Examining the genetics of congenital facial paralysis—a closer look at Moebius syndrome
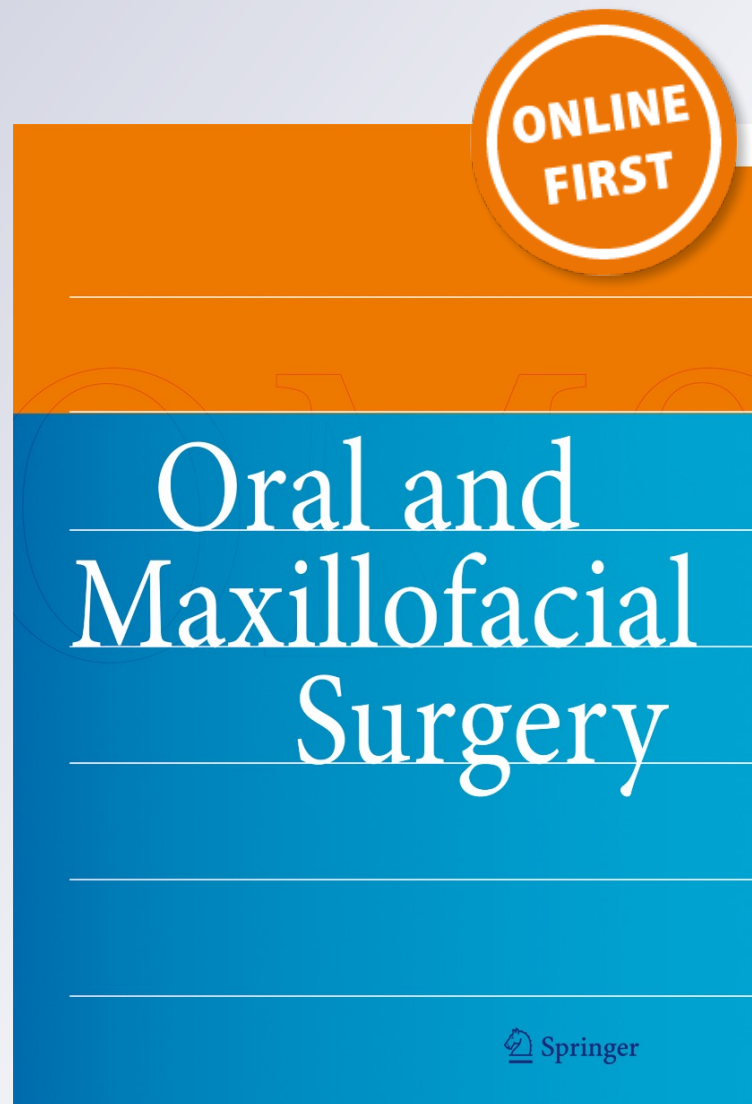
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REVIEW ARTICLE

Examining the genetics of congenital facial paralysis—a closer look at Moebius syndrome

Sameep Kadakia · Samuel N. Helman ·
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Abstract

Objectives The molecular underpinnings of Moebius syndrome (MBS) are diverse. This article provides a comprehensive summation of the genetic and etiologic literature underlying this disorder. Elucidating the genetic causes of the disorder can aid in earlier detection and treatment planning.

Design Articles from 1880–2013 were selected and reviewed by six researchers to understand all of the molecular theories and chronicity of advancements in the literature.

Results Mutations in the MBS1, MBS2, and MBS3 gene loci all have contributed to the development of MBS through various pathways. *HOX* family genes coding for homeobox domains, also, have been implicated in the abnormal development of the human brain. These are among the numerous genes that have been linked to the development of MBS.

Conclusion Our study codified nascent findings of the molecular determinants of MBS. These findings add to a growing database of MBS-associated mutations and can be used to diagnose MBS and clarify pathogenesis.

