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CORRESPONDENCE

Sir,
Intra-familial phenotype variability in patients with Jalili syndrome

Jalili syndrome[1] is a rare autosomal-recessive disorder, which is caused by mutations in the *CNNM4* gene.[2,3] Two phenotypes are proposed: associated with bull's eye maculopathy and peripheral retinal degeneration (type A), or with minor retinal dystrophy (type B).[4]

We report two new cases (siblings of 15 and 16 years of age) with different retinal findings, and their relationship with the existing phenotype classification. Fundus examination revealed severe bull's eye maculopathy in one sibling and diffuse retinal dystrophy in the other.

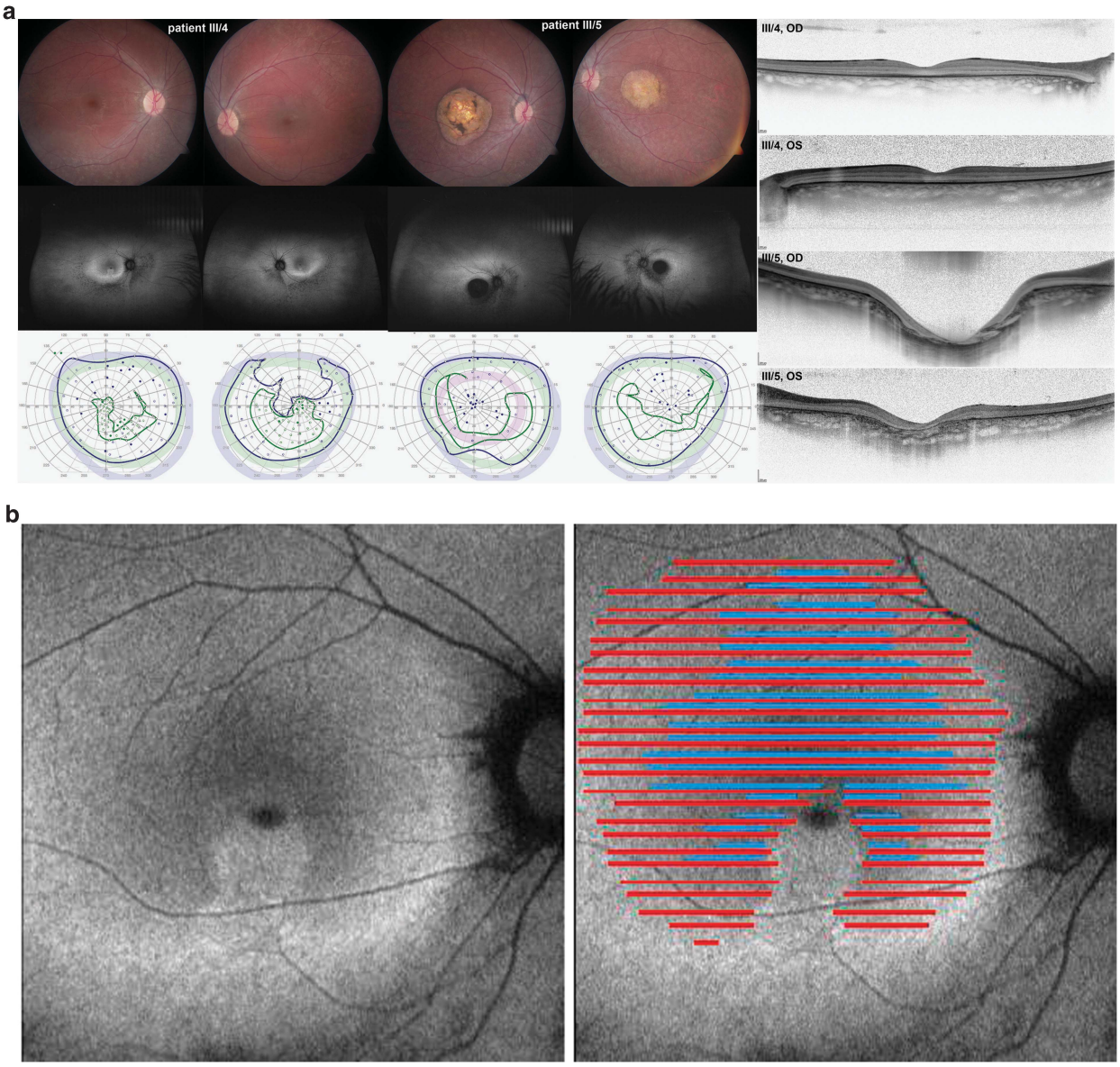

Figure 1 (a–e) Ocular and dental phenotype: ocular phenotype is illustrated by color fundus images and corresponding autofluoresence images, which show mild (III/4) to severe (III/5) maculopathy and retinopathy. Kinetic visual fields show a central scotoma and retained peripheral field sensitivity to large isopters (blue: