**RYR1 Mutations as a Cause of Ophthalmoplegia, Facial Weakness, and Malignant Hyperthermia**

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**IMPORTANCE** Total ophthalmoplegia can result from ryanodine receptor 1 (RYR1) mutations without overt associated skeletal myopathy. Patients carrying RYR1 mutations are at high risk of developing malignant hyperthermia. Ophthalmologists should be familiar with these important clinical associations.

**OBJECTIVE** To determine the genetic cause of congenital ptosis, ophthalmoplegia, facial paralysis, and mild hypotonia segregating in 2 pedigrees diagnosed with atypical Moebius syndrome or congenital fibrosis of the extraocular muscles.

**DESIGN, SETTING, AND PARTICIPANTS** Clinical data including medical and family histories were collected at research laboratories at Boston Children's Hospital and Jules Stein Eye Institute (Engle and Demer labs) for affected and unaffected family members from 2 pedigrees in which patients presented with total ophthalmoplegia, facial weakness, and myopathy.

**INTERVENTION** Homozygosity mapping and whole-exome sequencing were conducted to identify causative mutations in affected family members. Histories, physical examinations, and clinical data were reviewed.

**MAIN OUTCOME AND MEASURE** Mutations in RYR1.

**RESULTS** Missense mutations resulting in 2 homozygous RYR1 amino acid substitutions (E989G and R3772W) and 2 compound heterozygous RYR1 substitutions (H283R and R3772W) were identified in a consanguineous and a nonconsanguineous pedigree, respectively. Orbital magnetic resonance imaging revealed marked hypoplasia of extraocular muscles and intraorbital cranial nerves. Skeletal muscle biopsy specimens revealed nonspecific myopathic changes. Clinically, the patients' ophthalmoplegia and facial weakness were far more significant than their hypotonia and limb weakness and were accompanied by an unrecognized susceptibility to malignant hyperthermia.

**CONCLUSIONS AND RELEVANCE** Affected children presenting with severe congenital ophthalmoplegia and facial weakness in the setting of only mild skeletal myopathy harbored recessive mutations in RYR1, encoding the ryanodine receptor 1, and were susceptible to malignant hyperthermia. While ophthalmoplegia occurs rarely in RYR1-related myopathies, these children were atypical because they lacked significant weakness, respiratory insufficiency, or scoliosis. RYR1-associated myopathies should be included in the differential diagnosis of congenital ophthalmoplegia and facial weakness, even without clinical skeletal myopathy. These patients should also be considered susceptible to malignant hyperthermia, a life-threatening anesthetic complication avoidable if anticipated presurgically.
The RYR1 gene (OMIM 180901) on chromosome 19q13.1 encodes the skeletal muscle Ryanodine receptor RYR1, the principal sarcoplasmic reticulum calcium release channel that plays a pivotal role in excitation-contraction coupling in muscle. Both recessive and dominant mutations in RYR1 are increasingly recognized to cause a spectrum of congenital myopathies, including central core,\textsuperscript{1-4} multiminicore,\textsuperscript{5,6} nemaline,\textsuperscript{7} and congenital fiber-type disproportion myopathy.\textsuperscript{8} Congenital ophthalmoplegia can segregate with RYR1 mutations and, in particular, with multiminicore myopathy.\textsuperscript{9,10} Children with RYR1 mutations and ophthalmoplegia typically have severe skeletal myopathy accompanied by respiratory insufficiency and develop scoliosis.\textsuperscript{5,11} Some RYR1 mutations cause susceptibility to malignant hyperthermia,\textsuperscript{12-15} and ophthalmoplegia and malignant hyperthermia can also be co-inherited.\textsuperscript{16,17}

We previously reported 3 children within a consanguineous pedigree with congenital bilateral complete ophthalmoplegia, facial diplegia, and only mild hypotonia, who had been diagnosed with atypical Moebius syndrome.\textsuperscript{18} Subsequently, we identified a nonconsanguineous pedigree in which 2 children have a similar phenotype and had been diagnosed with congenital fibrosis of extraocular muscles.\textsuperscript{19} Using next-generation exome sequencing, we identify recessive RYR1 mutations in affected members of both families and also discover that these individuals are susceptible to malignant hyperthermia. These findings highlight the importance of recognizing RYR1-related myopathies in the differential diagnosis of congenital ophthalmoplegia and facial weakness.

