

## An Egyptian Family with Autosomal Recessive Familial Exudative Vitreoretinopathy and Newly Reported Associations

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**Abstract:** Back ground: Familial exudative vitreoretinopathy (FEVR) is a rare genetic ophthalmic disorder, having different modes of inheritance, affecting the retina and the vitreous body. In most cases, it takes a progressive course during childhood and adolescence. Aim of the work: to evaluate an Egyptian family with familial exudative vitreoretinopathy and newly reported associations. Patients and methods: All family members comprising parents, 5 sons and two daughters were subjected to detailed medical history, family pedigree study, clinical examinations and investigations including complete eye evaluation, fundus photography, electrocardiography, echo Doppler study, abdominal ultrasonography and plain radiological examination of the spine and chest. Also a complete blood picture was done and glucose 6- phosphate dehydrogenase (G6PD) activity was measured and finally, chromosomal studies were done for all family members using G- banding technique. Results: Fundus examination of the 5 sibs revealed the diagnosis of familial exudative vitreoretinopathy. The cardiac findings included mitral valve prolapse (MVP) diagnosed in all family members except the mother (8 cases). Family members also, had mild mitral regurge except the fifth son. Tricuspid valve prolapse and tricuspid regurge were diagnosed as well in one case while tricuspid regurge without prolapse was diagnosed in another one. Family pedigree analysis showed an autosomal dominant pattern of inheritance of mitral valve prolapse, and autosomal recessive (AR) pattern of inheritance of FEVR in the same family. Bony abnormalities included mid-dorsal scoliosis in one member and flat feet in 4 cases. Laboratory studies showed one case with G6PD deficiency and chromosomal studies revealed that all family members had normal karyotype. Conclusion: The examined family lives in Marsa Matrouh (West Lower Egypt), which is a closed region where several generations stick to the habit of marriage their direct cousins. This may explain the presence of more than one inherited disorder with different modes of inheritance in the same family and the appearance of new associations with the disorder.

**Key words:** AR, FEVR, Egypt.

### INTRODUCTION

Familial exudative vitreoretinopathy (FEVR) is a rare eye disease affecting the retina and the vitreous body. It is a progressive genetic disease running in families. In most cases, it takes a progressive course during childhood and adolescence. The progression usually stops by the age of 20 years<sup>[8]</sup>.

FEVR usually occurs in full-term newborns without previous treatment with hyperbaric oxygen<sup>[1]</sup>. It varies in intensity as severely affected patients may be legally blind during the 1st decade of life, whereas mildly affected individuals may not even be aware of symptoms and may only be diagnosed by fluorescein angiography<sup>[12]</sup>.

The autosomal dominant form (AD) is the most common form of inheritance of FEVR. Three dominant genes are known to cause dominant FEVR and there

still may be more genes that may cause dominant FEVR or react with the dominant, recessive or X-linked forms and cause different outcomes in patients. All of the dominant genes seem to be located near each other on the 11th chromosome. The second most common form of transmission is X-linked. Patients with the X-linked form have quite often mutations in the Norrie disease gene. It is quite possible that this type of FEVR may also be caused by other genes as well. Autosomal recessive type of inheritance is the rarest form; a candidate-locus-directed genome scan shows linkage to the region on chromosome 11q<sup>[6]</sup>.

Diagnosis and intervention is essential in view of the lifelong progression of the disease, late exacerbations, frequent involvement of family members and poor surgical results. Family screening and early prophylaxis are recommended to prevent avoidable blindness from this under -diagnosed disease<sup>[11]</sup>.

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Today only the symptoms of FEVR can be treated. In the future, it might be possible to find a specific curative treatment, either through gene therapy or through another modality, if enough knowledge is gained about the genetics of FEVR. Understanding the genetics of FEVR can also lead to the development of more genetic tests. By these genetic tests, a family with a history of FEVR can get more efficient counselling about their risk of having children with FEVR<sup>[6]</sup>.

In the present work, five members of one family were examined, including 4 sons and one daughter, affected by familial exudative vitreoretinopathy associated with other manifestations, to detect the pattern of inheritance, and to compare the associated findings in these patients with that reported in the literature.

