Identical Twins Exposed !

Best Disease, True Dominance ?

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Introduction

Best disease is generally perceived as a Mendelian macular dystrophy, transmitted as a dominant trait caused by mutations in the *BEST1* gene, but also autosomal recessive inheritance has been described. We report of a case of unusual expression of best-like disease in one sibling of a seven-year old twin-pair. Of whom, the father is known to have Best disease.

Methods

Clinical features of the proband were documented by means of Snellen best-corrected visual acuity (BCVA), color fundus photographs, fundus autofluorescence (FAF), optical coherence tomography (OCT), electro-oculogram (EOG), and a multifocal electroretinogram (mfERG).

His twin brother and his mother underwent a BCVA measurement, color fundus photograph, FAF, OCT, EOG, and a visual field test (Humphrey 30-2). Medical records of father were retrieved. Blood samples of both twins and parents were taken for genetic sequencing of the *BEST1* gene.

Results

The proband had a BCVA of 0.7 and 0.6. Color fundus photographs (**Figure 1A,B**) and FAF showed a diffuse irregularity of the reflex from the retinal pigment epithelium (RPE), including dispersed punctate flecks. OCT showed central macular detachments of the neuroretina with intraretinal cysts and small hyperreflective structures of the vitelliform material between the neuroretina and RPE, in the subretinal space (**Figure 2A,B**). The proband's eyes showed a very low EOG light rise (**Figure 3A, B**), and a reduced paracentral mfERG (**Figure 4**).

His twin and mother had a BCVA of 1.25 per eye. Photographs (**Figure 1C, D**), FAF and OCT (**Figure 2C, D**) of his twin brother and mother were normal. However, EOGs of his twin and mother were also subnormal (Arden ratio <1.9). Father had a BCVA of 0.4 per eye, and a vitelliform maculopathy.

DNA sequencing revealed that the proband had two heterozygous missense mutations in the *BEST1* gene: c.679T>A (p.(Tyr227Asn)) and c.934G>A (p.(Asp312Asn)). His twin was carrier of only one missense mutation: c.679T>A(p.(Tyr227Asn)). Both twins inherited c.679T>A (p.(Tyr227Asn)) from the father, and additionally the proband inherited c.934G>A (p.(Asp312Asn)) from the mother.

Conclusions

Two heterozygous missense mutations (c.679T>A (p.(Tyr227Asn)) and c.934G>A (p.(Asp312Asn)) in the *BEST1* gene lead to an early, atypical manifestation of Best disease in one sibling of a seven-year old twin-pair. The other family members had only one *BEST1* mutation. Surprisingly, the difference in *BEST1* genotype revealed that the presumed monozygotic twins were not identical! Both mutations have been described as autosomal dominant (Petruhkin et al. *Nature Genetics* 1998;19:241-6; Qu et al. *J Biol Chem* 2009;284:16473).

A marked difference in expressivity was observed within this family. All members showed electrophysiological abnormalities, but only the proband and the father had fundus lesions and subnormal vision. Although, further clinical manifestations may still occur later in life.

A possible explanation for the variable *BEST1*-associated phenotypes is the dependency on other genetic and environmental modifiers. Another explanation is that the proband's compound heterozygous mutations may have an additive effect. However, the future clinical course of each individual will show if Best disease is inherited as a true dominant trait within this family.

