Expanding the Phenotype of TRNT1-Related Immunodeficiency to Include Childhood Cataract and Inner Retinal Dysfunction

Sarah Hull, MA, FRCPophth; Aeesha N. J. Malik, MRCP, FRCPophth; Gavin Arno, PhD; Donna S. Mackay, PhD; Vincent Plagnol, MSc, PhD; Michel Michaelides, MD(Res), FRCPophth; Sahar Mansour, BMBS, FRCP; Assunta Albanese, MD(Res), FRCPCH; Katrina Tatton Brown, BM BCh, MD(Res); Graham E. Holder, MSc, PhD; Andrew R. Webster, MD(Res), FRCPophth; Paul T. Heath, FRACP, FRCPCH; Anthony T. Moore, MA, FRCPophth

Congenital sideroblastic anemia with immunodeficiency, periodic fever, and developmental delay (SIFD) (OMIM #616084) is a recessively inherited disorder due to mutations in tRNA nucleotidyltransferase CCA-adding, 1 (TRNT1, OMIM 612907).1,2 This gene encodes an ubiquitously expressed enzyme essential in the synthesis of the 3′-terminal CCA sequence of both mitochondrial and nuclear transfer RNA transcripts.3 In the initial reports2,4 on congenital SIFD, 14 patients from 12 families had multisystem involvement of variable severity and progression. Most cases presented in infancy with febrile illness, gastrointestinal upset, and anemia; 8 patients died in childhood. Ophthalmic involvement was reported in 5 patients: 3 cases of retinitis pigmentosa, 1 case of retinitis punctata albescens, and 1 case of ptosis with ophthalmoplegia; further details were not reported.1,2,4 A further report5 of 2 families identified retinitis pigmentosa with erythrocytic microcytosis; the mild hematologic features were identified only following the molecular diagnosis. The present report of 3 siblings further expands the ophthalmic phenotype to include cataract and inner retinal dysfunction with a milder systemic phenotype than those previously reported in SIFD.

Methods

The study protocol adhered to the tenets of the Declaration of Helsinki6 and received ethics committee approval from the National Research Ethics Service Committee and the Research Management Committee at Moorfields Eye Hospital. Written informed consent was provided by the parents. All 3 children underwent full clinical examination and investigation by members of the ophthalmology, pediatrics, and clinical genetics departments. Electrophysiologic testing was performed in all patients using gold-foil, corneal electrodes to incorporate the International Society for Clinical Electrophysiology of Vision standards.7,8

Full details of the molecular investigations are included in the eMethods in the Supplement. All 3 siblings underwent whole-exome sequencing.
Results

The 3 affected children had normal birth weights (2.7-3.2 kg); their parents were first cousins of Indian ethnicity. They all had poor growth, microcephaly, and sparse hair. Common systemic findings included borderline microcytic, hypochromic anemia without sideroblasts on blood film examination; moderate pan-hypogammaglobulinemia without B-cell lymphopenia; and excellent initial serologic responses to both conjugate and protein vaccines that were not sustained. All patients received regular intravenous immunoglobulin therapy following infections in childhood. A clinical summary of growth variables and endocrinologic investigations appears in the Table.

Patient 1 presented at age 9 months with failure to thrive and several episodes of fever without apparent causes. There was satisfactory response to a trial of growth hormone injections started at 8.9 years (eFigure 1 in the Supplement). She was prepubertal at 14.5 years, and low-dose estrogen therapy was initiated for primary ovarian failure; she also had poor balance. Ophthalmologic examination performed at 5 years to evaluate a 2-year history of reduced vision identified bilateral, posterior subcapsular cataracts (Figure 1). Best-corrected visual acuity was 0.8 logMAR (20/125 Snellen equivalent) OU. She underwent sequential cataract surgery with intraocular lens implantation. At 10 years, slight optic disc pallor was noted without other retinal abnormalities (eFigure 2 in the Supplement), and reduced night vision was reported. At her most recent review (15 years), best-corrected visual acuity was 0.10 logMAR (20/25 Snellen equivalent) OD and 0.14 logMAR (20/25 Snellen equivalent) OS.

