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HOXA1 mutations are not a common cause of Möbius syndrome

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Abstract

The *HOXA1*-related syndromes result from autosomal recessive truncating mutations in the homeobox transcription factor, *HOXA1*. Limited horizontal gaze and sensorineural deafness are the most common features; affected individuals can also have facial weakness, mental retardation, autism, motor disabilities, central hypoventilation, carotid artery and/or conotruncal heart defects. Möbius syndrome is also phenotypically heterogeneous, with minimal diagnostic criteria of nonprogressive facial weakness and impaired ocular abduction; mental retardation, autism, motor disabilities, additional eye movements restrictions, hearing loss, hypoventilation, and craniofacial, lingual, and limb abnormalities also occur. We asked, given the phenotypic overlap between these syndromes and the variable expressivity of both disorders, whether individuals with Möbius syndrome might harbor mutations in *HOXA1*. Our results suggest that *HOXA1* mutations are not a common cause of sporadic Möbius syndrome in the general population.

HOXA1-related syndromes include the Bosley-Salih-Alorainy syndrome (BSAS) identified in Saudi Arabian and Turkish families and the Athabascan brainstem dysgenesis syndrome (ABDS) identified in Native American families.[1,2] Both result from autosomal recessive truncating mutations in the homeobox transcription factor, *HOXA1*. The *HOXA1*-related syndrome phenotype is variable. The most common features in affected individuals are limited horizontal gaze (diagnosed as Duane syndrome in BSAS and horizontal gaze palsy in ABDS patients) and sensorineural deafness; facial weakness, mental retardation, autism, motor disabilities, central hypoventilation, carotid artery and/or conotruncal heart defects also occur.[1,2] The minimal diagnostic criteria for Möbius syndrome, which is also phenotypically heterogeneous, are nonprogressive facial weakness and impaired ocular abduction.[3,4] Affected individuals can also have mental retardation, autism, motor disabilities, additional eye movements restrictions, hearing loss, hypoventilation, and craniofacial, lingual, and limb abnormalities.[3] Approximately 20% of reported individuals with the *HOXA1*-related syndromes have both facial weakness and horizontal gaze palsy and thus meet diagnostic

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criteria for Möbius syndrome. Among this subgroup to date, none have globe retraction, all have deafness and central hypoventilation, and half have conotruncal cardiac defects.[1,2,5,6] We asked whether, given the phenotypic overlap between these syndromes and the variable expressivity of both disorders, individuals with Möbius syndrome might harbor mutations in *HOXA1*.

This study was approved by the local institutional review board and conducted in accordance with the Health Insurance Portability and Accountability Act with written informed consent of the participants and/or their guardians. We identified 40 probands with Möbius syndrome from among the participants enrolled in our study of complex strabismus, 25 of whom were recruited from the 8th International Moebius Syndrome Conference in 2008. All probands met the minimal criteria of Möbius syndrome as defined by consensus statement of the Moebius Syndrome Foundation Research Conference in April 2007, namely, "congenital, uni- or bilateral non-progressive facial weakness and limited abduction of the eye(s)."[4] Each participant underwent an orthoptic and targeted general examination, or records of these exams were reviewed, and each submitted a blood or salivary sample for DNA extraction. Genomic DNA was extracted from participants' blood using Qiagen Gentra Puregene DNA Isolation Kits or saliva samples using DNA Genotek Oragene saliva and saliva swab kits. *HOXA1* exons and their flanking intronic sequences were amplified, sequenced, and analyzed as previously described.[1]

Probands included individuals of European, and South, Central, and North American origin, including those of white, black, Hispanic, Native American, and Asian extraction. All cases were sporadic with the exception of 1 proband, whose sibling had Duane retraction syndrome. Among the 25 probands for which the information was available, 1 was exposed to misoprostol and 2 to cocaine *in utero*, and 3 were products of multiple gestation pregnancies. On further review of medical histories, some patients reported Poland anomaly, feeding difficulties in infancy with secondary failure to thrive, developmental delay, chronic dry eyes, frequent ear infections, difficulty hearing, dental problems, pulmonary infections and asthma, GERD, and delayed puberty. No patient reported deafness, central hypoventilation, or carotid artery or conotruncal heart defects. One patient reported heightened sensitivity to sound.