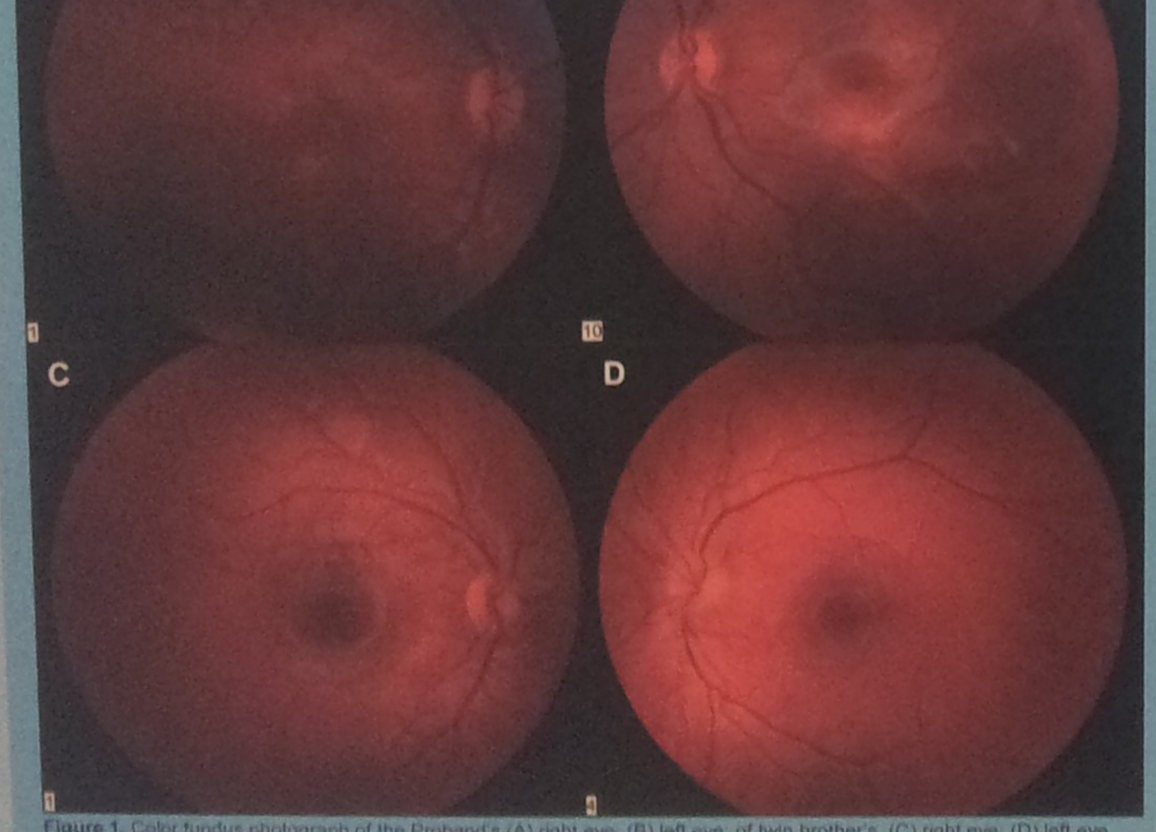

Figure 1. Color fundus photograph of the Proband's (A) right eye, (B) left eye, of twin brother's (C) right eye, (D) left eye

