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CASE REPORT

Familial Exudative Vitreoretinopathy caused by a Homozygous Mutation in *TSPAN12* in a Cystic Fibrosis Infant

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ABSTRACT

Familial exudative vitreoretinopathy (FEVR) is a genetic disease affecting the vascularization of the peripheral retina. The clinical manifestations are very heterogeneous, ranging from mildly affected patients, who could present no visual defects, to severe conditions which can also cause complete blindness at birth or in the first decade. FEVR can be inherited in all the three genetic forms: dominant, recessive and X-linked. To date, four genes have been associated with the condition: *TSPAN12*, *NDP*, *FDZ4* and *LRP5*. Interestingly, mutations in *TSPAN12* have been considered causative of both a dominant and recessive inheritance and a FEVR phenotype sensitive to the number of *TSPAN12* mutations has been supposed.

Here we describe a case of a female infant affected by cystic fibrosis and by a severe form of exudative vitreoretinopathy. In particular, we have detected the homozygous missense mutation c.668 T>C in *TSPAN12*. Neither of the heterozygous parents has ocular manifestations of the disease, suggesting a classic recessive mendelian pattern of inheritance.

Keywords: Cystic fibrosis, familial exudative vitreoretinopathy (FEVR), retinal vascularization, *TSPAN12*

INTRODUCTION

Familial exudative vitreoretinopathy (FEVR) is a genetic disorder caused by the defective development of the retinal vasculature.

Described first by Criswick and Schepens in 1969,[1] its phenotype is extremely heterogeneous with a great variability also among relatives. In particular, visual defects can lead to complete blindness in infancy in severely affected patients but can also be totally absent in those mildly affected. The diagnosis is, anyway, based on fluorescein angiography (FA) which shows areas of avascularity of variable sizes.

The partial or total absence of retinal vessels, leading to the pathological process, is due to a failure of the angiogenesis. From the subsequent ischemia, a neovascularization process arises, leading to the development of hyperpermeable blood vessels, ranging from a vitreo-retinal traction to a retinal detachment which is seen in 20% of the patients.

An absolute heterogeneity is also seen genetically. Up to now, four different causative genes, all

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encoding proteins involved in the Norrin-b-catenin pathway[2]), have been identified: *TSPAN12*,[3–6] *NDP*,[7] *FDZ4*,[8,9] and *LRP5*.[10,11] In particular, the *NDP* gene, located at Xp11.3, is responsible for an X-linked form of FEVR;[7] mutations in FRZ4 are recessive[8,9] while variations in *LRP5* and *TSPAN12* can be dominant or recessive.[3–6,10,11] Very recently, Poulter described three families in which the phenotype was due to recessive mutations in *TSPAN12*.[5] Interestingly, in two out of the three families, patients bearing a single mutation had a milder phenotype than those bearing two mutated alleles. These data suggest that the FEVR phenotype is sensitive to the number of *TSPAN12* mutations.

We have recently examined a female infant affected by FEVR and cystic fibrosis. The proband shares the same phenotype, the same mutation and the same ethnic origin as a patient described before.[5]

However, we have been able to perform an extensive clinical examination of the heterozygous parents who, currently, do not manifest any ocular symptoms. In our case, clinical and molecular data suggest a recessive inheritance of the mutation, determining the disease only in homozygosity.

CASE REPORT

We evaluated a female patient affected by cystic fibrosis and by exudative vitreoretinopathy. She was born in December 2010 from consanguineous parents of Pakistani origin after a spontaneous, uncomplicated pregnancy (Figure 1a).

The patient underwent neonatal screening for cystic fibrosis and was found to be affected by the disease after performing a Sweat test. *CFTR* gene sequencing revealed the presence of the mutation p.M1T (c.2T>C) in the homozygous state.[12]

The parents were both found to be carriers of the p.M1T mutation.

Meanwhile, an ophthalmologic examination was performed at the birth, suggesting a retinal disease, so the baby was referred to our eye clinic for further clinical investigations. At the age of 3 months, RetCam examination showed a mild exudation with no sign of neovascularization. At the follow-up examination after 2 months, a dramatic progression was observed, with the development of extensive central neovascularization and fibrovascular proliferation in both eyes and a particularly severe fibrosis in the left eye (Figure 1b). According to BEAT-ROP study dosage,[13] an injection of 0.625 mg in 0.0025 mL of Bevacizumab in the right eye was performed, obtaining a regression of the hemorrhagic component in the right eye. An advanced tractional retinal detachment was evident in the left eye. A vitrectomy was performed in the right eye and no treatment was attempted in the left eye. After 10 months of follow-up the retina was adherent, with some retinal folds still visible near the pale optic disk (Figure 1c).