#### Patients and Methods:

This study included 5 members (4 sons and one daughter) of one family who lives in Marsa Matrouh, complaining of gradual deterioration of vision at different ages of onset and with different durations. The patients were referred from the Retina Clinic (Research Institute of Ophthalmology) to the Genetic Unit for investigations. All family members comprising parents, 5 sons and two daughters were subjected to full medical history, family pedigree study, clinical examinations and investigations including complete eye evaluation, fundus photography, electrocardiography, echo Doppler study at rest through transthoracic approach [using Sigma 44 machine, Kontron Paris and 3.5 megahertz DS cardiac transducer], abdominal ultrasonography using the same machine with 3.5 megahertz abdominal transducer. Plain radiological examination [using Philips Diagnost 5 machine] of the spine extremities and chest. Also a complete blood picture was done and glucose 6- phosphate dehydrogenase (G6PD) activity was measured and finally, chromosomal studies were done for all family members using G- banding technique<sup>[9]</sup>.

#### RESULTS AND DISCUSSION

Parents were first cousins and fundus examination of the 5 sibs complaining of deterioration of visual acuity revealed the diagnosis of familial exudative vitreoretinopathy. Figure (1), showed the fundus picture of the disease. The cardiac findings included mitral valve prolapse (MVP) that was diagnosed in all family members except the mother (8 cases) associated with apical systolic murmur and mid to late systolic click. Figure (2) showed echocardiography of mitral valve prolapse in five members of the family. All family members including the mother had mild mitral regurge

except the fifth son. Mild thickening in the anterior mitral leaflet could be detected only in two cases. Tricuspid valve prolapse and tricuspid regurge were diagnosed as well in one case while tricuspid regurge without prolapse was diagnosed in another one. ECG findings revealed inferior (t) wave changes observed in the father and two sons. Family pedigree analysis is illustrated in figure (3) shows an autosomal dominant pattern of inheritance of mitral valve prolapse, while figure (4), illustrates the autosomal recessive pattern of inheritance of FEVR in the same family

The radiological findings were that of bony abnormalities as diagnosed by plain radiogram included mid-dorsal scoliosis in one member as seen in (figure 5), and flat feet in 4 cases. Mitralisation of the left cardiac border was shown in (Figure 6). Abdominal ultrasonography revealed renal calcifications in two sons and two daughters.

Laboratory studies showed one case with G6PD deficiency. Chromosomal studies revealed that all family members had normal karyotype.

The results of general examination and investigations are summarized in table (1).

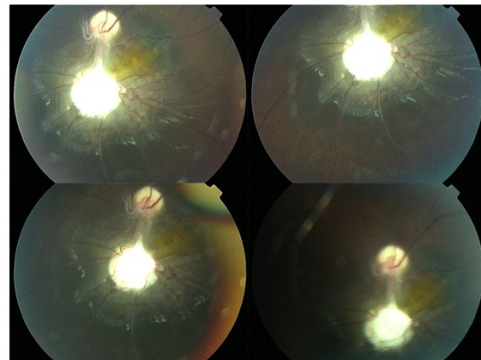
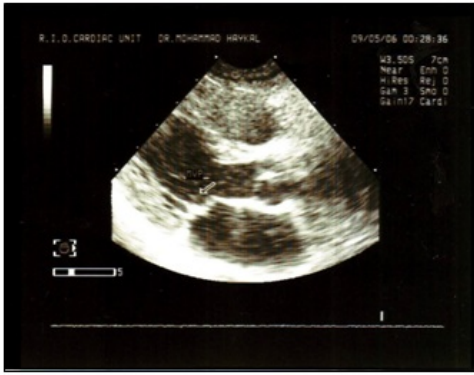


Fig. 1: Shows the fundus picture of familial exudative vitreoretinopathy



Case No. 1



Case No. 2



Case No. 3



Case No. 4



Case No. 5

Fig. 2: Two Dimensional echocardiography from Left lower parasternal longitudinal view showing mitral valve prolapse in five members of the family (cases1-5)

