Oculopharyngeal muscular dystrophy (OPMD) is a rare myopathy caused by polyalanine triplet repeat expansion in the gene for poly(A) binding protein 2 (PABP2) and is found in isolated cohorts throughout the world. We have observed numerous cases of OPMD in New Mexico.

**Objective** To characterize the clinical, genetic, and demographic features of the OPMD population in New Mexico.

**Design, Setting, and Participants** Cohort study with analysis of outpatient clinic medical records from 1965 to 2001 at the University of New Mexico Hospital and the New Mexico VA Health Care System in Albuquerque, which serve the entire state.

**Main Outcome Measures** Clinical phenotype, supplemented with genetic confirmation (n = 10 patients) and in-depth clinical evaluations (n = 49 patients).

**Results** We identified 216 cases of OPMD (99 women and 117 men) from 39 kindreds of New Mexicans spanning up to 4 generations. All patients were Hispanic, and the majority of probands came from northern New Mexico. In patients who had both ocular and pharyngeal muscle weakness, ptosis was just as likely to occur before or concurrent with dysphagia. Proximal limb muscle weakness and gait abnormalities were common and occurred later than ocular or pharyngeal weakness. The clinical expression of OPMD caused marked debility, although life-table analysis showed no decrease in life expectancy compared with unaffected family members (P = .81). Ten individuals from different kindreds were found to have an identical polyalanine triplet repeat expansion (GCCG)n in the PABP2 gene.

**Conclusions** Individuals in this cohort had clinical and genetic characteristics of classic OPMD. Longevity was not affected, but patients experienced considerable morbidity. The origin of the PABP2 mutation in New Mexican OPMD patients is unclear, although the geographic and genetic isolation of northern New Mexicans with a long ancestry in this region may have contributed to the development of this cohort. This disease cohort represents a large and previously unrecognized health care issue in the state of New Mexico and should serve to raise the awareness of this disorder among clinicians who treat Hispanics in the Southwest and throughout the United States.
Health Care System were reviewed for clinically documented OPMD cases from 1965 to 2001. This study was approved by the University of New Mexico Human Research Review Committee. A subset of these patients volunteered for in-depth clinical evaluation and adjudant studies. Historical cases, described by contemporary family members, were included if sufficient details were available to establish the clinical diagnosis of OPMD. Individuals and their families who recently immigrated to New Mexico were excluded.

The clinical diagnosis of OPMD was based on signs of progressive bilateral ptosis and/or dysphagia without another definable neurological syndrome and positive family history. Data, if available, were abstracted for place of birth, family history, clinical signs and symptoms and their dates of onset, physical examination and laboratory findings, relevant surgical procedures, and date of or age at death. Life expectancy was determined by life-table analysis of 50 affected individuals and 35 unaffected siblings older than 50 years from multiple kindreds (P < .05) (PROC LIFETEST, SAS/STAT version 6.12, SAS Institute Inc, Cary, NC).

**Genetic Analysis**

Polymerase chain reaction (PCR) amplification (primers 5'-CATGTTGACGGGCAAGC-3' and 5'-GCTCCCTAGGCTCAGTCC-3') was used to investigate the amino terminus of the PABP2 gene in genomic DNA extracted from peripheral blood leukocytes (Puregene kit, Gentra, Research Triangle Park, NC) from 10 patients (from 10 different kindreds) with OPMD who volunteered for genetic testing. Unaffected spouses provided genomic DNA for controls. Standard PCR conditions were used with 1 μl of (α-32P)-dATP (deoxyadenosine triphosphate), 1.5 units of Taq DNA polymerase (Promega, Madison, Wis), and 0.3 units of Pfu DNA polymerase (Strategene, La Jolla, Calif). Radioactive PCR products were electrophoresed (10% polyacrylamide gel with 7 M of urea), detected by autoradiography, and sequenced (primer 5'-GGCAGCGACGTGAGCTAATG-3'; Sequi-Therm ExCell II DNA kit; Epicentre Technologies, Madison, Wis) to determine the exact mutation. Gel purification of the PCR products was necessary for sequencing. Without purification, extensive contamination of the mutant allele with the product from the normal allele led to misinterpretation of the sequence (eg, the apparent presence of GCA insertions embedded within the normal [GCG]9 trinucleotide repeat).