Keywords Moebius · Diplegia · Facial nerve · Facial paralysis · Congenital · Abducens

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Introduction

The clinical findings of Möbius syndrome (MBS), namely congenital facial paralysis with concomitant ocular abduction deficits, were originally identified in 1880 by von Graefe, and further codified by Möbius in 1888 [1, 2]. MBS is a rare syndrome with an incidence of 1 in every 50,000 live births with no gender predominance [3, 4]. The disorder presents with varying phenotype and severity resulting in unilateral or bilateral paralysis of the facial and abducens cranial nerves. Other cranial neuropathies can also be found, most notably cranial nerves V, IX, X, and XII [4–6]. Some patients retain residual lower facial muscle activity suggesting aberrant innervation from other cranial nerves; some studies have suggested the possibility of cranial nerves V, IX, and XII [7]. Other abnormalities include lingual hypoplasia, sensorineural hearing loss, craniofacial malformations (epicanthic folds, micrognathia), and abnormalities of the extremities (syndactyly, pes planus, valgus femur) [6, 8]. Cardiovascular abnormalities are rarely present but can include dextrocardial, atrial, or ventricular septal defect, transposition of the great vessels, and total anomalous pulmonary venous connection [9–13]. Although most patients have normal intelligence, approximately 10 % of patients have mental retardation, and another 30–40 % may be diagnosed with autism [8, 9].

Cranial nerve dysfunction often presents in infancy with difficulties such as inadequate sucking, necessitating

nutritional supplementation [3, 5, 8, 14]. Less severely affected patients present in early childhood or later with significant attenuation of developmental milestones including speech delay and impaired social skills [4, 6]. Parental bonding with the newborn may be affected by the patient's lack of facial expressions [5, 15].

The specific etiology of MBS is unknown, and theories of the underlying pathophysiology and genetics are numerous [16]. The two theories underlying the pathogenesis of MBS are (1) an embryological developmental defect in the rhombomere segments including the facial nerve nuclei and (2) an interruption of the vascular supply resulting in ischemia [8, 17]. Additional theories proposed include peripheral nerve injury with degeneration and atrophy of the facial musculature [18]. Few cases are presumably caused by a genetic mutation as evidenced by familial inheritance; however, genetic and environmental causes are not mutually exclusive as unknown external factors could influence the intrauterine environment and play a modifying role in the syndrome's manifestations [6, 8]. The etiology and genetics will be discussed in greater detail further in this manuscript.

The goal of this review paper is to provide a thorough discussion of the genetics underlying Moebius syndrome. The manuscript will also provide the reader with an overview of the pathogenesis, features, and management of this disorder. This paper is not meant to be a comprehensive review of the syndrome, nor is it meant to discuss all of the reconstructive management; rather, the objective of this paper is to provide the reader with an up to date collection of the underlying possible genetic background of this intriguing disease.

Background of Moebius syndrome

Embryogenesis

To understand the pathogenesis of MBS, an understanding of the development of the afflicted structures is necessary. During the fourth and fifth week of development, cephalic neural crest cells begin to differentiate into neural structures, beginning with the cranial nerve nuclei [11, 19]. The close proximity between facial nerve fibers and the abducens nucleus at the cerebellopontine angle provide a possible reason for the development of concurrent palsies. [16]. Extremity development and cardiac organogenesis occurs during the fourth through seventh weeks, with the heart being complete at week 5, thus leading to the observed abnormalities. It can be surmised that the proposed disturbance in embryogenesis underlying Moebius syndrome occurs at some point during the fourth to seventh week of gestation [10, 11, 19].

Errors in the development of the vascular system have been implicated in the pathophysiology of MBS during the susceptible time period. The basilar artery originally supplies the nascent hindbrain; however, during the sixth week of gestation, the blood supply changes from the basilar to the vertebral artery as they fuse. Specific timing is crucial during the formation of the vertebral arteries and the regression of the primitive otic and hypoglossal arteries to ensure adequate blood supply to the cranial nerve nuclei [16, 20].