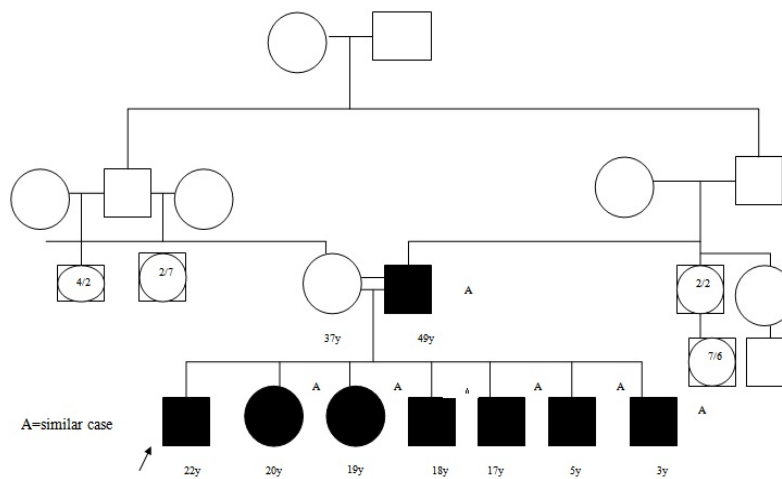
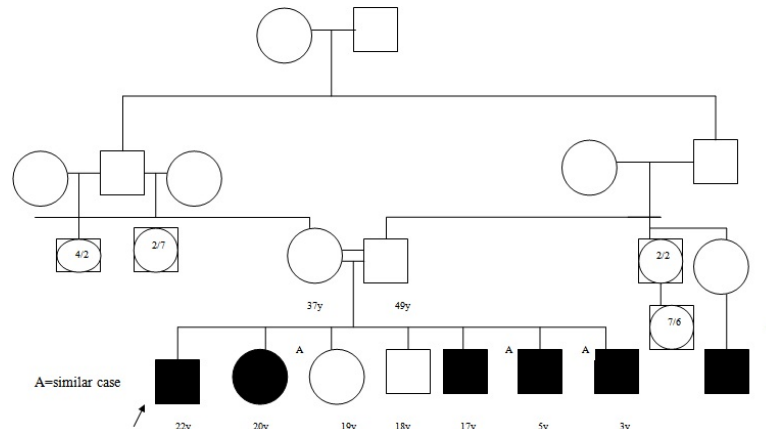


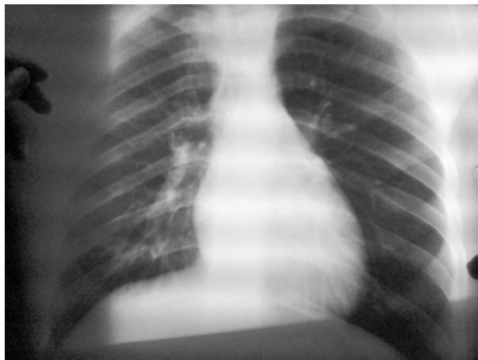
Fig. 3: Pedigree of the examined family showing autosomal dominant pattern of inheritance of mitral valve prolapse



**Fig. 4:** Pedigree of the examined family showing autosomal recessive pattern of inheritance of familial exudative vitreoretinopathy.



**Fig. 5:** Plain chest radiogram showing mid-dorsal scoliosis concave to the left side



**Fig. 6:** Plain chest radiogram showing mitralization manifested by straightened of the left cardiac border with rounding of the right cardiac border denoting mitral valve disease.

**Discussion:**

FEVR is genetically heterogeneous, with an autosomal dominant, an X-linked, and a rare autosomal recessive mode of inheritance described, with the

autosomal dominant mode of inheritance being the most common<sup>[12]</sup>. In the present work, a family with FEVR was described. Family pedigree analysis revealed that the mode of inheritance is autosomal recessive. Few reports of autosomal recessive pattern of inheritance of FEVR have been published. The first report was in 1997, by<sup>[10]</sup> In 1998. De Crecchio *et al.*, described two unrelated families with FEVR that showed apparent autosomal recessive inheritance. They reported that, compared with autosomal dominant and X-linked recessive inheritance, the recessive form showed earlier onset at birth and a more severe and progressive course Jiao *et al.*<sup>[5]</sup>, described autosomal recessive FEVR in multiple individuals from three consanguineous families of European descent.