Because of the recent paper by Poulter,[5] we supposed that *TSPAN12* could also have been the causative gene in our case. The Sanger sequencing of all its exons evidenced a homozygous point mutation (c.668 T>C, p.L223P). As already evidenced elsewhere,[5] the leucine 223 is extremely conserved among orthologues, and the mutation is predicted to be pathogenic. The same mutation has already been identified in the affected member of the family VL described by Poulter.[5] Moreover, both the patients had Pakistani parents and were affected, in addition to FEVR, by cystic fibrosis (the authors did not mention *CFTR* mutations), suggesting a possible blood relationship. However, in the published case, no examination of the proband's parents had been performed to evidence or exclude an ocular, although mild, manifestation.

Our patient's parents, heterozygous for the mutation in *TSPAN12*, underwent a full eye examination, with particular care given to the peripheral retina; direct and indirect ophthalmoscopy showed a normal retinal vascularization, with no signs of exudation or avascularity; also no zones of retinal traction or neovascularization were noticed.

In conclusion, clinical and molecular data strongly suggest a mendelian recessive pattern of inheritance of the ocular disease in our family, composed of two

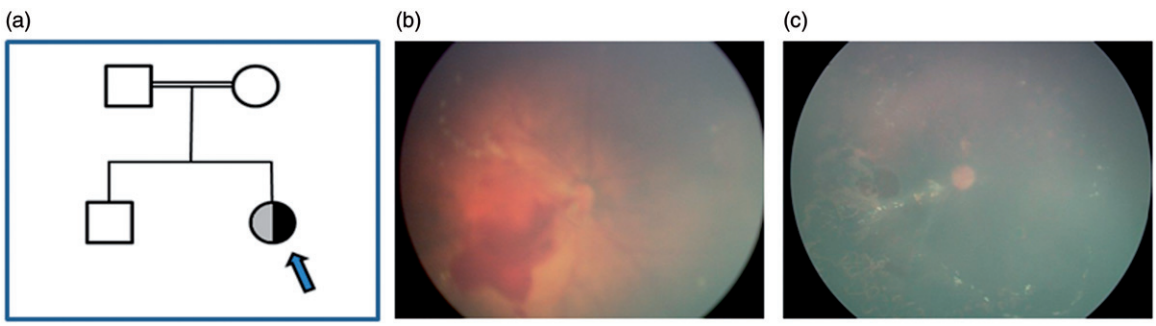

FIGURE 1. (a) Pedigree of the family: the consanguineous healthy parents carry point mutations in CFTR and TSPAN12, resulting in a daughter affected by cystic fibrosis and FEVR. (b) Photograph of the fundus of the right eye showing extensive neovascularization at the diagnosis. (c) Photograph of the fundus 10 months after the vitrectomy.

apparently healthy carrier parents and a severely affected homozygous daughter.

DISCUSSION

On the basis of the recent paper describing recessive mutations in *TSPAN12*,[5] we screened this gene in a patient affected by exudative vitreoretinopathy and cystic fibrosis. We identified the same homozygous causative mutation (c.668 T>C) already detected by Poulter.[5] Further evidence, including the Pakistani origin and the contemporary presence of cystic fibrosis and FEVR, suggests a blood relationship between the patients in both studies. Other families described in the same paper indicate a dosage sensitive phenotype. In particular, a severe condition is related to the presence of two mutations. A single variation causes only a mild phenotype. To correctly clarify the pattern of inheritance, we evaluated our proband's parents, bearing the heterozygous mutation. The complete absence of visual and retinal defects in the carriers provides strong evidence of the recessive transmission of the disease: in our case, subjects with a single heterozygous mutation in *TSPAN12* do not have any ocular phenotype, while the homozygous patient shows the disease.

As described before, the proband is affected by cystic fibrosis and by vitreoretinopathy. The co-segregation of two mutations in two different disease genes is an interesting finding. Even if it is a rare event, other patients affected by cystic fibrosis and FEVR can probably be identified. In such a case, especially for consanguineous families, mutations in *TSPAN12* could be prioritized, considering the cytogenetic localization of *TSPAN12* and *CFTR*.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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