Homozygous mutation in ABCA4 associated with cone rod dystrophy in a patient with Turner syndrome

Dystrophie rétinienne liée à une mutation homozygote dans le gène ABCA4 associée à un syndrome de Turner

Yousra Falfoul[1], Imen Habibi[2], Ahmed Turki[1], Achraf Ben Yakhlef[1], Khaled El Matri[1], Ahmed Chebil[1], Nibrass Chaker[1], Daniel Schorderet[2], Leila El Matri[1]

1-Service B, Institut Hédi Raies d'ophtalmologie de Tunis, Université Tunis El Manar, Faculté de Médecine de Tunis
2-Institute for Research in Ophthalmology (IRO), Sion, Switzerland,UNIL, Lausanne

RÉSUMÉ

But: Nous rapportons l'observation d'une fille ayant un syndrome de Turner avec une dystrophie rétinienne de type cônes-bâtonnets liée à une mutation dans le gène ABCA4.

Méthodes: Il s'agit d'une fille de 12 ans adressée pour baisse progressive de l'acuité visuelle associée à une héméralopie et à un retard statural. Nous avons effectué une étude clinique, un caryotype du sang périphérique et une analyse moléculaire. L'ADN a été adressé pour séquençage haut débit et les variants localisés dans les régions homozygotes ont été validées par séquençage Sanger.

Résultats: L'examen du fond d'oeil a révélé une dystrophie rétinienne de type cônes-bâtonnets. L'examen général a montré une coarctation de l'aorte et un utérus infantile. Le caryotype du sang périphérique a révélé une monosomie 45X. le séquençage moléculaire a montré une mutation homozygote c.[885delC];[885delC] dans le gène ABCA4 et a exclu les mutations dans RPGR et dans ODF15.

Conclusions : Le syndrome de Turner peut s'associer à diverses manifestations oculaires. Cependant, dans ce cas nous postulons l'hypothèse d'une association rare entre une monosomie X ayant occasionné un syndrome de Turner et d'une dystrophie rétinienne par mutation dans ABCA4.

Mot clés : syndrome de Turner, dystrophie de type cônes-bâtonnets, gène ABCA4

SUMMARY

Purpose: We report a special case of a patient who presented with two rare genetic diseases, Turner syndrome and cone-rod dystrophy (CRD), caused by mutation in the ABCA4 gene.

Methods: We present a case of a 12-year-old female with a progressive visual loss, poor night vision and short stature. We performed a clinical, karyotype of peripheral blood and molecular genetic study. DNA sample from the index patient was subjected to whole exome sequencing. Variants localized in homozygous regions were validated by Sanger sequencing.

Results: Fundus examination presented CRD phenotype and the general examination revealed short stature, aortic coarctation and infantile uterus, without visible ovaries on pelvic ultrasound. The karyotype of peripheral blood showed monosomy 45,X. We identified a known homozygous deletion c.[885delC];[885delC] in ABCA4, resulting in a frameshift at the position p.[L296Cfs*4];[L296Cfs*4] . In addition, mutations in RPGR and ORF15 were excluded.

Conclusions : Several ocular disorders are known to be associated with Turner syndrome, however, in this case, we hypothesize that CRD is not related to Turner syndrome but may be a manifestation of the lack of a normal X chromosome with ABCA4 mutation.

Key-words: Turner syndrome, cone rod dystrophy, ABCA4 mutation

Correspondance
Yousra Falfoul
Service B, Institut Hédi Raies d'ophtalmologie de Tunis / Université Tunis El Manar, Faculté de Médecine de Tunis
yosra.falfoul@yahoo.fr

INTRODUCTION

Turner syndrome results from chromosomal aberration that consists of the absence of the X chromosome. Its incidence is estimated to be 1/2000 to 1/3000 among live births in females [1,2]. Clinically, this syndrome is characterized by a female phenotype with short stature and ovarian dysgenesis. Several ocular disorders are associated with Turner syndrome including amblyopia, strabismus, ametropia, ptosis, nystagmus, hypertelorism, antimongoloid palpebral fissures, red-green deficiency, congenital glaucoma and blue sclera [3–6].

We report the phenotypic characteristics and genetic results in a 12-year-old female with Turner syndrome.