Pathologic features

Pathologic changes in MBS include alterations in the cranial nerve nuclei and are generally limited to the brainstem and choroid plexus of the lateral ventricles. Segmental foci with mineral deposits suggest facial nerve necrosis possibly due to ischemia [20, 21]. Necrosis is also found in the lower pontine tegmentum involving the course of the sixth and seventh cranial nerves [22, 23]. Towfighi et al. classified the pathological findings into categories with proposed etiologies and suggested embryonic maldevelopment or hypoxia as inciting factors [18].

Radiographic findings

A wide array of different imaging abnormalities have been described in MBS. CT or MRI imaging shows hypoplasia of the lower brainstem as well as other cerebral malformations including the absence of the middle cerebellar peduncles and the thinning of the corpus callosum [4, 7, 22, 23]. Microcalcifications may be present in locations adjacent to the abducens nuclei possibly indicative of ischemic destruction [4, 18, 22, 24].

Management

Treatment of patients with MBS utilizes a multidisciplinary approach based on symptoms. Facial reanimation surgery may improve facial expression and often involves free muscle transfer. The most common operation for reanimating MBS patients is bilateral gracilis free-tissue transfer, comprising of a gracilis muscle harvest from the medial thigh, and grafting it to the corners of the mouth. The free flap can be neurotized in multiple ways, one example being the masseteric branch of the trigeminal nerve [25, 26]. Upper lip augmentation is also especially helpful in some MBS patients, achieved by using a dermal graft to elongate the upper lip [3, 26, 27]. Most patients express improved self-confidence and satisfaction with their new appearance and function [25, 26]. Other therapies include physical, occupational, and/or speech therapy, eye lubrication to prevent exposure keratitis, and additional surgery to correct anatomical limb deformities [4, 5, 26]. A full description of the management of this disorder along with the multitudes of surgical options is beyond the scope of this paper, and readers are encouraged to look at the literature for further information.

Associated syndromes

Many associated congenital syndromes have been identified which may be coincidental or etiologically related. A common vascular etiology was proposed to explain the association of Poland syndrome and Klippel-Feil anomaly with MBS [20]. Other syndromes described in association with MBS in case reports include Kallmann syndrome, Hanhart syndrome, hypopituitarism, Klinefelter syndrome, Duane's retraction syndrome, Goldenhar syndrome, and hypoglossia-hypodactyly anomaly [16, 28–32].

Etiology and genetics

The etiology of MBS is unknown, but may be the result of vascular insufficiency, teratogens, infection, maternal or birth trauma, and genetics. It is possible that this disorder may have a multifactorial emergence pattern. The most salient and well supported of these relates to vascular insufficiency during embryogenesis. Bavinck and Weaver developed the theory of subclavian artery supply distribution sequence (SASDS) hypothesis in which the subclavian and similarly derived vertebrobasilar arteries fail to sufficiently supply the nascent hindbrain. As the primitive otic and hypoglossal arteries regress and the vertebral arteries advance, inadequate blood supply to the cranial nerve nuclei may result in ischemia and malformation [20]. Conditions that may lead to attenuated blood flow include exposure to vasoconstrictive substances and maternal homocystinemia, which may cause subsequent ischemia of the hindbrain [12, 23, 33–38]. Infection, hyperthermia, hypoxia, and vasculitis can also interfere with blood flow [16].

Teratogenic exposure may be associated and in utero exposure to misoprostol, milfepristone, cocaine, ergot alkaloids, thalidomide, and benzodiazepines. These have all been implicated as putative agents [12, 23, 33–35, 37–40].

Maternal or birth trauma such as the use of forceps has been associated with MBS due to peripheral nerve injury, although it would be hard to explain abducens nerve palsy with this theory [18, 41].