Examination of the family members in the present study revealed associated mitral valve prolapse in all sibs, mid-dorsal scoliosis in the elder male patient, mitralized cardiac border in the youngest female daughter, renal parenchymal calcifications in 2 sons and 2 daughters and glucose 6 phosphate dehydrogenase deficiency in the 3<sup>rd</sup> son. Examination of the parents revealed mitral valve prolapse and mitral regurge in the father but only mitral regurge in the mother, and no bony abnormalities. Review of the London Dysmorphology Data Base (LDDb), OMIM, and recent medical literature searching for these associations showed that these associations were not previously reported. Bony abnormalities associated with FEVR in the form of osteoporosis-pseudoglioma were described by<sup>[3]</sup>. The association of the FEVR and dorsal scoliosis observed in the first case could be considered as a new syndrome of autosomal recessive inheritance or together with mitral valve prolapse and flat feet may represent a form of non-differentiated connective tissue dysplasia. The association of FEVR and glucose 6 phosphate dehydrogenase deficiency, which is inherited as an X-

**Table 1:** General examination and investigations of family members with familial exudative vitreoretinopathy.

CRIETERIA	Father	Mother	1 <sup>st</sup> Son	2 <sup>nd</sup> Son	3 <sup>rd</sup> Son	4 <sup>th</sup> Son	5 <sup>th</sup> Son	1 <sup>st</sup> Daughter	2 <sup>nd</sup> Daughter
FEVER	no	no	+ve	+ve	+ve	+ve	no	+ve	no
Scoliosis	no	no	+ve	no	no	no	no	no	no
Flat feet	no	no	+ve	+ve	+ve	no	+ve	no	no
Renal calcification	no	no	+ve	no	+ve	no	no	+ve	+ve
Mitralized cardiac border	no	no	no	no	no	no	no	no	+ve
Mitral valve prolapse	+ve	no	+ve	+ve	+ve	+ve	+ve	+ve	+ve
Thick cusp	no	no	no	+ve	no	no	+ve	no	no
Systolic click	+ve	no	+ve	+ve	+ve	+ve	+ve	+ve	+ve
Systolic murmur	+ve	no	+ve	+ve	+ve	+ve	+ve	+ve	+ve
Mitral regurge	+ve	+ve	+ve	+ve	+ve	+ve	no	+ve	+ve
Tricuspid prolapse	no	no	no	no	+ve	no	no	no	no
Tricuspid regurge	no	no	no	+ve	+ve	no	no	no	no
T wave change	+ve	no	+ve	no	+ve	no	no	no	no
G6-PD deficiency	no	no	no	no	+ve	no	no	no	no
Chromosomal studies	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal

linked recessive disorder, may be considered as a new association. The reported mitral valve prolapse in all patients may be an association or a different additional inherited disorder as it is presented in the parents and unaffected sibs. Familial mitral valve prolapse is an autosomal dominant disorder, characterized by prolapse of one or both mitral leaflets into the left atrium during systole. It seems to be the most common inherited cardiovascular disorder. The disorder is common and affects 4-8% of young adults and it is usually benign and non progressive, but chordal rupture, bacterial endocarditis, and even sudden death may occur. A gene for the condition has been mapped to human chromosome 16 (16p12.1-p11.2). Mitral valve prolapse presentation may also, be attributed to magnesium deficiency. Identification of Mg deficiency in prenatal or post natal period may prevent the appearance of mitral valve prolapse syndrome in genetically prone individuals<sup>[4]</sup>. Some cases were associated with Marfan syndrome, Ehlers-Danlos syndrome, and osteogenesis imperfecta. Persons with mitral valve prolapse may have an increased incidence of keratoconus, but this claim is disputed<sup>[7]</sup>.

The examined family lives in Marsa Matrouh (West Lower Egypt), which is a closed region where several generations stick to the habit of marriage their direct cousins. This may explain the presence of more than one inherited disorder with different modes of inheritance in the same family and the appearance of new associations with the syndrome.

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