CASE PRESENTATION

We report the case of a 12-year-old female who was admitted to the B Department Hédi Raies institut of Ophtalmology in Tunis, Tunisia suffering from progressive visual loss and poor night vision. She did not report any pathological or ophthalmological history in the family, nor parental consanguinity. The general examination was normal, except for a short stature (-3 SD). A complete ophthalmological evaluation was performed as well as fundus photography; fundus autofluorescence (FAF) (Heidelberg Spectralis; Heidelberg-Engineering, Heidelberg, Germany); optical coherence tomography (OCT) (Swept source DRI OCT-A Triton®, Topcon, Tokyo,

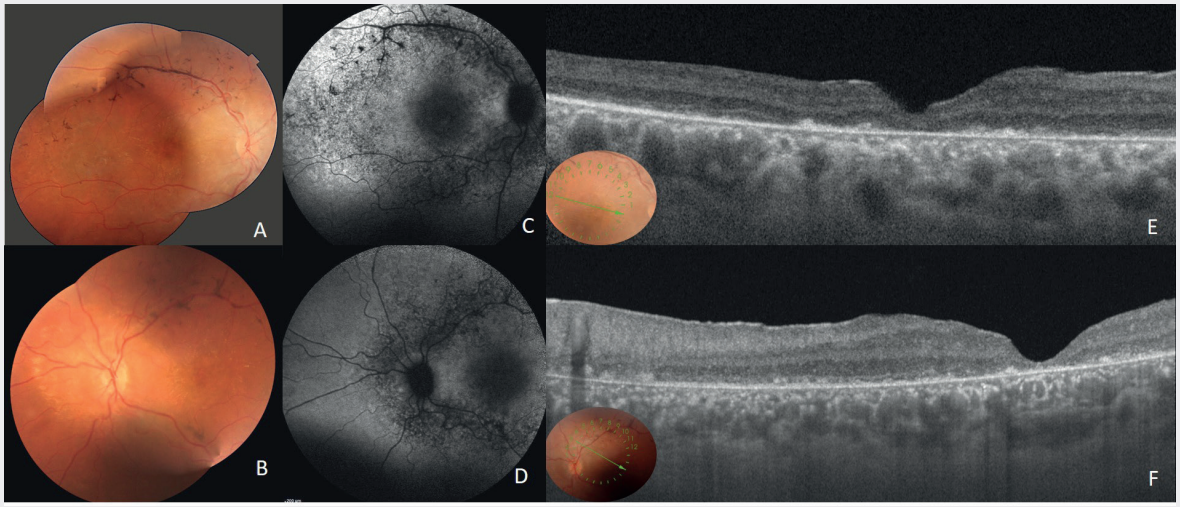

Figure 1. Fundus photo, autofluorescence and OCT. CRD (A, B) with heterogeneous diffuse hypo autofluorescence (C, D). Alteration of ellipsoid zone and diffuse retinal atrophy (E, F).

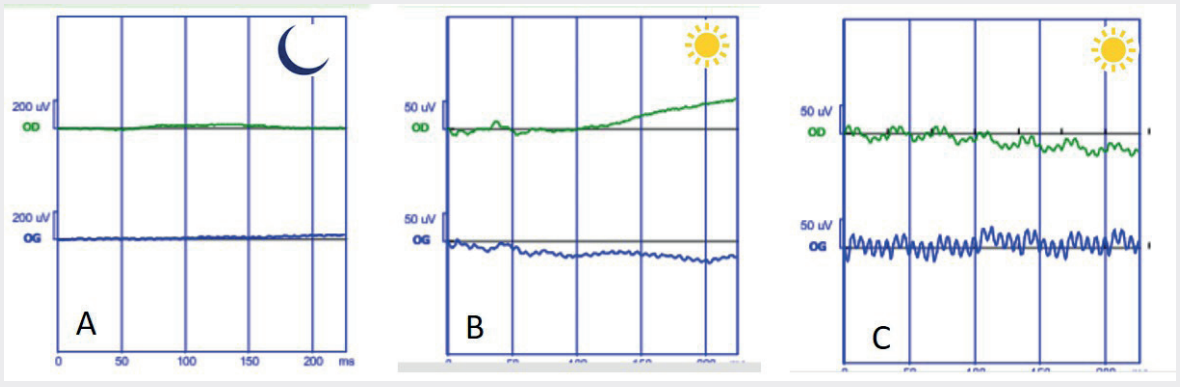

Figure 2. Full field ERG. Decreased scotopic (A), photopic (B) and flicker (C) responses