Patient 2 was diagnosed with hypogammaglobulinemia at 7 months. He also had poor balance. Posterior subcapsular cataracts were observed at 6 years, necessitating surgery with intraocular lens implantation (Figure 1). Fundus examination revealed mild disc pallor (eFigure 2 in the Supplement). His best-corrected visual acuity at 13 years was 0.12 logMAR (20/25 Snellen equivalent) OU with normal color vision determined using Ishihara plates.

Patient 3 was diagnosed with hypogammaglobulinemia in early infancy after having been investigated because of the family history. At age 4 months, profound sensorineural hearing loss was diagnosed, and right cochlear implant surgery was performed at 3 years. There were no balance problems. Cataracts were not observed at birth, but a dense right cataract was noted at 2 years; a mild left, posterior subcapsular cataract became dense over 2 months (Figure 1). Both eyes underwent cataract surgery with intraocular lens implantation. Fundus examination revealed only mild disc pallor (eFigure 2 in the Supplement). At the last clinic visit, her best-corrected visual acuity was 0.14 logMAR (20/25 Snellen equivalent) OD and 0.00 logMAR (Snellen equivalent 20/20) OS.

Electrophysiologic examination showed consistent findings (Figure 2). Rod-specific electroretinograms (ERGs) (dark adapted, 0.01) were undetectable; bright-flash (dark adapted, 10.0) ERGs were profoundly electronegative with normal a-waves; cone-flicker ERGs (light adapted, 30 Hz) were delayed and subnormal; and cone-single flash ERGs (light adapted, 3.0) showed a broadened a-wave trough with a sharply rising b-wave and a reduced b:a ratio, which is the waveform characteristic of off-pathway sparing and on-pathway loss. The findings indicate relatively severe generalized inner retinal dysfunction affecting both rod and cone systems. Pattern ERG was undetectable (patient 1), indicating severe macular dysfunction.

From whole-exome sequencing, one mutation in TRNT1, c.295C>T (p.Arg99Thr), that was predicted to be damaging in silico (Sorting Intolerant from Tolerant score, 0 [http://sift.jcvi.org]; Polymorphism Phenotyping, version 2 score, 1.000 [http://genetics.bwh.harvard.edu/pph2/]) was identified as a likely candidate given the association of TRNT1 with immunodeficiency. To our knowledge, it has not been previously reported as a pathogenic variant but is present in the ExAC database (http://exac.broadinstitute.org/) at a minor allele frequency of 3 in the 121128 alleles. Previous sequencing in patient 3 had identified a homozygous mutation, c.71G>A (p.Trp24*) in GJB2, (OMIM 120111), previously reported in association with nonsyndromic deafness. This mutation was confirmed on whole-exome sequencing in the homozygous state and was heterozygous in patient 1 but not found in patient 2.

Discussion

This report expands the ocular phenotype of patients with TRNT1 mutations and characterizes the ERG changes. The siblings share common features with previous patients (ie, immunodeficiency, poor growth, and poor balance in patients 1 and 2) but without sideroblastic anemia, developmental delay, or other organ involvement. Variable sensorineural hearing loss has been reported with TRNT1. Given the normal hearing of patients 1 and 2, the hearing loss in patient 3 was most likely related to the homozygous GJB2 mutation rather than TRNT1, representing a second recessive condition within this family. The immunodeficiency is compatible with that previously reported. Although recurrent or periodic fever was not universally found and B-cell lymphopenia was not demonstrated, persistent, moderate
pan-hypogammaglobulinemia was a consistent feature. In addition, the oldest child has primary ovarian failure, which, to our knowledge, has not been previously described in this disorder.