**RESULTS**

We identified 216 persons (99 women and 117 men) from 39 separate kindreds that fulfilled the clinical diagnosis of OPMD and reported heritage in the state of New Mexico. The largest concentration of probands lived in northern New Mexico (Figure). All affected individuals were reported, or self-described, as Hispanic. From the entire cohort of 216 cases (including historical cases with limited data), 190 (88%; with 19 [9%] unknown) had ptosis and 127 (59%; with 74 [34%] unknown) had dysphagia. In the subset of cases in which ptosis and dysphagia were both present and the age of onset was known (n = 47 [22%]), ptosis was noted before dysphagia in 20 cases (43%), both signs were noted concurrently in 20 cases (43%), and dysphagia was reported before ptosis in 7 cases (14%). Thirty-six patients had ptosis surgery and 15 patients reported surgical procedures for dysphagia (criopharyngeal myotomy, botulinum toxin injection, esophageal dilatation, gastrostomy/ nasogastric tube placement, or tracheotomy). At the close of our study period, 94 patients were living (44%), 68 were deceased (31%), and the status of 54 (25%) was unknown. The mean (SD) age at death was 71 (12) years (median, 71 years; range, 46-95 years). There was no decrease in life expectancy of patients with OPMD who lived beyond 50 years when affected individuals were compared with unaffected family members by life-table analysis (χ² = 0.53; P = .81).

A subset of this cohort volunteered for in-depth clinical studies (n = 49 [23%]; 17 women and 32 men; data for all variables not available for all patients) allowing us to evaluate clinical variables that cannot be reliably extracted from historical cases obtained from family members (Table). For patients in whom this information was known, the mean age at onset for ptosis (n = 36) was 52 years (median, 51; range, 32-72 years), for dysphagia (n = 28) it was 54 years (median, 54; range, 32-76 years), and for proximal weakness (n = 15) it was 63 years (median, 51; range, 27-74 years). Ice water swallowing time was available for 14 cases and was prolonged in 12 (86%). Myopathic changes were seen on electromyography in 9 of 13 cases (69%) and by pathological examination in 14 cases that underwent biopsy. An identical heterozygous [GCG]9 polyalanine repeat expansion in the PABP2 gene was found in all 10 patients (from 10 different kindreds) examined. Unaffected spouses were homozygous for the normal [GCG]0 sequence.

**COMMENT**

Oculopharyngeal muscular dystrophy is a rare disorder, with very few cases...
reported in the United States. In this study, we identified an OPMD population of 216 Hispanic New Mexicans from 39 different kindreds over a 4-generation period. This cohort is likely the largest in the United States, second largest in North America, and one of the largest clusters of OPMD in the world. The identification and characterization of this previously unrecognized population has raised several points related to the clinical features, the genetics and molecular epidemiology, and the health care impact of this population that should be of interest to clinicians, geneticists, population epidemiologists, and scientists studying triplet repeat disorders. The spectrum of clinical signs and symptoms of the New Mexican OPMD population is similar to that previously reported. We found that ptosis preceded or occurred simultaneously with dysphagia in the majority of patients and that proximal limb muscle weakness tended to follow ptosis and dysphagia. Deblility was more profound in this cohort of patients who presented for evaluation and historically reported affected individuals than initially predicted for a myopathy of specialized musculature. However, the cohort was selected from outpatient clinics rather than a general population. The more profound debility was primarily due to progressive swallowing dysfunction and decreases in mobility. Many patients benefited from surgical procedures to address their progressive symptoms. The clinical phenotype was highly variable, ranging from physically active individuals with mild ptosis to patients of similar age with significant dietary restrictions and debilitating systemic muscle weakness. The full spectrum of this disorder will be the focus of future studies. The full spectrum of this disorder will be the focus of future studies.

The origin of the OPMD mutation in New Mexico is not known. These cases may be from a new mutation(s) with geographical isolation (founder effect) at a “hot spot” in the genome that has a predilection for limited expansion. This mutation also may have been introduced by Spanish colonists who explored this region in the 1500s or by French-Canadian fur trappers in the 1800s. All affected individuals in our cohort are Hispanic, as are the majority of patients with OPMD recently reported in the United States. Many of our patients can trace their ancestry to colonial Spanish families that settled in New Mexico in the 16th and 17th centuries. This alone does not resolve the origin of the mutation in this region since the [GCG]3-codon expansion has been reported in patients from both Spain and Quebec. It has been proposed that a California OPMD cohort and a US family of Scottish descent are likely new mutations by haplotype and higher order genomic analyses. We found that the majority of the New Mexican probands were born in northern New Mexico in the Rio Grande River basin. This region is very rural and mountainous with limited health care resources. We expect that many more affected individuals live in this region who may benefit from recognizing that ptosis is not simply a family trait, but a medical disorder that can be treated. Despite the marked debility reported by affected individuals in this population, we found no adverse effect of the OPMD mutation on life expectancy when compared with longevity in unaffected siblings. This suggests that the as yet unknown mechanism of disease in OPMD does not alter critical cellular pathways that shorten lifespan, and future interventional measures that interrupt the manifestations of the mutant protein may have a significant impact on this and other OPMD cohorts.