V:4e; green: I:4e) in both patients, with the exception of the left eye of III/4 (lower panel). Horizontal line scans through the center of the macular are shown at the right. (a) Detailed retinal OCT analysis of the horizontal scans in this area of increased AF shows loss of the inner segment ellipsoid (illustrated by the absence of blue lines) and severe reduction of the outer retinal layers with merging of the outer limiting membrane (OLM) and the retinal pigment epithelium (RPE)/Bruch's membrane complex (absence of red lines). (b) Three stages of retinal layer changes are demonstrated on one horizontal line scan (yellow line, inset): absent inner segment ellipsoid (blue arrow), enhanced visibility of the inner plexiform layer (green arrow), and merging of the OLM and the RPE (red arrows). (c) Full-field ERG waveforms of the two patients and one age-matched control show severely reduced cone and rod function. (d) Color dental images and radiography show typical signs of AI (e).

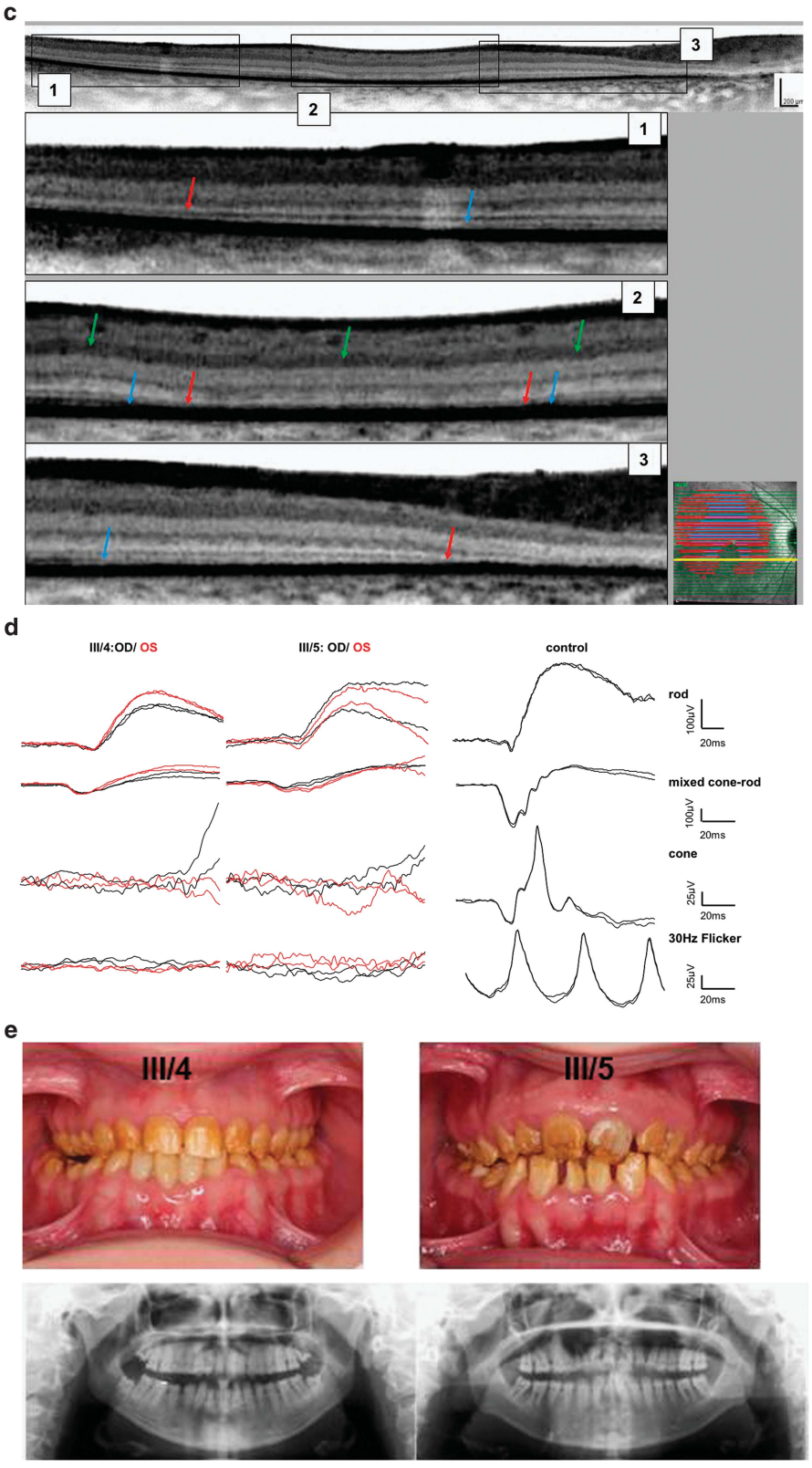

Figure 1 (Continued)

