL, Honavar SG, Demirci H, Cater J. Classification and management of Coats disease: the 2000 Proctor Lecture. *Am J Ophthalmol* 2001; **131**: 572–583.

88 Haddad R, Font RL, Reeser F. Persistent hyperplastic primary vitreous. A clinicopathologic study of 62 cases and review of the literature. *Surv Ophthalmol* 1978; **23**: 123–134.

89 Khaliq S, Hameed A, Ismail M, Anwar K, Leroy B, Payne AM *et al.* Locus for autosomal recessive nonsyndromic persistent hyperplastic primary vitreous. *Invest Ophthalmol Vis Sci* 2001; **42**: 2225–2228.

90 Galal AH, Kotoury AI, Azzab AA. Bilateral persistent hyperplastic primary vitreous: an Egyptian family supporting a rare autosomal dominant inheritance. *Genet Couns* 2006; **17**: 441–447.

91 Paysse EA, McCreery KM, Coats DK. Surgical management of the lens and retrolenticular fibrotic membranes associated with persistent fetal vasculature. *J Cataract Refract Surg* 2002; **28**: 816–820.

92 Prasov L, Masud T, Khaliq S, Mehdi SQ, Abid A, Oliver ER *et al.* ATOH7 mutations cause autosomal recessive persistent hyperplasia of the primary vitreous. *Hum Mol Genet* 2012; **21**: 3681–3694.

93 Ardelean D, Pope E. Incontinentia pigmenti in boys: a series and review of the literature. *Pediatr Dermatol* 2006; **23**: 523–527.

94 Smahi A, Courtois G, Vabres P, Yamaoka S, Heuertz S, Munnich A *et al.* Genomic rearrangement in NEMO impairs NF-kappaB activation and is a cause of incontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium. *Nature* 2000; **405**: 466–472.

95 Rothwarf DM, Zandi E, Natoli G, Karin M. IKK-gamma is an essential regulatory subunit of the IkappaB kinase complex. *Nature* 1998; **395**: 297–300.

96 Pasparakis M. Regulation of tissue homeostasis by NF-kappaB signalling: implications for inflammatory diseases. *Nat Rev Immunol* 2009; **9**: 778–788.

97 Mohamed S, Schaa K, Cooper ME, Ahrens E, Alvarado A, Colaizy T *et al.* Genetic contributions to the development of retinopathy of prematurity. *Pediatr Res* 2009; **65**: 193–197.

98 Ells A, Guernsey DL, Wallace K, Zheng B, Vincer M, Allen A *et al.* Severe retinopathy of prematurity associated with FZD4 mutations. *Ophthalmic Genet* 2010; **31**: 37–43.

99 Talks SJ, Ebenezer N, Hykin P, Adams G, Yang F, Schulenberg E *et al. De novo* mutations in the 5′ regulatory region of the Norrie disease gene in retinopathy of prematurity. *J Med Genet* 2001; **38**: E46.

100 Shastry BS, Pendergast SD, Hartzer MK, Liu X, Trese MT. Identification of missense mutations in the Norrie disease gene associated with advanced retinopathy of prematurity. *Arch Ophthalmol* 1997; **115**: 651–655.

101 Kondo H, Kusaka S, Yoshinaga A, Uchio E, Tawara A, Tahira T. Genetic variants of FZD4 and LRP5 genes in patients with advanced retinopathy of prematurity. *Mol Vis* 2013; **19**: 476–485.

102 Haider MZ, Devarajan LV, Al-Essa M, Srivastva BS, Kumar H, Azad R *et al.* Missense mutations in Norrie disease gene are not associated with advanced stages of retinopathy of prematurity in Kuwaiti arabs. *Biol Neonate* 2000; **77**: 88–91.

103 Haider MZ, Devarajan LV, Al-Essa M, Srivastva BS, Kumar H, Azad R *et al.* Retinopathy of prematurity: mutations in the Norrie disease gene and the risk of progression to advanced stages. *Pediatr Int* 2001; **43**: 120–123.

104 Hutcheson KA, Paluru PC, Bernstein SL, Koh J, Rappaport EF, Leach RA *et al.* Norrie disease gene sequence variants in an ethnically diverse population with retinopathy of prematurity. *Mol Vis* 2005; **11**: 501–508.

105 Dickinson JL, Sale MM, Passmore A, FitzGerald LM, Wheatley CM, Burdon KP *et al.* Mutations in the NDP gene: contribution to Norrie disease, familial exudative vitreoretinopathy and retinopathy of prematurity. *Clin Experiment Ophthalmol* 2006; **34**: 682–688.

106 Chen Y, Hu Y, Zhou T, Zhou KK, Mott R, Wu M *et al.* Activation of the Wnt pathway plays a pathogenic role in diabetic retinopathy in humans and animal models. *Am J Pathol* 2009; **175**: 2676–2685.

107 Liu Q, Li J, Cheng R, Chen Y, Lee K, Hu Y *et al.* Nitrosative stress plays an important role in Wnt pathway activation in diabetic retinopathy. *Antioxid Redox Signal* 2013; **18**: 1141–1153.

108 Liu X, Zhang B, McBride JD, Zhou K, Lee K, Zhou Y *et al.* Antiangiogenic and antineuroinflammatory effects of kallistatin through interactions with the canonical wnt pathway. *Diabetes* 2013; **62**: 4228–4238.

109 Lee K, Hu Y, Ding L, Chen Y, Takahashi Y, Mott R *et al.* Therapeutic potential of a monoclonal antibody blocking the Wnt pathway in diabetic retinopathy. *Diabetes* 2012; **61**: 2948–2957.