UCLA

UCLA Previously Published Works

Title

Broad-Spectrum Möbius Syndrome Associated with a 1;11 Chromosome Translocation

Permalink

<https://escholarship.org/uc/item/9n27j2kn>

Authors

Gorin, MB
Donahue, SP
Wenger, SL
[et al.](#)

Publication Date

2022-12-17

Peer reviewed

Broad-Spectrum Möbius Syndrome Associated with a 1;11 Chromosome Translocation

Sean P. Donahue, Sharon L. Wenger, Mark W. Steele & Michael B. Gorin

To cite this article: Sean P. Donahue, Sharon L. Wenger, Mark W. Steele & Michael B. Gorin (1993) Broad-Spectrum Möbius Syndrome Associated with a 1;11 Chromosome Translocation, Ophthalmic Paediatrics and Genetics, 14:1, 17-21, DOI: [10.3109/13816819309087618](https://doi.org/10.3109/13816819309087618)

To link to this article: <http://dx.doi.org/10.3109/13816819309087618>

Published online: 08 Jul 2009.

Submit your article to this journal [↗](#)

Article views: 14

View related articles [↗](#)

Citing articles: 2 View citing articles [↗](#)

Broad-spectrum Möbius syndrome associated with a 1;11 chromosome translocation

SEAN P. DONAHUE¹, SHARON L. WENGER^{2,3}, MARK W. STEELE^{2,3} and
MICHAEL B. GORIN^{1,3*}

¹*The Eye & Ear Institute of Pittsburgh, Department of Ophthalmology, University of Pittsburgh School of Medicine;* ²*Department of Pediatric Genetics, Children's Hospital of Pittsburgh;* ³*Department of Human Genetics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA*

ABSTRACT. The authors report a case of Möbius syndrome with Poland syndrome, cleft palate, dextrocardia, mandibular hypoplasia, and multiple areas of diffuse brain volume loss. Karyotype demonstrated a t(1;11)(p22;p13) translocation in the patient and his phenotypically normal father and brother. This case extends the spectrum of congenital disorders that are associated with Möbius syndrome and raises the possibility of genetic heterogeneity for the Möbius disorder.

Key words: Möbius syndrome; Poland anomaly; dextrocardia; micrognathia; cleft palate; chromosome translocation; uniparental disomy

INTRODUCTION

The Möbius syndrome represents a diverse spectrum of congenital anomalies with a wide variety of inheritance patterns. We recently encountered a case of Möbius syndrome having the broadest sequence of anomalies thus reported, and possessing a t(1;11)(p22;p13) translocation. Previous reports based on cytogenetic findings in two families have suggested a location for a Möbius gene on chromosome 13. In one family a microdeletion of chromosome 13 was found¹. In a second family a balanced translocation, t(1;13)(p34;q13), was reported to completely segregate with a variant of the Möbius-Poland

syndrome in seven individuals over three generations², although this variant lacked abducens palsy. Our case represents an association of the Möbius-Poland syndrome in conjunction with cardiac and central nervous system anomalies. The balanced translocation identified in the proband was also found to be present in the phenotypically normal father and brother. While the observation of these syndromes and this translocation may be coincidental, it is possible that the Möbius syndrome is heterogeneous and that the translocation may have unmasked a locus at chromosome 1p22 or chromosome 11p13 (near the WAGR locus), contributed to a recessive form of the syndrome, or predisposed the affected individual to uniparental disomy.

* Correspondence and reprint requests to: Michael B. Gorin, M.D., Ph.D., The Eye & Ear Institute of Pittsburgh, 203 Lothrop Street, Pittsburgh, PA 15213, USA

CASE REPORT

A 3500 g 40-week male infant was born to a 30-year-old mother and was the second child of nonconsanguineous parents. The pregnancy and antenatal course were uncomplicated and the baby was delivered by vertex vaginal delivery with low forceps assistance. There was no known exposure to teratogenic agents during the pregnancy. Apgar scores were four at one minute and eight at five minutes. In the delivery room, the baby was noted to have abnormal facies, concavity of the left chest, cleft palate, micrognathia with a locked jaw, right-sided heart tones, and a left hand deformity. Neurological evaluation demonstrated a slightly decreased muscle tone throughout with a weak suck. There was a marked esotropia with bilateral failure of abduction. Ocular fundi, pupillary reactions and corneal sensation were normal. The echocardiogram of the chest demonstrated dextrocardia with normal intracardiac anatomy and no structural defects. MRI scan of the head demonstrated calcifications of the left pons and medullary region anterolateral to the fourth ventricle, diffuse brain volume loss in the cerebellum and brainstem as well as in the left temporal lobe, micrognathia, and thickening of the quadrigeminal plate. At 22 months of age, the patient is profoundly developmentally delayed and has limited visual capacity as well as bilateral sensorineural hearing deficit.