The genetics underlying MBS remain elusive with multiple localized chromosomal regions but no definitive data regarding exact genetic foci. There is only 2 % of inheritance risk of MBS with skeletal findings, but this risk increases without these abnormalities [42]. These cases have provided evidence for gene localization through linkage analysis and chromosomal abnormalities. Table 1 details the common chromosomal abnormalities with their associated phenotypic expressions based on existing literature [14, 43–57]. Translocations with breakpoints may lead to microdeletions or aberrant genetic sequences [44]. Familial cases have demonstrated autosomal dominant, autosomal recessive, and X-linked modes of inheritance [4, 5, 8]. The individual phenotypes vary slightly suggesting genetic heterogeneity in the syndrome as well as incomplete penetrance. Other genetic factors or environmental may affect development, but it is unclear of each contribution to the MBS phenotype [8]. The most implicated loci include 1p22, 3q21-q22 (MBS2), 10q21.3-q22.1 (MBS3), and 13q12.2-13 (MBS1) [58].

Genetic studies are undertaken by analyzing potential chromosomal loci, selecting candidate genes, and examining the genomes of MBS patients for mutations in these genes. These studies have been difficult due to genetic heterogeneity. The incidence of genetic MBS makes it difficult to locate patients, other than familial patterns, with a genetic etiology. Some studies, randomly, may not include the patients with a genetic etiology, and therefore do not uncover an aberrant gene. In addition, studies that look at particular genes may not include patients with that specific gene being mutated. And studies may focus only on mutations within the gene and not in flanking regions [59].

Multiple genes, including homeodomain-containing transcription factors, are involved in founding the lower brainstem and nerve nuclei. Homeobox genes are differentially expressed in spatial and temporal patterns to create the embryological rhombomeres [59]. Mouse models with cranial nerve and craniofacial abnormalities have been generated by creating mutations in each of the four *HOX* genes as well as in genes in the endothelin pathway [16]. In addition, there are numerous other developmental genes that may interact with environmental factors during the required time period of brainstem growth [8]. Table 2 lists the proposed candidate genes and their function based on previous studies in the literature [46, 48, 53, 54, 58–65].

MBS1 locus

Deletions in the chromosome 13q12.2-13 of the specific candidate genes of *FGF9*, *GSH1*, *CDX2*, and *FLT1/VEGFR1* have been examined. *FGF9* encodes fibroblast growth factor 9 that is expressed in motor nuclei of the brainstem including the facial nucleus. The pathogenesis may be related to aberrant gap coupling in astroglia and affecting a lesion sensing process. *GSH1* encodes genomic-screened homeobox 1 and *CDX2* encodes caudal-type homeobox 2. Both of these genes are homeobox genes expressed in the developing hindbrain and are essential in defining rhombomeres and motor neuron identification and migration. *FLT1/VEGFR1* was also reported as a candidate gene due to its regulation of facial nerve migration and hindbrain vascularization. This hypothesis may link the vascular theory of MBS with a genetic cause. None of the patients studied were found to have mutations in these genes [59].

Table 1 List of genetic MBS cases from the literature along with chromosomal abnormality, characteristic phenotype, and inheritance pattern