**Methods**

**Participants**

The study was approved by Boston Children’s Hospital and University of California, Los Angeles institutional review boards. Written informed consent was obtained from participating family members or from their guardians. All investigations were conducted in accordance with the principles of the Declaration of Helsinki. Pedigree OH is a consanguineous pedigree of Mexican ethnicity (Figure 1A), and we previously reported the medical histories and ophthalmic examinations of the affected family members, III:3, III:4, and IV:1.\textsuperscript{19} Pedigree DR is a previously unreported nonconsanguineous pedigree of Portuguese origin with 2 affected children who are dizygotic twins (Figure 1B).

**Mutation Identification in Pedigree OH**

**Homozygosity Mapping**

To identify the genetic etiology for the clinical phenotype in pedigree OH, DNA was extracted from the peripheral blood of 3 affected family members (III:3, III:4, and IV:1) and 3 unaffected parents (II:4, III:1, and III:2) using the Puregenekit (Qiagen). Genotyping was performed using the GeneChip Human Mapping 10K Xba array (Affymetrix Inc)\textsuperscript{19} based on previously published protocols.\textsuperscript{20} Given consanguinity in the family, we assumed a recessive mode of inheritance and predicted the causative variant would fall in a region of shared homozygosity. Homozygosity mapping was performed using Chip software.\textsuperscript{21,22}

**Figure 1. Pedigree Structures of OH and DR**

Schematic of pedigrees OH (A) and DR (B). Genotypes of RYR1 variants c.2966A>G and c.11314C>T in pedigree OH and variants c.848A>G and c.11314C>T in pedigree DR are shown under genotyped family members; black schematic haplotype bars denote wild-type sequence, while red schematic haplotype bars denote mutant sequence. Note that the clinically unaffected parents in pedigree OH each harbor the same 2 RYR1 mutations on 1 allele (red) and have 1 wild-type allele (black). The clinically unaffected parents in pedigree DR each harbor a single, different RYR1 mutation on 1 allele (half red and half black) and have 1 wild-type allele (black). Individual DR I:1 harbors the identical c.11314C>T mutation as 1 of the 2 mutations carried by individuals OH II:4, III:1, and III:2. *Those enrolled in the study. Circles indicate females; filled symbols, affected individuals; and squares, males.
Exome Capture and Sequencing, Read Mapping, and Variant Annotation
We performed whole-exome sequencing on DNA from individuals III:3, III:4, and IV:1. Three micrograms of genomic DNA were processed with the SureSelect Human All Exon Kit version 1 (Agilent Technologies).23 Captured libraries were sequenced on a HiScanSQ (Illumina).24 After sequencing, high-quality reads were aligned to the human reference genome sequence (UCSC hg18, NCBI build 36.1) via the ELAND version 2 program (Illumina). Variant calling of single-nucleotide polymorphisms (SNPs) and insertions/deletions (indels) was done with CASAVA software (Illumina).

Data Analysis and Mutation Identification
The ANNOVAR annotation package25 was used for variant annotation. Polymorphisms were excluded by filtering high-quality variants against dbSNP13026 and 1000 Genomes Project27 data as well as by excluding variants with more than 1% frequency in the Exome Variant Server, NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/). Only novel coding splice site, missense, and nonsense variants and indels were retained for final variant analysis. Prediction of functional consequences of nonsynonymous mutations was done using the SIFT,28 PolyPhen-2,29 and Pmut30 algorithms. Putative mutations were then confirmed and segregation with affection status was tested among family members using Sanger sequencing.