On physical examination, facial weakness was most often bilateral and asymmetric. Abduction deficits were frequently severe, with most patients unable to abduct past midline. Horizontal gaze palsy with limited adduction was also common, while globe retraction was documented in only 4 participants, none of whom had facial weakness. Sufficient neurodevelopmental data to establish or rule out the diagnosis of autism was available for 24 (60%) probands, among whom one had been diagnosed with autism and a second was felt likely to have autism spectrum disorder. Additional physical findings frequently observed included craniofacial, tongue, ear, and limb anomalies. The clinical characteristics of the subset of probands (33 of 40) recruited at the 8th International Moebius Syndrome Conference 2008 will be more fully described in a forthcoming paper.

No disease mutations were detected in *HOXA1* exons or flanking intronic sequences in any of the 40 probands. Three nonsynonymous coding sequence variants were found in exon 1, all of which we had previously identified as polymorphisms in controls and in individuals with Duane syndrome[7] (Table 1). Although these changes are polymorphisms, it is still unknown what effect, if any, they may have on *HOXA1* function. Among these, however, the *HOXA1* 218A>G polymorphism has been reported to be associated with increased susceptibility to isolated autism.[9] We found a 5% to 10% prevalence of autism among this Möbius syndrome cohort compared to a 1% prevalence in the general population.[8] Neither of the participants with Möbius syndrome and autism spectrum disorder harbored the 218A>G polymorphism, and all 4 participants harboring the polymorphism were older than 20 months of age and had no signs

concerning for autism spectrum disorder. Thus, similar to other studies,[10] we did not replicate this finding among our cohort.

The *HOXA1*-related syndromes overlap clinically with both Möbius and Duane syndromes. We previously reported the absence of *HOXA1* mutations among a cohort of 131 individuals with Duane anomaly.[7] Our results now suggest that *HOXA1* mutations are also not a common cause of sporadic Möbius syndrome in the general population. Clinical characteristics may help distinguish patients with sporadic Möbius syndrome from the subset of individuals with *HOXA1*-truncating mutations that fit the diagnostic criteria for Möbius syndrome; no patients in our Möbius cohort reported deafness, central hypoventilation, or cerebrovascular anomalies, while these are present in the majority of individuals with truncating mutations in *HOXA1*. Therefore, we do not recommend screening individuals with sporadic Möbius syndrome for mutations in *HOXA1* unless they have additional risk factors more specific for the *HOXA1*-related syndromes such as congenital sensorineural deafness, carotid artery anomalies, conotruncal heart defects, central hypoventilation, and/or are offspring of consanguineous parentage.

Literature Search

MEDLINE was searched without date or language restrictions for the following terms: *Moebius/Mobius syndrome/sequence*, *BSAS*, *ABDS*, HOXA1-*related syndromes*, *autism/autism spectrum disorder and Moebius/Mobius*, and HOXA1. Articles cited in reference lists of other articles were also reviewed.

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Table 1

HOXA1 single nucleotide variants observed among Moebius probands

No. Möbius probands with variant (rare allele frequency)	Location of change*	Amino acid substitution	dbSNP reference ID	Duane's Probands Previously reported†	Controls of mixed ethnicity Previously reported
4/40 (0.050) Caucasian	218A>G	H73R	rs10951154	16/131 (0.061)	0.10‡
1/40 (0.013) Hispanic	220-222delCAC	Del His74	none	10/131 (0.038)	0.047†
1/40 (0.013) Caucasian	436C>A	H146N	rs45571645	2/131 (0.007)	0.035†

*Nucleotide numbering refers to the cDNA sequence specifying the 336 amino acid residues of *HOXA1*, commencing at the +1 position of the initiation codon (BC032547).

†Tischfield et al.[7]

‡Ingram et al.[9]