The patient's mother, father, and older male sibling were nonconsanguineous and were phenotypically normal. High resolution banding of chromosomes demonstrated a normal maternal karyotype, and karyotypes of 46 XY, t(1;11)(p22;p13) in the proband, the father, and the proband's brother (Fig. 1). The patient's family declined additional genetic studies.

DISCUSSION

The clinical syndrome known as Möbius syndrome represents a broad spectrum of findings and appears to have a diverse etiology. The syndrome of congenital facial diplegia was described concurrently in 1880, both by von

Graefe³ and by Harlan⁴. In 1888, Möbius described five cases, two of which had associated lid abnormalities^{5,6}. The current clinical description of Möbius syndrome now is restricted to cases with congenital sixth and seventh nerve paralysis with skeletal defects^{7,8}. Additional isolated anomalies of the jaw, teeth, and tongue^{7,9}, the hypothalamic-pituitary axis¹⁰, the cardiovascular system^{9,11,12}, and the brainstem and cerebellum¹³ have been described. Although multiple modes of transmission, including autosomal dominant, autosomal recessive, and X-linked have been described¹⁴, only two previous reports have documented abnormal karyotypes. Ziter *et al.*² described a 'Möbius syndrome variant' pedigree which consisted of seven individuals all of whom possessed a reciprocal translocation t(1;13)(p34;q14). Patients in this pedigree had an incomplete Möbius syndrome which lacked the characteristic bilateral abducens palsy. A more recent report¹ describes a patient with a deletion in the q12.2 region of chromosome 13. While this patient did not have limb abnormalities, she possessed micrognathia, a high arched palate and a small tongue with hypoglossal weakness. The mother's karyotype appeared normal and the father was deceased and not studied. The authors concluded that the responsible gene was located in the q12.2 band region of chromosome 13.

Unlike those cases specifically associated with chromosome 13 abnormalities, our patient had multiple associated anomalies, all of which have been described before in isolation with the Möbius syndrome (Table 1). In addition to the classic Möbius syndrome findings of facial diplegia, bilateral abducens palsy and the Poland syndrome, our case also had dextrocardia with normal cardiac anatomy, small mandible with cleft palate, hypotonia, and brain

Fig. 1. Karyotype of proband. Metaphase chromosomes were prepared by standard methods and Giemsa stained. The arrows indicate the locations of the translocations. This karyotype is identical to that observed in the phenotypically normal father and brother.

TABLE 1. Extent of phenotypic abnormalities associated with the Möbius syndrome

Anomaly	Reference										
	1	2	3	4	5	6	7	8	9	10	11
Möbius syndrome	+	+	+	+	+	+	+	+	+	+	
– bilateral abduction palsy											
– bilateral facial diplegia											
Poland anomaly				+	+	+	+	+	+	+	+
– absent sternal head of pectoralis major											
– absent pectoralis minor											
– syndactyly of ipsilateral hand											
– hypoplastic nipple											
Dextrocardia, with or without other cardiac defects					+	+			+	+	+
Cleft palate, micrognathia or other mandibular abnormalities		+		+			+		+	+	+
Brain abnormalities	+		+							+	

References: 1, Kawai *et al.*¹⁰; 2, Slee *et al.*¹; 3, Harbord *et al.*¹³; 4, MacDermot *et al.*⁷; 5, Bosch-Banyeras *et al.*¹²; 6, Rarogue *et al.*¹¹; 7, Miller *et al.*⁸; 8, Ziter *et al.*²; 9, Caravella *et al.*⁹; 10, this report, 11, Hanka and Fox²³

abnormalities which included diffuse volume loss in the cerebellum, brainstem, and left temporal lobe. This case manifests the most broadly based set of associated abnormalities that have been described with Möbius syndrome. The extensiveness of the clinical findings is compatible with the hypothesis that this child's findings are the results of disruption of a contiguous set of genes, which would be consistent with a cytogenetic rearrangement, or expression of a genetic defect affecting early developmental programming such as a homeobox-like gene¹⁵. The associated chromosomal abnormalities observed in this case may indicate a greater genetic heterogeneity for Möbius syndrome than previously realized and await further cytogenetic analysis.

There have been other recent reports on dysmorphic offspring with heritable reciprocal translocations^{16–18}. This might reflect some relationship between the breakpoints in reciprocal translocations and naturally occurring fragile sites. Fragile sites at the breakpoints may

facilitate unequal crossing over during meiosis resulting in submicroscopic DNA duplications/deletions^{19,20}. This causal relationship has been challenged by Steinbach²¹, who attributes the association to ascertainment bias. Alternatively, phenotypic abnormalities in individuals with inherited reciprocal translocations might be uniparental disomy resulting in disturbance of 'imprintable' genetic regions. Wang *et al.*²² recently demonstrated this mechanism in a phenotypically abnormal girl with a 13/14 Robertsonian translocation inherited from her normal father. Unfortunately, we did not have an opportunity to do the molecular genetic analyses necessary to test the above possibilities in our family.