Mutation Identification in Pedigree DR
Whole-exome sequencing was performed on a DNA sample from the affected individual DR II:2. Three micrograms of genomic DNA were processed with the SureSelect Human All Exon Kit version 4 plus untranslated regions. Captured libraries were sequenced on a HiSeq 2000 (Illumina). High-quality reads were aligned to the human reference genome sequence (UCSC hg19, NCBI build 37.1) via the Burrows-Wheeler Aligner program.31 Variant calling of SNPs and indels was done using SAMtools.32 Resulting data were realigned to the human reference genomesequence (UCSChg19, NCBI build 37.1) via the Burrows-Wheeler Aligner program.31 Variant calling of SNPs and indels was done using SAMtools.32 Resulting data were analyzed assuming recessive inheritance where both homozygous and compound heterozygous variants were investigated. The methods described earlier for mutation identification and to confirm segregation were followed.

Clinical, Radiological, and Pathological Assessment
Following analysis of the genetic results, 11-year-old individual OH IV:1 underwent confirmatory clinical diagnostic DNA testing and a battery of clinical procedures including muscle biopsy, electromyography, nerve conduction velocity, electrocardiography, pulmonary function tests, and blood and cerebrospinal fluid analyses. Available medical histories of the other 2 affected individuals in pedigree OH were reviewed.

Full ophthalmic and neurological examinations were conducted when individuals DR II:2 and DR II:3 were 8 months old. Individual DR II:2 had had cyto genetic analysis and underwent real-time sonographic imaging and nonenhanced computerized tomography of the brain, as well as magnetic described.33 Their available subsequent medical histories were reviewed.

Muscle specimens from individuals OH IV:1 and DR II:2 were obtained for clinical diagnostic studies from the quadriceps muscle under local anesthesia. Specimens were frozen immediately in isopentane-cooled liquid nitrogen and stored at −80°C. Sections of fresh frozen muscle were stained for hematoxylin–eosin, modified trichrome, myofibrillar adenosine triphosphatase at pH 4.5, 4.6, and 9.4, periodic acid–Schiff (without and with diastase), Oil Red O, nicotinamide adenine dinucleotide dehydrogenase-tetrazolium reductase, succinic dehydrogenase, cytochrome-c oxidase, alkaline phosphatase, and acid phosphatase. Samples for electron microscopy were fixed in glutaraldehyde, 5%, and osmium tetroxide, 1%, in 0.1M cacodylate buffer.

Results

Genetic Analysis
Homozygosity mapping in pedigree OH revealed only 1 homozygous region greater than 2 Mb that was shared among the 3 affected individuals and not the unaffected parents. This approximately 3-Mb region on chromosome 19q13.12-19q13.2 was flanked by markers rs725985 and rs883433 (Figure 2A). Because there were more than 150 genes in the region, we proceeded with whole-exome sequencing for causative variant identification. We obtained mean coverage of 88% at ×10 resulting in approximately 18 000 exonic variants in each sample. Because we hypothesized a recessive mode of inheritance, we investigated the homozygous novel variants falling within the shared region of homozygosity (19q13.12-19q13.2) that were not in the dbSNP, 1000 Genomes, or Exome Variant Server databases. This analysis resulted in only 2 homozygous missense variants, both of which fell within the RYR1 gene (c.2966A>G; p.E989G and c.11314C>T; p.R3772W) (Table). Both residues are highly conserved (Figure 2D) and in silico analysis predicted both to be damaging. Both variants were absent from control DNA samples and segregated with affection status; unaffected parents were heterozygous and the affected individuals were homozygous for the mutant alleles (Figure 2B).