Report	Mutation	Phenotype in addition to classic MBS	Inheritance pattern
Ziter et al. 1977 [43]	t(1;13)(p34;q13)	Finger flexion, metatarsus varus deformity of feet	Autosomal dominant
Nishikawa et al. 1997 [44]	t(1;2)(p22.3;q21.1)	Craniofacial deformities, partial CN III involvement	De novo
Donahue et al. 1993 [45]	t(1;11)(p22;p13)	Unilateral MBS, Poland syndrome, bilateral sensorineural hearing loss, craniofacial deformities, dextrocardia, diffuse brain volume loss	Autosomal recessive or uniparental disomy with de novo disturbance
Kremer et al. 1996 [46]	del(3q21-22)	Unilateral MBS	Autosomal dominant with variable penetrance (95 %)
Flores et al. 2013 [47]	dup(3q23)	Asymmetric MBS, Poland syndrome	De novo
Schröder et al. 2013 [48]	del(5q31.1)	Sensorineural deafness, balance disorder, craniofacial deformities, torticollis, hypoplastic genitalia, faulty foot posture	Autosomal recessive
Kersey and Vivian 2006 [49]	Inv(8)(q21.3;q24.13) Paracentric inversion	Unilateral MBS, bilateral metatarsus varus	De novo (paternal chromosomal studies unknown)
Verzijl et al. 1999 [50]	del(10q21.3-22.1)	Unilateral or bilateral MBS, hearing loss	Autosomal dominant with variable penetrance (60 %)
Slee et al. 1991 [51]	del(13q12.2)	Unilateral MBS, craniofacial deformities	De novo (paternal chromosomal studies unknown)
Borck et al. 2001 [52]	Complex translocation with breakpoints at 7q21.1; 8q21.3; 11p14.3; 13q21.2	Craniofacial deformities, short metacarpals and metatarsals	De novo
Chew et al. 2013 [53]	16q24.2	Kallmann syndrome, craniofacial deformities	De novo
Shaaban et al. 2013 [54]	del(19q13.12-2)	Risk of malignant hyperthermia	Autosomal recessive
Hanissian et al. 1970 [14]	Unknown	Poland syndrome, craniofacial deformities, joint arthrogryposis	Possibly de novo or autosomal recessive
Graziadio et al. 2010 [55]	Unknown	Lower limb skeletal findings	Autosomal dominant
van der Wiel 1957 [56]	Unknown	Unilateral or bilateral MBS	Irregular autosomal dominant
Becker-Christensen and Lund 1974 [57]	Unknown	Unilateral MBS, sensorineural hearing loss	Autosomal dominant

MBS2 locus

The MBS2 locus at 3q21-22 contains approximately 25 candidate genes with only a few having a developmental function. Zinc finger protein 9 (*ZNF9*) is involved in regulating cellular cholesterol levels, which may be important in the cholesterol content of plasma membranes. *CRBP1* in mouse models affects the migrating nucleus of the facial and trigeminal nerves. However, genetic screening did not indicate any mutations in the patients studied [46]. *PBX2* is a homeobox gene, and genomic DNA suggests that this copy is a processed pseudogene. Of note, a locus for another craniofacial deformity is located in this region [46]. Van der Zwaag et al. studied the effect of *PLEXIN-A1* that acts as a signal-transducing subunit of the neuronal neuropilin receptor, which is implicated in axon guidance and neuronal migration. Neuropilins are ligand-binding receptors for class 3 semaphorins, which are known as neuronal guidance cues. Neuropilins also interact with *VEGF* during angiogenesis [62]. *PLEXIN-D1* is in the family of transmembrane receptors implicated in axonal guidance and cell–cell contact. In mouse models, it is expressed in the central and peripheral nervous system as well as in the developing vascular endothelium. Analysis of the MBS cohort did not find significant mutations in either of these genes [61, 62]. SRY box 14 (*SOX14*) is a homeobox gene expressed in the neural tube and apical ectodermal ridge, and its function includes marking interneurons for dorsoventral positioning. Its genetic locus is distal to the MBS2 locus, but promoter or enhancer elements could be mutated. However, the analysis of MBS patients does not reveal any mutations in this gene [63]. GATA-binding protein 2 (*GATA2*) was analyzed due to its role as a transcription factor and its expression in rhombomere 4 of the developing hindbrain and that it is regulated by *HOXB1*. However, in the cohort of patients analyzed, there were no mutations in *GATA2* found [58].

MBS3 locus

One possible gene at this locus was identified as early growth response 2 (*EGR2*) on chromosome 10q21.3-22.1. A mouse ortholog gene (*Krox-20*) is found preferentially in rhombomeres 3 and 5 and is critical in regulating multiple homeobox genes [58]. In the mouse model, mutations in *Krox-20* result in elimination of rhombomeres 3 and 5 with