ACKNOWLEDGEMENTS

We greatly appreciate the assistance and comments by Dr. Basil J. Zitelli, professor of pediatrics, Children's Hospital of Pittsburgh/University of Pittsburgh. This work was supported in part by The Eye & Ear Institute of Pittsburgh.

REFERENCES

1. Slee J, Smart R, Viljeon D. Deletion of chromosome 13 in Möbius syndrome. *J Med Genet* 1991; 28:413–414.
2. Ziter F, Wiser W, Robinson A. Three generation pedigree of a Möbius syndrome variant with chromosome translocation. *Arch Neurol* 1977; 34:437–442.
3. Von Graefe A. Graefe-Saemisch's Handbuch der Gesamten Augenheilkunde. Leipzig: Engelmann, 1880; 60:vol. 6.
4. Harlan G. Congenital paralysis of both abducens and both facial nerves. *Trans Am Ophthalmol Soc* 1880; 3:216.
5. Henderson J. The congenital facial diplegia syndrome: clinical features, pathology and etiology. A review of sixty-one cases. *Brain* 1939; 62:381–403.
6. Möbius P. Ueber angeborene doppelseitige Abducens-Facialis Lähmung. *Munch Med Wschr* 1888; 35:91–94.
7. MacDermot K, Winter R, Taylor D, Baraitser M. Oculofacial bulbar palsy in mother and son: review of 26 reports of familial transmission within the Möbius spectrum of defects. *J Med Genet* 1990; 27:18–26.
8. Miller M, Ray V, Owens P, Chen F. Möbius and Möbius-like syndromes. *J Ped Ophthalmol Strabismus* 1989; 26:176–187.
9. Caravella L, Rogers G. Dextrocardia and ventricular septal defect in the Möbius syndrome. *Ann Ophthalmol* 1978; 10:572–575.
10. Kawai M, Momoi T, Fujii T et al. The syndrome of Möbius sequence, Peripheral neuropathy and hypogonadotropic hypogonadism. *Am J Med Genet* 1990; 37:578–582.
11. Raroque H, Hershewe G, Snyder R. Möbius syndrome and transposition of the great vessels. *Neurology* 1988; 38:1894–1895.
12. Bosch-Banyeras J, Zuasuabar A, Puig A, Catala M, Cuatrecasas J. Poland-Möbius syndrome associated with dextrocardia. *J Med Genet* 1984; 21:70–71.

13. Harbord M, Finn J, Hall-Craggs M, Brett E, Baraitser M. Möbius syndrome with unilateral cerebellar hypoplasia. *J Med Genet* 1989; 26:579–582.
14. McKusick V (editor). *Mendelian Inheritance in Man. Catalog of AD, AR, and X-linked Disorders*. 9th edn. Baltimore: Johns Hopkins University Press, 1990; 618–619.
15. Ivens A, Flavin N, Williamson R, Dixon M et al. The human homeobox gene HOX7 maps to chromosome 4p16.1 and may be implicated in Wolf-Hirschhorn syndrome. *Hum Genet* 1990; 84:473–476.
16. Fryns J, Kleczkowska A, Kubien E, Van den Berge H. Excess of mental retardation and/or congenital malformation in reciprocal translocations in man. *Hum Genet* 1986; 72:1–8.
17. Van Heerden K, De Jong G, Fox M et al. Balanced chromosome translocations and abnormal phenotypes. *SA Med J* 1986; 69:825–828.
18. Wenger S, Steele M, Boone L et al. Dysmorphic newborns with a reciprocal chromosome translocation inherited from a normal parent. *Am J Hum Genet* 49(Suppl) 1991; A 289.
19. Hecht F, Hecht B. Fragile sites and chromosome breakpoints in constitutional rearrangements II. Spontaneous abortions, stillbirths and newborns. *Clin Genet* 1984; 26:174–177.
20. Wenger S, Steele M, Boone L et al. Reciprocal translocations and fragile sites. *Dysmorphology and Clin Genetics*, in press 1993.
21. Steinbach P. Letter to the Editors 'Excess of mental retardation and/or congenital malformation in reciprocal translocations in man'. *Hum Genet* 1986; 73:379.
22. Wang Jin-Chen C, Passage M, Yen P, Shapiro L, Mohandas T. Uniparental heterodisomy for chromosome 14 in a phenotypically abnormal familial balanced 13/14 Robertsonian translocation carrier. *Am J Hum Genet* 1991; 48:1069–1074.
23. Hanka S, Fox V. Dextrocardia associated with Poland's syndrome. *J Pediatr* 1975; 86:312.