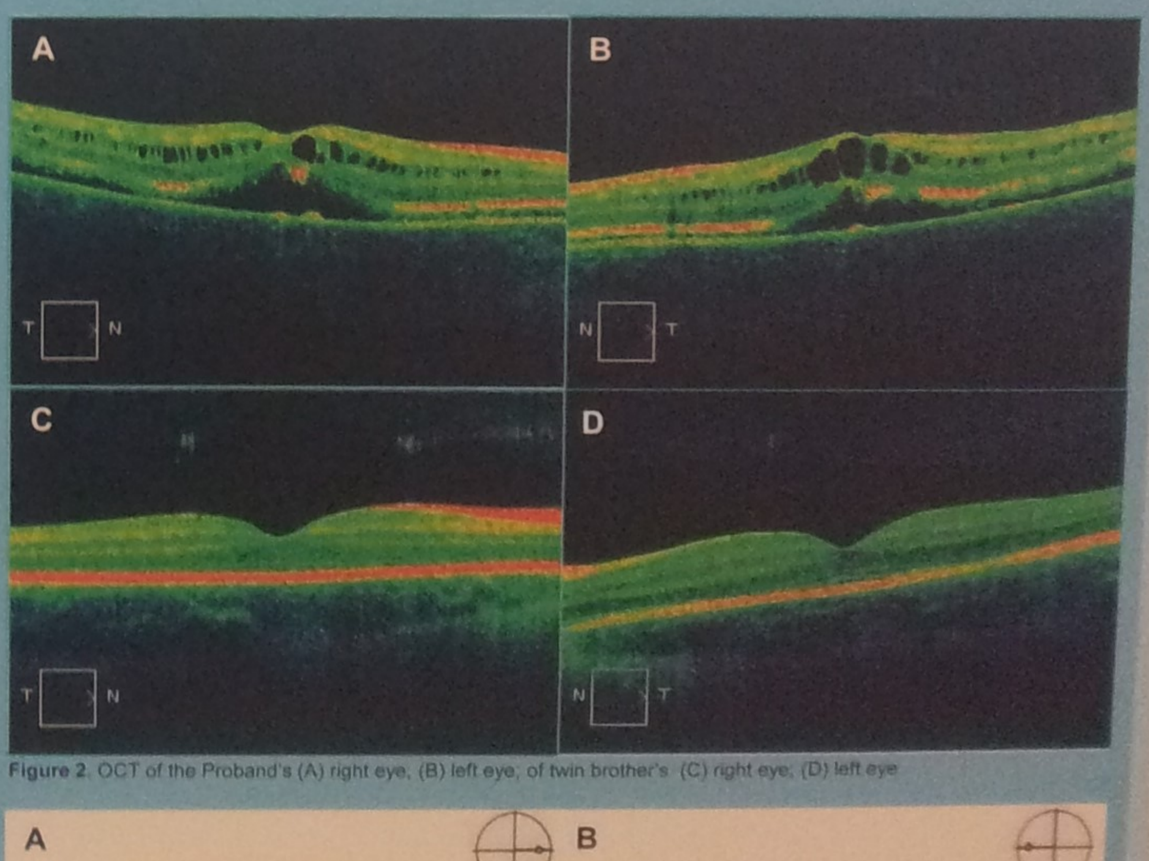

Figure 2. OCT of the Proband's (A) right eye, (B) left eye, of twin brother's (C) right eye, (D) left eye

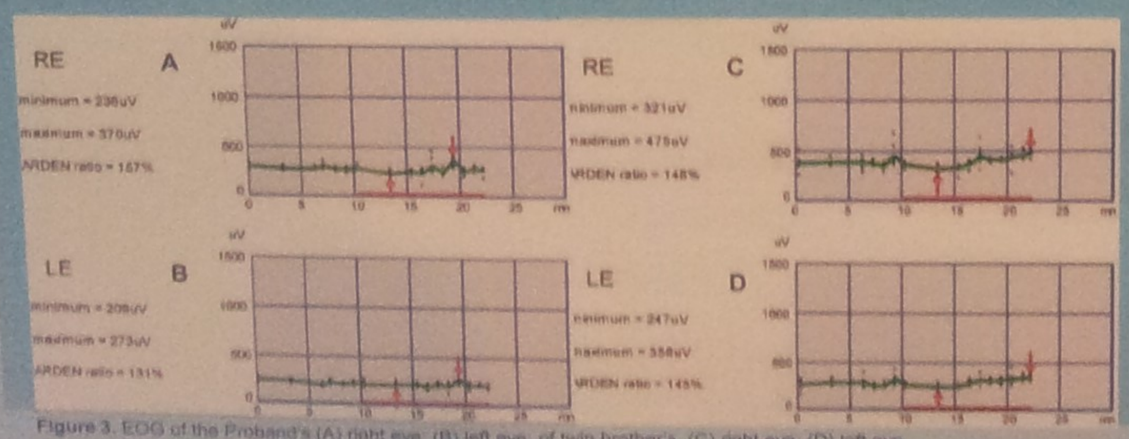

Figure 3. EOG of the Proband's (A) right eye, (B) left eye, of twin brother's (C) right eye, (D) left eye

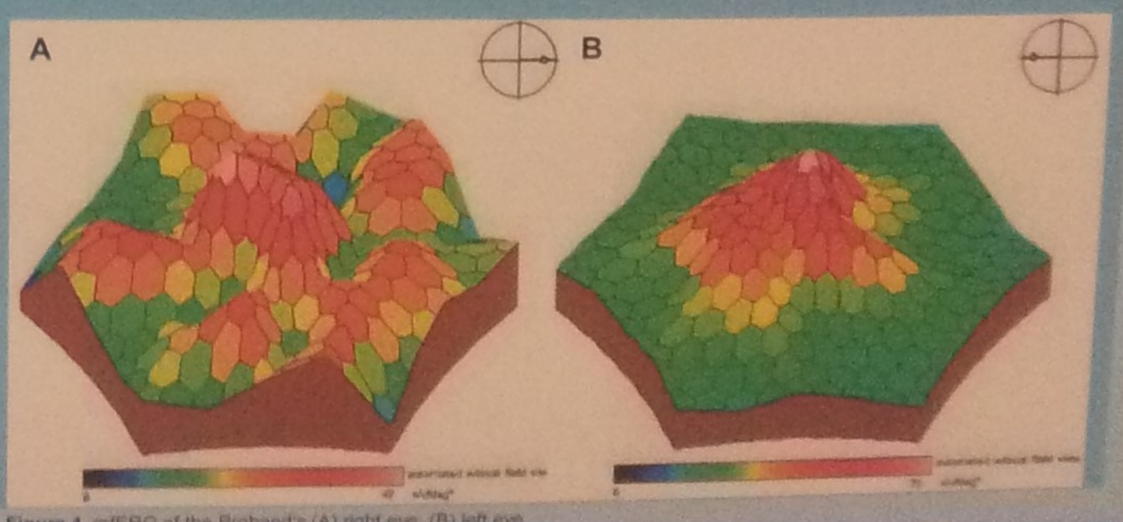

Figure 4. mfERG of the Proband's (A) right eye, (B) left eye