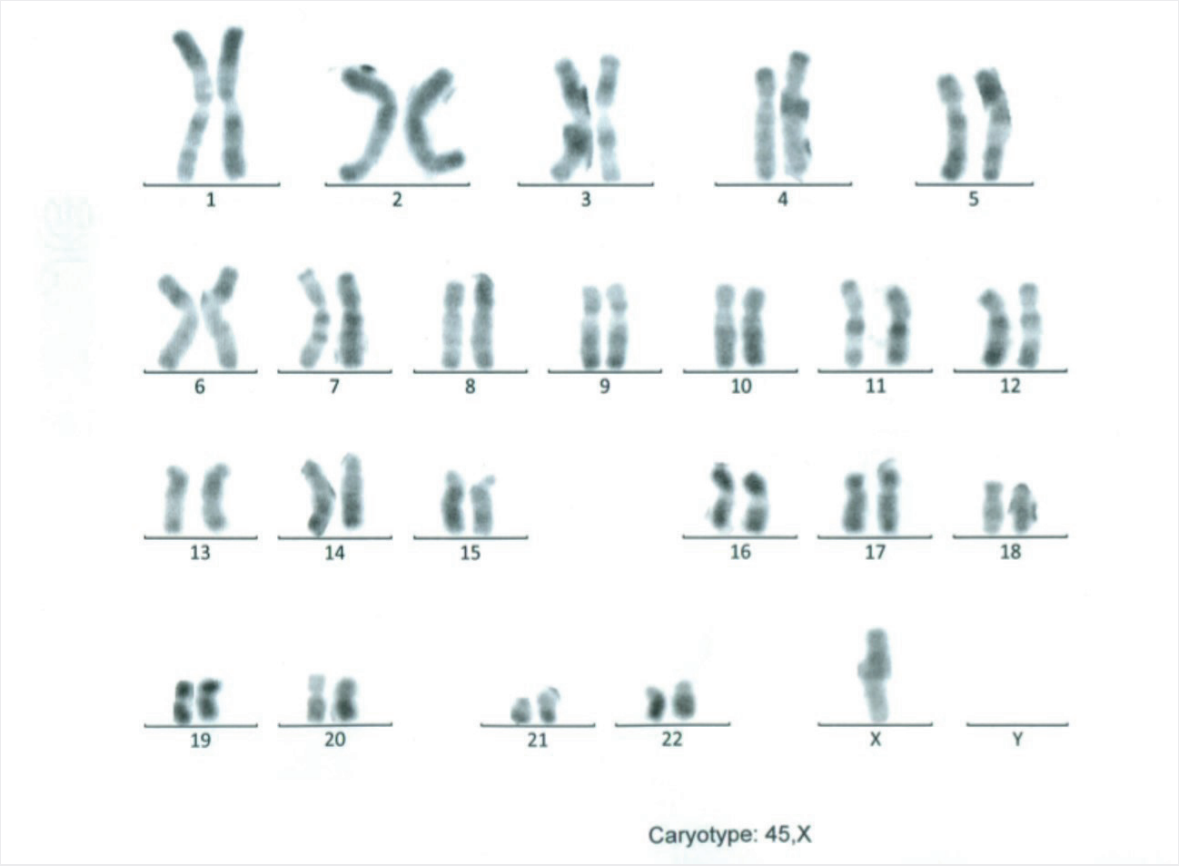

Figure 3. Karyotype. monosomy 45,X

Japan) and full-field electroretinogram (ERG) (Métrovision, France). The best corrected visual acuity was 1/20 in both eyes. Anterior segment and intraocular pressure were normal. The eye fundus examination showed pallor of the optic disc, attenuated retinal vessels, paravascular bone spiculed pigmentations and an epimacular membrane (Figure 1 A and B). FAF showed paravascular and macular heterogeneous hypoautofluorescence (Figure 1 C and D). The OCT confirmed the presence of membrane and showed diffuse alteration of ellipsoid zone (Figure 1 E and F). Additionally, full-field ERG showed decreased photopic and scotopic responses, attesting the damage of both cones and rods (Figure 2). In light of this clinical presentation, CRD was suspected and the patient was referred to Charles Nicolle hospital hereditary diseases department for genetic analysis.

The karyotype of peripheral blood showed monosomy 45,X confirming the diagnosis of Turner syndrome (Figure 3). Cardiovascular examination revealed aortic coarctation. Pelvic ultrasound showed an infantile uterus and the ovaries were not visible.

Whole exome sequencing analysis identified a known ABCA4 deletion (c.885delC), resulting in a frameshift followed by a premature stop codon at position p.L296Cfs*4. This mutation was homozygous in the affected child and heterozygous in the unaffected mother. In addition, we excluded the presence of mutations in RPGR and ORF15 .

DISCUSSION

Turner syndrome is one of the most frequent sex chromosome aberrations [7] and it is caused by the

only viable monosomy, that of X chromosome. To our knowledge, four cases of Turner syndrome with retinitis pigmentosa have been previously reported in the literature, however, three of these were presented without molecular genetic confirmation [8]. The fourth case was that of a 28-year-old patient in which the genetic analysis showed a novel mutation in the RPGR [8].

Our patient is a 12-year-old female diagnosed with CRD whose karyotype analysis revealed a homogeneous X monosomy. The identification of X-linked mutation was expected, however, the molecular genetic analysis uncovered a rare variant in ABCA4 (c.885delC, p.L296Cfs*4). The deletion (c.885delC) discovered in our patient is predicted to cause a frameshift at p.296 followed by a premature stop at p.299, generating a truncated ABCA4 protein [9]. This rare variant has been previously described in a patient with autosomal recessive Stargardt disease. However, the phenotype of our patient was different as ERG revealed severe cone and rod involvement. To our knowledge, this is the first reported case of CRD due to ABCA4 mutation in a patient with Turner syndrome.

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