Table 1 Review of published *CNNM4* mutations and associated phenotype

Mutation 1	*Mutation 2*	*Author*	N	*M*	*F*	*Age (years)*	*VA*	*Nystagmus*	*Refraction (SE) (Dpt)*	*Fundus*	*ERG*[a]	*Origin*
c.1312dupC: p.L438P*fs**9	c.1312dupC: p.L438P*fs**9	Present study	2	0	2	15, 16	20/200, 20/400 (1/2 progressive)	Fine pendular (1/2)	−0.5 to +2.0	Optic atrophy Macular atrophy of minor to severe extent	Scotopic: reduced, delayed Photopic: NR	Kosovo
c.1312dupC: p.L438P*fs**9	c.1312dupC: p.L438P*fs**9	Polok *et al*[3]	2	1	1	7, 14	20/100 to 20/320	Pendular	Highly hypermetropic	Optic atrophy Macular atrophy w/ pigment mottling, periphery: white dots, 1/2: bone spiculae	Scotopic: b-wave reduced, slightly delayed Photopic: NR Repeat after 7 yrs: progressive deterioration	Kosovo
c.1312dupC: p.L438P*fs**9	c.1312dupC: p.L438P*fs**9	Parry *et al*[2] Michaelides *et al*[6]	2	2	0	8, 10	3/60	Fine pendular	Hypermetropic astigmatism	Macular atrophy and pigmentation	Rod response: abnormal Cone response: NR Repeat after 4 yrs: progressive deterioration	Kosovo
c.1312dupC: p.L438P*fs**9	c.1312dupC: p.L438P*fs**9	Zobor *et al*[7]	1	0	1	9	0.05, 0.125		Slight myopia, astigmatism	Optic atrophy RPE atrophy macula	Scotopic: slightly delayed Cone response: NR	Kosovo
c.1312dupC: p.L438Pfs9*	c.1312dupC: p.L438Pfs9*	Luder *et al*[5]	2	2		3, 4	20/200	Fine pendular to jerky	+8.0, +9.0	Optic atrophy Macular atrophy	Scotopic: reduced Photopic: NR	Kosovo
c.599C>A: p.S200Y	c.599C>A: p.Ser200Y	Parry *et al*[2] Jalili and Smith[1] Jalili[4]	31	17	14	0.25–50	6/36 to NLP	Fine pendular to jerky	average +3.0	RPE macular atrophy, normal optic disc (early) Chorioretinal atrophy, optic atrophy (late)	Scotopic ($n=3$): slightly to severely reduced b-wave Flicker response: NR	Gaza A
c.1813C>T: p.R605*	c.1813C>T: p.R605*	Parry *et al*[2] Jalili[4]	3	1	2	5, 6, 10	2/60 to 6/60	Fine	+2.0 to 4.0	Normal macula, few RPE changes (1/3), optic disc unremarkable	b-wave impaired, NR at age 10, cone: impaired to NR	Gaza B
c.586T>C: p.S196P	c.586T>C: p.S196P	Parry *et al*[2]	2[b]		2	5, 6						Turkey
c.1-?_1403+?del	c.1-?_1403+?del	Parry *et al*[2]	4[b]	3	1							Iran
c.2149C>T: p.Q717*	c.62_145 del: L21H*fs**185	Parry *et al*[2]	5[b]	5								Guatemala
c.971T>C: p.L324P	c.1690T>C: p.Q564*	Parry *et al*[2]	1[b]	1								Scotland
c.707G>A: p.R236Q	c.707G>A: p.R236Q	Polok *et al*[3]	3	2	1	2, 6, 12	Low	Rapid			Scotopic: normal to reduced, photopic: severely attenuated to NR	Lebanon
		Polok *et al*[3]	1	0	1	38					NR	

Table (Continued)