Neither of the mutations fell in any of the dominant “hot-spot” regions of RYR1 mutations, consistent with previously reported recessive RYR1 mutations that appear to alter residues anywhere along the length of RYR1 protein.33 On identification of RYR1 mutations in pedigree OH, we reviewed the cohort of families referred to us with ophthalmoplegia and facial weakness and identified a second pedigree, DR, with a phenotype similar to pedigree OH. We hypothesized that RYR1 mutations could also be causative in this pedigree, and because the RYR1 gene is a very large gene encoded by 106 exons, we performed whole-exome sequencing on affected individual DR II:2 and targeted our sequence analysis to the RYR1 gene. We obtained an average coverage of more than 95% at ×10 resulting in 23 236 exonic variants. Data were analyzed as described for pedigree OH except, because of the absence of consanguinity, we assumed a compound heterozygous model of inheritance. We identified 2 heterozygous RYR1 missense mutations, a novel c.848A>G; p.H283R that falls in the first RYR1 hot-spot mutation region and the recurrent mutation c.11314C>T;
p.R3772W (Figure 2C). Neither variant existed in any of the common databases or were present in control individuals, both were predicted to be damaging, both altered highly conserved residues, and segregation analysis confirmed that 1 mutation was inherited from each parent. The unaffected sibling DR II:1 carried the heterozygous missense c.11314C>T mutation (Figure 2C).

**Clinical Assessments**

**Pedigree OH**

As previously reported, 16 the 3 affected members of pedigree OH had normal gestational and birth histories and were born full term. Each had congenital complete ophthalmoplegia. At near central gaze, individual OH III:3 had exotropia of 18 prism
diopeters (Δ), individual OH III:4 had exotropia of 18Δ and 10Δ hypertropia, and individual OH IV:1 showed alignment between orthotropia to 10Δ exotropia. All 3 children had in addition bilateral ptosis and bilateral facial diplegia, while hypotonia was reported for individuals III:3 and IV:1. Magnetic resonance imaging of the affected children had revealed apically narrowed bony orbits, marked extracocular muscle hypoplasia, abnormally small motor nerves within the orbit, yet normal-appearing brainstems and subarachnoid portions of the cranial nerves innervating the extraocular muscles.18 The children were diagnosed with atypical Moebius syndrome. The proband, IV:1, underwent additional clinical evaluations at age 11 years. Intellectual and social development were normal. She had nonprogressive complete ophthalmoplegia, ptosis, and facial weakness. She had mild hypotonia, deep tendon reflexes were grade +1, and she had normal axial and limb muscle strength apart from weak ankle dorsiflexion. She had ankle contractures and toe-walked; otherwise, her gait was normal. Sensory examination and coordination were normal and she had no history of respiratory compromise or scoliosis. Nerve conduction velocity and repetitive nerve stimulation were normal, while electromyography revealed decreased motor unit duration and early recruitment in the anterior tibialis consistent with a myopathic process. Electrocardiography and echocardiography were normal while pulmonary function tests showed a low maximum expiratory pressure. Creatine kinase levels were normal. Tests for metabolic and mitochondrial diseases including genetic screening were found to be normal except for low free and total carnitine levels. Individual IV:1 was receiving carnitine and vitamin supplements and physiotherapy for her ankle contractures.

Review of the intervening medical histories of her 2 affected cousins revealed nonprogressive ophthalmoplegia, ptosis, and facial weakness, mild hypotonia, and grade +1 deep tendon reflexes, with normal sensory testing. Individual III:3 had a history of delayed motor milestones. Individual III:4 had undergone an emergency surgery for a ruptured appendix, complicated by malignant hyperthermia requiring hospitalization with intensive care for 2 weeks.

Pedigree DR
The dizygotic twins were born full term following a pregnancy remarkable only for in vitro fertilization. The first twin was born vaginally and the second required cesarean section. Both infants had severe neonatal hypotonia and axial weakness. When examined at 8 months of age, tone and muscle strength had improved significantly since birth, but they remained hypotonic; both boys could sit without support for 30 seconds and could pull to stand. They had complete ophthalmoplegia with 16Δ exotropia in central gaze at near, bilateral ptosis, and facial weakness. Deep tendon reflexes were grade 2+ and symmetric, with no pathological reflexes. At age 12 years, intellectual and social development were normal. Ophthalmoplegia and facial weakness were unchanged, and both boys had been diagnosed with congenital fibrosis of extraocular muscles and undergone ptosis surgery. Inability to fully close their eyes led to drying and corneal perforation in 1 twin, requiring corneal transplant. Both boys had difficulties with chewing and swallowing. Both boys had absent patellar reflexes, yet muscle tone was only mildly decreased in one and normal in the other. Neither boy had respiratory compromise or scoliosis. Laboratory and genetic investigations revealed no metabolic or mitochondrial abnormalities. High-resolution magnetic resonance imaging of the orbit performed for individual DR II:2 at 8 months of age revealed atrophy of extraocular muscles with intramuscular fat; the inferior rectus muscles were partially spared. The posterior halves of the superior oblique muscles were more affected than their anterior halves. The intraorbital nerves to the extraocular muscles were thin and appeared hypoplastic while the optic nerve appeared normal (Figure 3).