The multiorgan involvement and variability of phenotype in patients with SIFD is suggestive of mitochondrial cytopathy.\textsuperscript{2,4,11} Cataract, a known association with mitochondrial disease, is identified as a novel TRNT1-related feature in

### Table. Summary of Systemic Clinical Data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Last Review, y</th>
<th>Immunodeficiency</th>
<th>Related Infections</th>
<th>Growth Variables, SD</th>
<th>Growth Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>Hepatitis A</td>
<td>requiring intensive care, bronchiectasis</td>
<td>12.7 -2.7 -2.1 -2.3</td>
<td>Normal GH stimulation test, low IGF-1 and IGF-1 BP3 with a mild increase on IGF-1 generation test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>2 Croup episodes</td>
<td>requiring intensive care</td>
<td>10.8 -2.1 -2.1 -2.1</td>
<td>GH/IGF-1 axis normal</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>Mild bronchiectasis</td>
<td>on chest CT</td>
<td>9.8 -3.9 -4.0 -3.2</td>
<td>GH/IGF-1 axis normal</td>
</tr>
</tbody>
</table>

Abbreviations: AMH, anti-Müllerian hormone; CT, computed tomography; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor 1; IGF-1 BP3, IGF-binding protein 3; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; OFC, occipitofrontal circumference.

### Figure 1. Anterior Segment Photographs of Cataracts in All Patients

<table>
<thead>
<tr>
<th>Right eye</th>
<th>Left eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td></td>
</tr>
<tr>
<td>Patient 2</td>
<td></td>
</tr>
<tr>
<td>Patient 3</td>
<td></td>
</tr>
</tbody>
</table>

Patient 1, cortical spoke-like cataract; patient 2, posterior subcapsular cataract; and patient 3, white nuclear cataract (measurement scale not available).
this family.\textsuperscript{12,13} No mutation in reported recessive cataract genes was identified on whole-exome sequencing.

Inner retinal dysfunction may be seen in a number of systemic disorders but has not previously been reported in TRNT1 related or other mitochondrial disease.\textsuperscript{9} The retinal phenotype in this family resembles “complete” congenital stationary night blindness, which often has a normal retinal appearance although usually in conjunction with moderate reduction of vision and nystagmus.\textsuperscript{14} Recessive congenital stationary night blindness usually arises from mutations in \textit{TRPM1}, \textit{GPR179}, \textit{GRM6}, or \textit{LRIT3}, none of which was identified in the patients described herein.

There have been 20 reported \textit{TRNT1} mutations to date, including 10 missense mutations.\textsuperscript{1,2,5} The novel p.Arg99Trp variant arises outside of the active site of the enzyme and is presumed to have a less deleterious effect on protein function than other mutations; further confirmatory functional studies are needed.\textsuperscript{5}

Conclusions

This report expands the phenotype of disease due to mutations in \textit{TRNT1}, identifies additional ocular features, and for the first time describes the results of detailed electrophysiologic testing of retinal function. The findings suggest that all patients with \textit{TRNT1} mutations should have ophthalmic evaluation.
Expanding the Phenotype of TRNT1-Related Immunodeficiency

Drafting of the manuscript: authors.

Acquisition, analysis, or interpretation of data: Moore.

Obtained funding: Webster, Heath, Moore.

Michaelides, Mansour, Albanese, Brown, Holder, intellectual content: Michaelides, Heath.

Critical revision of the manuscript for important intellectual content: Hull, Malik, Arno, Mackay, Michaelides, Mansour, Albanese, Brown, Holder, Webster, Heath, Moore.

Study concept and design: co–first authors, had full access to all the data for the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contributions: Drs Hull and Malik are co–first authors, had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hull, Malik, Webster, Moore.

Acquisition, analysis, or interpretation of data: All authors.

Critical revision of the manuscript for important intellectual content: Hull, Malik, Plagnol, Michaelides, Heath.

Obtained funding: Malik, Mackay, Webster, Moore.

Administrative, technical, or material support: Malik, Mackay, Albano, Malik, Webster, Moore.

Study supervision: Michaelides, Holder, Webster, Moore.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: Funding for the study was provided by the National Institute for Health Research (UK) and Biomedical Research Centre at Moorfields Eye Hospital and grants BRC2_003 from the University College London Institute of Ophthalmology, C-CL: O7TO-0505-MEH10-02 from The Foundation Fighting Blindness (FFB), 131B and 1801 from Fight for Sight, and ST1109B from Moorfields Eye Hospital Special Trustees. Dr Michaelides is supported by an FFB Career Development Award.

Role of the Funder/Sponsor: The funding bodies had no specific role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the family of the patients for granting permission to publish this information.

REFERENCES