The correlation of clinical and cellular dysfunction with the presumed toxic gain of function of mutant proteins in the triplet repeat disorders is a matter of much discussion and study. It is not clear how a ubiquitously expressed mutant protein exerts such a selective effect on a specific cell population such as the eyelid and pharyngeal muscle group in OPMD. In addition, it appears that there are thresholds of cellular dysfunction in these disorders that vary over time because they are adult-onset diseases, even though the mutant protein has been expressed for the entire lifespan, and there is a progressive continuum from limited muscle group involvement to widespread skeletal muscle involvement in individual patients. It also has not been established how the pathological hallmark of the triplet repeat disorders, intranuclear inclusions of mutant protein, correlates with aberrant cellular processes or the clinical phenotype.

We found that the genetic abnormality of the New Mexican OPMD patients from 10 kindreds studied to date is an identical expansion of 3 extra codons that code for alanine ([GCG]3 genotype). This confirms the findings of several other studies that this small triplet repeat expansion is correlated with clinical OPMD as opposed to the other triplet repeat disorders, in which expansions are in the tens to hundreds of nucleotides. The origin of the OPMD mutation in New Mexico is not known. These cases may be from a new mutation(s) with geographical isolation (founder effect) at a “hot spot” in the genome that has a predilection for limited expansion. This mutation also may have been introduced by Spanish colonists who explored this region in the 1500s or by French-Canadian fur trappers in the 1800s. All affected individuals in our cohort are Hispanic, as are the majority of patients with OPMD recently reported in the United States. Many of our patients can trace their ancestry to colonial Spanish families that settled in New Mexico in the 16th and 17th centuries. This alone does not resolve the origin of the mutation in this region since the [GCG]3-codon expansion has been reported in patients from both Spain and Quebec. It has been proposed that a California OPMD cohort and a US family of Scottish descent are likely new mutations by haplotype and higher order genomic analyses.

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Finally, identification of this large Hispanic OPMD population has several practical benefits. It should raise the awareness of clinicians, both in the United States and internationally, to the clinical presentation of this disorder and the genetic abnormality that is the basis for its pathogenesis. Further studies of the clinical phenotype, the genotypic abnormality, and the epidemiologic characteristics of this population will provide important insights into the mechanisms of disease in OPMD and may lead to the development of novel therapeutic strategies for this devastating disorder.

### Table. Clinical Signs in a Subset of the New Mexico OPMD Cohort (n = 49)*

<table>
<thead>
<tr>
<th>Sign</th>
<th>Present</th>
<th>Absent</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ptosis</td>
<td>45 (92)</td>
<td>1 (2)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>37 (76)</td>
<td>4 (8)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>20 (41)</td>
<td>7 (14)</td>
<td>22 (45)</td>
</tr>
<tr>
<td>Proximal weakness</td>
<td>32 (65)</td>
<td>11 (23)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Abnormal gait</td>
<td>17 (35)</td>
<td>14 (28)</td>
<td>18 (37)</td>
</tr>
</tbody>
</table>

*OPMD indicates oculopharyngeal muscular dystrophy.
†Distribution was facial (n = 2), arm (n = 2), leg (n = 8), arm and leg (n = 1), and unspecified (n = 19).
Oculopharyngeal Muscular Dystrophy

Southwest and throughout the United States, that OMD in North America is not limited to the French-Canadian population of Quebec but may be found in Hispanic individuals. We expect that the communication of this disorder to rural-based health care providers will optimize the care of these patients, encourage referral of rural patients for multidisciplinary treatment, direct state-level resources to address this disorder, and ultimately contribute to research that will advance the knowledge of the first discovered polyalanine triplet repeat disorder, OMD.

Author Contributions: Study concept and design: Becker, Morrison, Davis, Mak, Bear. Acquisition of data: Morrison, Davis, Mak, King, Bicknell, Reinert, Bartolo, Bear. Analysis and interpretation of data: Becker, Morrison, Davis, Mak, King, Bear.

Critical revision of the manuscript for important intellectual content: Becker, Morrison, Davis, Mak, King, Bicknell, Bartolo, Bear.

Statistical expertise: King.

Obtained funding: Morrison, Bear.

Administrative, technical, or material support: Becker, Morrison, Davis, King, Bicknell, Reinert, Bartolo, Bear.

Study supervision: Becker, Davis, Mak, Bear.

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REFERENCES


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