Mutation 1	*Mutation 2*	*Author*	*N*	*M*	*F*	*Age (years)*	*VA*	*Nystagmus*	*Refraction (SE) (Dpt)*	*Fundus*	*ERG*[a]	*Origin*
c.971T>C: p.L324P	c.971T>C: p.L324P						LP (10/200 at age 6)		Slight myopia, astigmatism	Optic atrophy, macular atrophy, bone spiculae in midperiphery		
c.1555C>T: p.R519*	c.1555C>T: p.R519*	Doucette *et al*[8]	4	1	3	16–28 (f.u. 16–20)	20/200 to HM, progression	Yes	Myopia	1/4 Maculopathy, 1/4 bone spiculae, 2/4 ND	1/4 Rod normal, cone absent, 1/4 rod borderline, cone absent, 2/4 ND CRD (not sure if ERG was done)	Northern Europe
c.1484C>T p.T495I	c.1484C>T p.T495I	Abu-Safieh *et al*[9]	1									
c.189del	c.189del	Coppieters	3	2	1					1/3 Reported: maculopathy, outer retinal atrophy w/ pigmentation		Algeria
p.D63E*fs**12	p.D63E*fs**12	*et al*[10]										

Abbreviations: CRD, cone–rod dystrophy; Dpt, diopter; ERG, full-field electroretinography; F, female; f.u., follow-up; HM, hand motion detection; LP, light perception; M, male; ND, not done; NLP, no light perception; NR, non-recordable; RPE, retinal pigment epithelium; SE, spherical equivalent; VA, visual acuity; w/, with; yrs, years.

[a]ERG description as written in publication.

[b]Numbers are based on the pedigree shown in publication.

Figure 2 Genetic testing results: Sanger DNA sequencing revealed a homozygous mutation in the two affected siblings (III:4 and III:5) as shown in the forward and reverse sequencing profiles from the DNA of the two patients. The mutation elongates the Oligo-C stretch in exon 1 of the *CNNM4* gene, which consists of six cytosine residues in the reference sequence, by 1 nucleotide (c.1312dup; p.Leu438Pro*fs**9). The DNA from the mother (II:4) is heterozygous for this mutation.

ERG showed cone–rod dysfunction. OCT demonstrated thinning of the outer retinal layers, in particular the outer nuclear layer and the outer photoreceptor segments. Both patients showed amelogenesis imperfecta (Figure 1). Phenotype details in comparison with the reported patients with *CNNM4* mutations are listed in Table 1. The same homozygous mutation c.1312dup; p.Leu438Pro*fs**9 was found in the affected patients (III:4, III:5). The mother (II:4) was heterozygous for this sequence alteration in *CNNM4* (Figure 2). The mutation within the cystathionine beta-synthase domain most likely results in a premature termination codon and nonsense-mediated mRNA decay of the mutant transcript. No mutation in the *ABCA4* gene was identified.

A similar dental phenotype with the characteristics of AI is described in all publications of patients with *CNNM4* mutations. In his phenotype dissection, Jalili described anterior open bite (AOB) in 2/30 and posterior open bite in 1/30 'type A' patients, whereas AOB was present in all three patients of the 'type B' phenotype. No open bite abnormality was seen on examination in our two patients and in one of the two patients reported by Luder *et al*.[5]

The intra-familial variability presented here is not consistent with a strict phenotype–genotype correlation, and may also argue against a rigid phenotype differentiation.[4] As the patients with 'type B' phenotype were examined at a younger age than the patient with 'type A', it is possible that those patients with 'type B' may have shown minimal macular signs as most of them had a visual impairment and signs of a cone–rod dystrophy.

The proposed strict differentiation between type A and B may not be applicable to all affected patients and families.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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C Gerth-Kahlert[1], B Seebauer[2,3], S Dold[2,3], JVM Hanson[1], H Wildberger[1], A Spörri[4], H van Waes[4] and W Berger[2,3,5]

[1]Department of Ophthalmology, University Hospital Zurich, Zurich, Switzerland
[2]Institute of Medical Molecular Genetics, Zurich, Switzerland
[3]Neuroscience Center Zurich, University and ETH Zurich, Zurich, Switzerland
[4]Clinic of Orthodontics and Paediatric Dentistry, Center of Dental Medicine, Zurich, Switzerland
[5]Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland
E-mail: christina.gerth-kahlert@usz.ch
Data were presented partially at the 2013 ARVO Annual Meeting.

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Sir,
Rupture of Descemet's membrane secondary to presumed non-accidental injury

We present the first case of multiple uniocular breaks in Descemet's membrane secondary to presumed non-accidental injury (NAI).

Case report

The first of twins, born at 35 weeks by spontaneous unassisted vaginal delivery, presented with a 2-week history of unexplained corneal haze in her left eye at the age of 4 months. Topical antibiotics and steroids were