Table 2 List of candidate gene and function

Locus	Candidate gene	Function
13q12.2-13 (MBS1)	FGF9	Astroglial gap junctional communication in brainstem motor nuclei [59]
	GSH1	Homeobox gene in developing hindbrain [59]
	CDX2	Homeobox gene in developing hindbrain [59]
	FLT1/VEGFR1	Migration of facial nerve and hindbrain vascularization [59]
	TPΨg-BASP1	Regulates BASP1 [60]
3q21-22 (MBS2)	ZNF9	Regulating cellular cholesterol levels [46]
	CRBP1	Homeobox gene in developing hindbrain [46]
	PBX2	Homeobox gene, processed pseudogene [46]
	PLEXIN-A1/D1	Neuronal signal-transducing transmembrane receptors [61, 62]
	SOX14	Homeobox gene in neural tube and ectodermal tube [63]
	GATA2	Transcription factor in developing hindbrain [58]
10q21.3-22.1 (MBS3)	EGR2 (Krox-20)	Regulates homeobox genes in the hindbrain [58]
5q31.1	NEUROG1	Neuronal differentiation for sensory neurons [48]
5p15.1-2	BASP1	Neuronal growth and migration [60]
7p15.3	HOXA1	Homeobox gene in developing hindbrain and angiogenesis [64]
17q21.3	HOXB1	Homeobox gene in developing hindbrain [65]
16q24.2	TUBB3	Axon guidance in neural crest cells [53]
19q13.12-2	RYR1	Skeletal muscle sarcoplasmic reticulum calcium release channel [54]

cranial nerves V, VI, VII, and IX being affected [50]. Patients with other neuropathies have been described with mutations in *EGR2*. But patients with this mutation were not found in the studied cohort [62].

Genes at other loci

A boy with sporadic MBS was found to have a deletion of 5q31.1. Neurogenin 1 (*NEUROG1*) is located in this region and mutations in mouse models stop the development of proximal cranial sensory neurons. It is also important in neuronal differentiation from embryonic ectodermal cells. MBS has primarily motor symptoms that make *NEUROG1* less likely [48].

Uzumca et al. put forward the theory of *BASP1* gene mutation causing MBS. It is located on chromosome 5p15.1-2 and encodes NAP-22 (CAP-23) protein which is found in growth cones in axon termini and localizes into plasma membrane cholesterol rafts. It interacts with calmodulin and protein kinase C and regulates actin dynamics by responding to extracellular stimuli implicating it in neuronal sprouting, anatomical plasticity, and axonal path finding [60]. In mouse models, mutations in this gene cause facial nerve anomalies. *BASP1* is possibly regulated by a processed pseudogene *TPΨg-BASP1* which is located near the MBS1 locus which may implicate another method of neuronal defects in MBS. Of note, another gene in this location is *CTNND2* that is implicated in the pathogenesis of cri-du-chat syndrome, another craniofacial disorder [60].

Tischfield et al. described a congenital syndrome characterized by limited ocular abduction and sensorineural hearing loss with about 20 % of patients also demonstrating facial weakness. This syndrome is linked to a mutation in homeobox transcription factor (*HOXA1*) located at chromosome 7p15.3 (NCBI Gene, http://www.ncbi.nlm.nih.gov). *HOXA1* is involved in the hindbrain development, specifically in rhombomere 5. Its role in causing migration of neural crest cells may also affect alteration of the embryological vascular system [64]. *HOXA1* is expressed in embryos at gestational weeks 7 and 8 but not at 22 placing the temporal expression of the gene during the crucial time period to cause the MBS findings [64]. Rankin et al. analyzed the genomes of MBS patients but did not find *HOXA1* to be a common mutated gene [66].

Another homeobox transcription factor (*HOXB1*) on chromosome 17q21.3 (NCBI Gene, http://www.ncbi.nlm.nih.gov) was examined in a family of patients with facial weakness but normal ocular abduction. The gene is expressed in the embryological spinal cord and hindbrain and is essential in rhombomere 4 development [65].

A possible link with microtubules has been suggested through the neuronal specific protein β-tubulin isotype 3 (*TUBB3*) on chromosome 16q24.2 (NCBI Gene, http://www.ncbi.nlm.nih.gov) which supports axon guidance. It is transitorily expressed in neural crest cells and substitutional mutations, specifically E410K, alter a kinesin-binding site which will affect the development of specific cranial nerves and even the branches. Mutations cause congenital fibrosis of the extraocular muscles (CEFOM) but are also hypothesized

to be associated with Kallman syndrome and MBS because of the clinical phenotype [53].

