Clinical and genetic features of Jalili syndrome in a North American patient cohort

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Introduction

Jalili syndrome is a rare multisystem disorder with most prominent features of cone-rod dystrophy and amelogenesis imperfecta[1,2]. Most cases have been described in large consanguineous families on multiple continents[3], with few cases reported in the Americas. One gene, *CNNM4*, has been implicated as a cause for this syndrome, and encodes a transmembrane protein with critical role in magnesium homeostasis[4,5].

Methods

We describe a retrospective case series of Jalili syndrome patients seen at the National Eye Institute Ophthalmic Genetics Clinic from 2016-2019. Three unrelated sporadic cases were systematically evaluated for ocular and systemic phenotype.

Results

Patient 1

- 15-year-old girl born from Guatemalan parents who presented with poor central vision, nystagmus, and light sensitivity.
- Snellen BCVA at distance of 20/250 in the right eye and 20/200 in the left eye.
- Auto-refraction showed a myopic refraction with astigmatism: -2.75+2.25x103 and -3.00+3.00x076 in the right and left eye, respectively.
- High frequency, low amplitude horizontal nystagmus, orthophoric.
- Anterior segment exam was unremarkable.
- Farnsworth D15 color vision testing revealed multiple axis errors.
- Scotopic electroretinography showed diminished amplitudes (~50%) and mildly delayed implicit times, while photopic bright flash and flicker ERG responses were unrecordable.
- **Genetic testing:** Molecular Vision Lab Panel v1
  - **homozygous *CNNM4* c.706C>T (p.Arg236Trp) variant** with one copy inherited from each parent.

Patient 2

- 16-year-old boy from Guatemala, who presented with poor central vision and light sensitivity.
- Snellen BCVA at distance of 20/200 in the right eye and 20/160 in the left eye
- Manifest refraction of +1.00+4.50x109 and -0.25+4.25x069, respectively.
- Mild end-gaze nystagmus and orthophoric.
- Anterior segment exam was unremarkable.
- Color vision testing by Farnsworth D15 revealed multiple axis errors.
- Scotopic ERG showed mildly diminished amplitudes and delayed implicit times, while photopic bright flash and flicker ERG were flat.
- **Genetic testing**: Molecular Vision Lab NGS Retinal Dystrophy SmartPanel v11
  - **homozygous *CNNM4* c.706C>T (p.Arg236Trp) variant** with one copy inherited from each parent.

Patient 3

- 3-year-old boy born from a Puerto Rican father and Caucasian mother with light sensitivity.
- Binocular visual acuity was 2.4cy/cm by Teller acuity cards (approximately 20/360 Snellen equivalent).
- Cycloplegic refraction showed myopia with astigmatism in both eyes: -3.25+2.25x090 and -3.25+2.50x095, in the right and left eye, respectively.
- Anterior segment exam was unremarkable.
- Systemic evaluation was notable for spastic paraplegia, developmental delay, and fatty liver. The patient was dependent on tracheostomy for respiration and gastrostomy tube for feeding.
- **Genetic testing**: Clinical exome sequencing
  - **homozygous for a frameshift variant in *CNNM4*: c.279delC (p.Phe93Leufs*31)**
  - variant was present in only the patient's father and not mother
  - SNP analysis revealed paternal uniparental isodisomy (UPD) for chromosome 2p22-2q37

