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Clinical report

Incomplete penetrance of biallelic *ALDH1A3* mutations

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ABSTRACT

The formation of a properly shaped eye is a complex developmental event that requires the coordination of many induction processes and differentiation pathways. Microphthalmia and anophthalmia (MA) represent the most severe defects that can affect the ocular globe during embryonic development. When genetic, these ocular disorders exhibit large genetic heterogeneity and extreme variable expressivity. Around 20 monogenic diseases are known to be associated with MA as main phenotype and the penetrance of mutations is usually full in the patients. Some of these genes encode proteins involved in the vitamin A pathway, tightly regulated during eye development. One of those retinoic acid synthesis genes is *ALDH1A3* and biallelic mutations in that gene have been recently found to lead to MA phenotype in patients. Interestingly, we report here the lack of ocular defect in a girl carrying the same homozygous mutation in the *ALDH1A3* gene than the affected members of her family. Thus, this report brings new information for the phenotype–genotype correlation of *ALDH1A3* mutations and raises important questions, especially in terms of genetic counselling given to the patients and their families. Furthermore, these data contribute to the more general understanding that we have for the complex genetic inheritance of these MA phenotypes.

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1. Introduction

Microphthalmia and anophthalmia (MA) represent the most severe defects that can affect the ocular globe during embryonic development. These malformations are relatively common with an estimated prevalence of 1 per 10,000 and 1 per 5000 live births respectively [Verma and Fitzpatrick 2007]. Clinical anophthalmia is defined as the clinical absence of the ocular globe (in the presence of ocular adnexa) and microphthalmia as an eye with a reduced size, which is by definition less than −2 SD in size in relation with the age.

While infectious or toxic factors are known causes, genetic origin is actually a predominant etiology for these ocular globe anomalies [Bermejo and Martinez-Frias 1998] and is highly heterogeneous. Indeed, while mutations in the *SOX2* gene are the major cause of these MA disorders, representing around 10–15% of the MA population [Chassaing et al., 2014, Fantes et al., 2003], more than 20 genes are currently known to be responsible for this spectrum of ocular defects [Williamson and FitzPatrick, 2014]. All inheritance patterns have been described with mutations in these genes (autosomal recessive, autosomal dominant and X-linked patterns) and the penetrance of mutations in genes involved in such ocular anomalies is usually full in the patients. Moreover, these genetic disorders also exhibit variable expressivity, both between patients and within families. Indeed, each of these two ocular globe anomalies can affect one or both eyes, as well as being associated. These eye anomalies can also be isolated or associated

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with malformations affecting other systems [Slavotinek 2011].

Incomplete penetrance and variable expressivity are phenomena usually associated with mutations with dominant inheritance, rarely with recessive inheritance. Simply because, in dominant patterns, the expression of the unaltered allele can modify or compensate the effect of the altered allele on the phenotype, whereas, for recessive inheritance, there is classically a complete loss of function that cannot be restored by one of the alleles.

Nevertheless, the individual in the following pedigree illustrates a completely different phenomenon, that of incomplete penetrance of biallelic mutations in a known autosomal recessive disease. Indeed, we report herein the lack of ocular involvement in a girl carrying the same homozygous mutation in the *ALDH1A3* gene than the affected members of her family.

2. Clinical report

Semerci et al. [2014] recently described a large consanguineous Turkish family, in which a homozygous synonymous mutation (c.666G>A) involving the last nucleotide of the *ALDH1A3* exon 6, was found in siblings affected by MA [Semerci et al., 2014]. They demonstrated by RT-PCR the effect of this variation on splicing, leading to the skipping of the exon 6 and the in-frame deletion of 43 amino-acids (p.Trp180_Glu222del).

Here we report siblings belonging to the family described by Semerci et al. [2014] (respectively numbered by VI:2, VI:3, VI:4 and VI:5 both in the pedigree published by Semerci et al. [2014] and in the Fig. 1 shown in this article) in which the asymptomatic sister is carrying the same homozygous mutation in the *ALDH1A3* gene than her affected brothers and relatives (Fig. 1).

The proband (VI:2, Fig. 1) is a 10 year-old girl who has no medical history. She has normal eye examination with A scan ultrasonography showing an axial length estimated at 21,10 mm for the right globe (OR) and 21,06 mm for the left globe (OS) at 10 years-old and a normal eye fundus (Fig. 2).