Histochemistry and Electron Microscopy Findings
Histochemistry and electron microscopy of the muscle biopsy specimens from individuals OH IV:1 and DR II:2 revealed nonspecific myopathic changes (Figure 4). Histochemical analysis revealed variability in fiber size, increased endomysial connective tissue, and some internalized nuclei. Type I and type II fibers were observed, with predominance of type I fibers. Multiminicores, central cores, and nemaline rods were not observed. Electron microscopy examination showed similar variation in fiber size with fatty infiltration. Some fibers contained degenerative material with focal accumulation of mitochondria with glycogen and lipid deposition. Focal areas of Z-disc streaming were observed.

Discussion
We studied the affected members of 2 pedigrees diagnosed with atypical Moebius syndrome or congenital fibrosis of extraocular muscles and found them to harbor homozygous or compound heterozygous missense mutations in RYRI, leading to

Table. Exome Sequence Data (Pedigree OH)

<table>
<thead>
<tr>
<th>Individual</th>
<th>OH III:3</th>
<th>OH III:4</th>
<th>OH IV:1</th>
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<tr>
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<td>84</td>
<td>89.9</td>
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<td>17 115</td>
<td>18 662</td>
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<td>(+) No. of pathogenic variants</td>
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<td>725</td>
<td>471</td>
</tr>
<tr>
<td>(+) No. of homozygous variants</td>
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<td>120</td>
<td>42</td>
</tr>
<tr>
<td>(+) No. of chromosome 13q13.12-19q13.2 variants</td>
<td>3</td>
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<td>3</td>
</tr>
<tr>
<td>(+) No. of variants shared by other 2 affected individuals</td>
<td>2</td>
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Abbreviation: SNP, single-nucleotide polymorphism.
their rediagnosis with RYR1-related myopathy with total opthalmoplegia and susceptibility to malignant hyperthermia. These families highlight RYR1-related myopathies in the differential diagnosis of congenital ophthalmoplegia and facial weakness and remind us that risk of malignant hyperthermia can segregate with congenital ophthalmoplegia. They also contribute to the broadening phenotypes associated with RYR1 mutations. Unlike what is typically found in patients with extraocular muscle involvement and RYR1 mutations, these patients had relatively mild hypotonia, quite good muscle strength, and no scoliosis or history of respiratory impairment.

We identified the disease-causing mutations in these patients using next-generation exome sequencing, which appears to be a promising diagnostic tool particularly for this disorder. With 106 exons, RYR1 is expensive and time consuming to Sanger sequence for clinical diagnostics. In addition, RYR1 mutations cause more than 70% of cases of malignant hyperthermia, which is often inherited as a dominant trait. To make a clinical diagnosis of susceptibility to malignant hyperthermia, a patient must undergo a muscle biopsy and in vitro contracture test, which can yield false-negative results. Thus, exome sequencing can be an important and efficient approach to identify recurrent or novel RYR1 mutations.