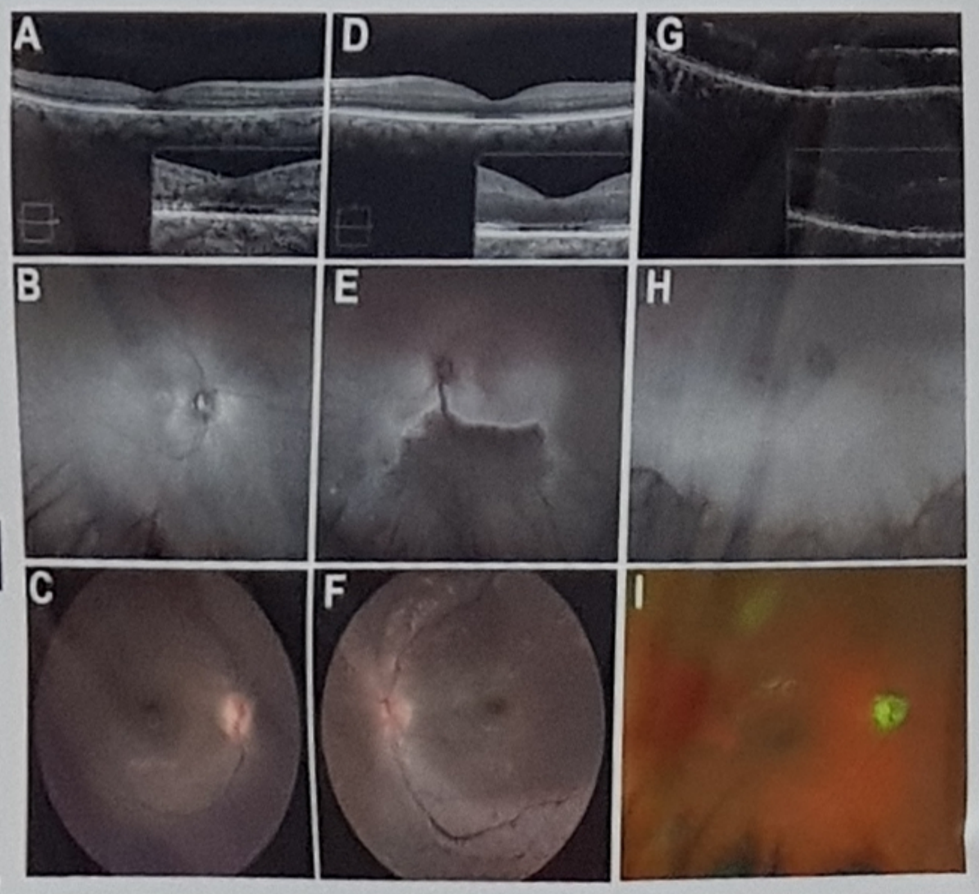

Figure 1. Ocular features of Jalili syndrome cases. (A-C) Multimodal imaging of the right eye of patient 1 showing SD-OCT (A), wide-field Optos autofluorescence (B), and 50 degree color fundus photo (C). (D-F) Multimodal imaging of patient 2's left eye showing OCT (D), wide-field Optos autofluorescence (E), and color fundus photo (F). (G-I) Multimodal imaging of patient 3's right eye showing Bioptogen OCT (G), wide-field Optos autofluorescence (I), and wide-field Optos color photograph (I). All patients share bull's eye maculopathy appearance, with loss of ellipsoid and interdigitation zone as evidenced by the hyporeflective dark area under the fovea. However, patient 2 also notably has a large hypoautofluorescent area of pigment clumping in the periphery (E,F).

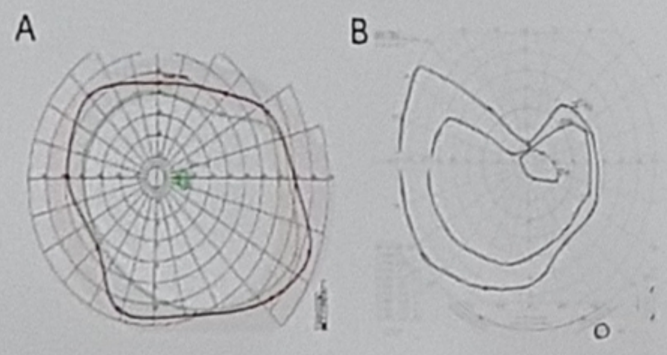

Figure 2. Goldmann visual field from Jalili syndrome patients. (A) Goldmann visual field of the right eye of patient 1 showing loss of the I1e isopter, but relative preservation of peripheral visual field. (B) Goldmann visual field of the left eye of patient 2, showing superior visual field constriction in addition to loss of the I1e isopter. Visual field testing matches the retinal changes seen on fundus imaging for each of these patients.

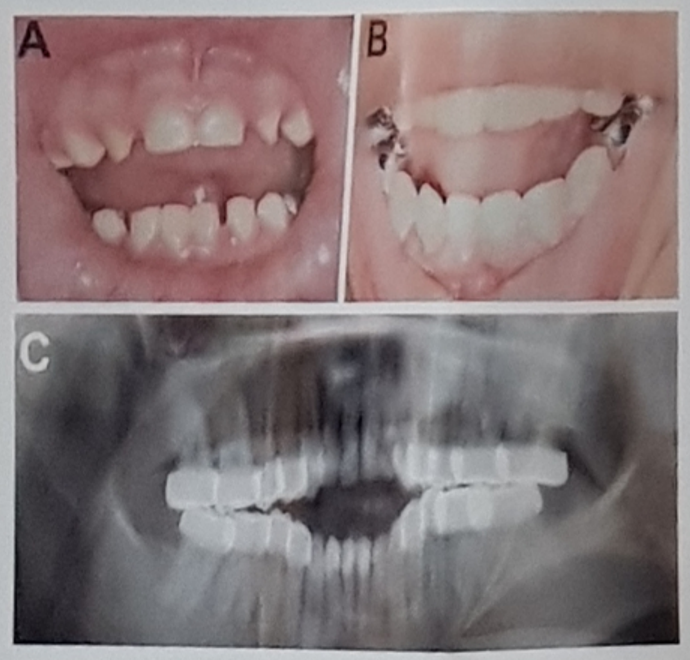

Figure 3: Dental features of Jalili syndrome cases. (A-B) External photos of mouth of patient 3 (A) and patient 1 (B) showing tooth decay and crowns on multiple teeth. (C) Panorex X-ray of patient 1 showing crowns on all adult molar teeth.

Conclusions

- Our work highlights the genotypic variability of Jalili syndrome and expands the genotypic and phenotypic spectrum of this condition.
- Common features among all of our cases include cone-rod dystrophy and amelogenesis imperfecta.
- We demonstrate the first case of uniparental isodisomy leading to Jalili syndrome plus other systemic features
- We identified a novel CNNM4 missense variant in unrelated patients of Guatemalan descent, suggesting a distant founder variant.

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