Shaaban et al. identified three patients with MBS who also had a mutation in ryanodine receptor 1 (*RYR1*) on chromosome 19q13.12-2. The relevant mutation was not found in the parents but was shared in two patients without MBS but who also had elements of facial weakness. This may be a myopathic cause of muscle weakness because *RYR1* is involved in the sarcoplasmic reticulum calcium release channel of the skeletal muscles [54].

Jennings suggests that the finding of MBS with the associated Kallman syndrome may be related to a single mutation in *KAL* at Xp22.3 [29].

Discussion

MBS is a rare congenital disorder of uncertain but possibly multifactorial etiology. Abnormalities characteristically occur in the abducens and facial cranial nerves, but other anomalies in the extremities, craniofacial features, and trunk can occur. Possible teratogenic and vascular etiologies for the disorder are the most developed, but other genetic factors seem to play a role in some cases of MBS. The differing spectrum of disease may indicate that different etiologies create different phenotypes.

The genetic aspect of MBS is complicated, and multiple modes of inheritance have been demonstrated. However, even in familial cases of MBS, genetics seems to play only one role in the pathogenesis of the syndrome as evidenced by the variable penetrance rate in many familial patterns. There is considerable genetic heterogeneity with multiple genes and even chromosomes being implicated, and each case of MBS presents with different anomalies of variable severity.

Several implicated genes including *HOXA1*, *HOXB1*, and *SOX14* are related to homeobox genes necessary for spatial and temporal development of the brain. The effects of these genes also extend to the other genes that are influenced. Therefore, mutations in homeobox genes or downstream genes may both result in MBS with varying phenotypes. Other developmental genes required specifically for neuronal development that have been suggested are *PLEXIN-A1*, *GATA2*, *EGR2*, *BASP1*, *TUBB3*, and the plexin family. These are the likely candidates given that the characteristic abnormalities defining the syndrome are the cranial nerve nuclei. *BASP1*, *TUBB3*, and additional plexin genes or their downstream effectors have only been theorized and have not yet been analyzed in a cohort of MBS patients. The pseudogene *TPΨg-BASP1* should also be analyzed in a cohort especially given its proximity to the common MBS1 locus.

An interesting implicated gene is *FLT1/VEGFR1* resulting in aberrant vascular growth due to the proposed SASDS theory. This may suggest a genetic etiology for the vascular theory of MBS. Of course, this suggests that other genes in the angiogenesis pathway may be causative as well, such as *HOXA1* and the plexin family of genes.

Many of these genes have also been considered as the causative mutation in other craniofacial and neurologic disorders. These can include blepharophimosis, ptosis, and epicanthus inversus syndrome; Bosley-Salih-Alorainy syndrome; Athabascan brainstem dysgenesis syndrome; and congenital fibrosis of the extraocular muscles [13, 46, 64]. Understanding these genes and the effects of their mutations will not only further the understanding of MBS but also these other syndromes.

Despite all of these possibilities, genetic studies usually fail to find a link between the genetics and the disease. This may be due to many factors including the genetic heterogeneity of the disease and the presence of nongenetic causes of MBS. The selection and recruitment of MBS patients to examine for genetic mutations must be carefully undertaken in order to find a causative MBS mutation.

Conclusion

The genetic causes of MBS are not completely understood and are still at the stage of hypothesis. Many genes have been implicated through linkage analysis and chromosomal studies, but most genetic studies have not made any concrete link between gene and disease.

The study of the genetic basis of MBS is relevant for diagnosis, possibly even prenatally, and treatment of the patients with MBS. It will help in the genetic counseling of familial instances of MBS, as well as understanding the best methods of restoring facial emotions. Collating the literature is also helpful for furthering scientific knowledge by understanding the implicated genes in the organogenesis of the central nervous system and cranial nerves. It is our hope that this paper organizes the current genetic information and primes further research on this subject.

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