The 3 affected children in pedigree OH harbor 2 different homozygous RYR1 missense mutations. The first is a novel c.2966 A>G substitution replacing a glutamic acid with a glycine at the highly conserved residue 989. The negative charge of the wild-type residue is lost as a result of this mutation, and this, together with the smaller size of the mutated residue, could disturb the function of RYR1 or alter its interaction with other molecules. The second homozygous mutation is a c.11314C>T substitution replacing an arginine for a tryptophan at residue 3772, which pedigree DR also harbors in the heterozygous state. R3772 is buried within the core of the protein. The pathologic neural tryptophan residue is larger than the negatively charged wild-type arginine residue and thus may disrupt protein-protein interactions within the core structure.
In addition to the heterozygous R3772W substitution, the affected dizygotic twins in pedigree DR also harbor a novel heterozygous c.848A>G substitution that replaces a histidine for an arginine at residue 283. The wild-type residue is predicted to form hydrogen bonds with threonine and arginine at positions 286 and 256, respectively, and these bonds are predicted to be disrupted when a neutral histidine is replaced with the larger and positively charged arginine.36

The heterozygous R3772W substitution was previously reported to cause dominantly inherited malignant hyperthermia.37 In our families, it occurs as a recessive mutation in the homozygous or compound heterozygous state and contributes to a broader phenotype that extends beyond susceptibility to malignant hyperthermia. It is interesting that a similar observation was noted for the R3772Q substitution at the same residue: the heterozygous R3772Q substitution was reported to cause malignant hyperthermia,38 while the homozygous or compound heterozygous R3772Q substitution was found to cause a more severe phenotype including ptosis, facial weakness, nonspecific myopathy, and/or malignant hyperthermia.37,39-40

The affected children in pedigree OH harbor 2 homozygous mutations that are both present in their parents in the heterozygous state; thus, both variants are present on the founder allele shared by the 3 parents. Double-variant mutations in RYR1 have been reported previously in recessively and dominantly inherited phenotypes,17,37,39-42 yet their significance remains controversial. In a study of malignant hyperthermia due to RYR1 mutations, there was no overt difference in the clinical presentation or muscle response to halothane or caffeine comparing patients with double mutations on the same allele and those with single mutations, except for a significantly higher level of creatinine kinase in the former group.28 On the other hand, as in our report, it appears that when malignant hyperthermia-causing RYR1 mutations are associated with a second RYR1 mutation, the resulting phenotype can be more extensive.37,40-43 Given these observations, the combination of the homozygous R3772W substitution with the novel homozygous E989G substitution in pedigree OH, or the combination of the heterozygous R3772W substitution with the heterozygous H283R substitution in pedigree DR, could explain the more extensive phenotypes seen in our patients. Moreover, the parents and other family members who harbor heterozygous mutations may, themselves, be at risk of malignant hyperthermia.

It is important for ophthalmologists to consider RYR1 myopathies in the differential diagnosis of total ophthalmoplegia. Recognizing the clinical associations presented in this report would protect patients and their asymptomatic relatives from the potential risk of malignant hyperthermia.

Figure 4. Morphological Findings of Quadriceps Muscle Biopsy Sections From Affected Individual OH IV:1

A, Hematoxylin-eosin stain showing variability of fiber sizes with increased endomysial connective tissue and some internalized nuclei (original magnification ×20). B, Myosin adenosine triphosphatase 9.4 stain demonstrating fibers of variable sizes with small type I (light) and II (dark) fibers (original magnification ×10). C and D, Electron micrographs show focal accumulation of mitochondria accompanied by glycogen and lipid droplets (C) (original magnification ×4000), with some fibers showing an internalized nucleus (D) (original magnification ×2500).
RYR1-Associated Myopathies

ARTICLE INFORMATION

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Author Contributions: Dr Engle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.


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REFERENCES


Choroidal Detachment Due to Hypotony After Intravitreal Injection of Dexamethasone Implant

Gonzaga Garay-Aramburu, MD; Angela Gomez-Moreno, MD

A, Choroidal detachment in the inferior vascular arcade due to hypotony the day after an intravitreal dexamethasone implant injection. It resolves spontaneously within 4 days. B, Anterior segment optical coherence tomography (Topcon 3D OCT-1000) the day after the injection. The image shows the oblique scleral tunnel open as the cause of hypotony.