She has two affected brothers. The first one (VI:3, Fig. 1) was born after a full term and normal delivery from a normal pregnancy. The infant was referred at 5 day-old to the ophthalmology department for orbital anomalies. His sensory and motor development was normal. On ophthalmological examination, there were no visible eyeball with a deep conjunctival cul-de-sac in the orbit and a bilateral small palpebral fissure was observed. The clinical diagnosis of anophthalmia was confirmed by A and B scan ultrasonography (Quantel medical) showing only a small mass (Fig. 3, A). The younger brother (VI:4, Fig. 1) was also born at term after a normal pregnancy and normal delivery. His examination showed a severe microphthalmia with microcornea OR and anophthalmia OS with short palpebral fissures (Fig. 3, B). Moderate autism was diagnosed at the age of 5 years.

ALDH1A3 gene (ENST00000329841) direct Sanger sequencing revealed the homozygous c.666G>A mutation in the *ALDH1A3* gene in the two affected brothers as well as in the unaffected sister. Repeated sequencing analyses on three independent samples confirmed the presence of the biallelic homozygous mutation in the asymptomatic sister. The c.666G>A mutation in the *ALDH1A3* gene was found heterozygous in both parents and in the other asymptomatic sister VI:5.

The deleterious effect of the mutation on *ALDH1A3* exon 6 splicing (exon 6 skipping) was confirmed by RT-PCR analysis in the unaffected individual VI:2 and the affected individuals VI:3 and VI:4. This analysis showed comparable amount of aberrantly spliced transcripts and residual normal splicing between those three siblings (Fig. 4).

3. Discussion

The formation of a properly shaped eye is the resulting sequence of coordinated induction processes and differentiation pathways. Any disruption in one of these events has the potential to generate a MA phenotype. One of the key signaling pathways in eye

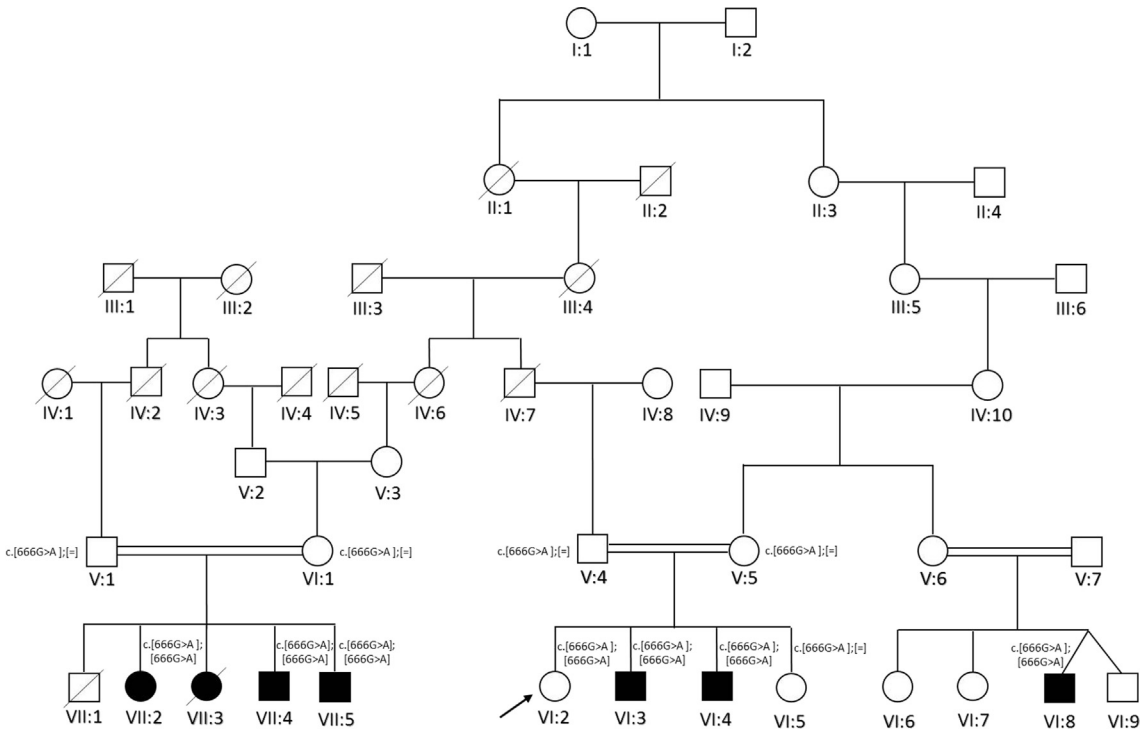

Fig. 1. Pedigree of the family. Black squares and circles represent the affected males and females respectively. The proband is indicated by an arrow.

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