Familial Congenital Facial Synkinesis Due to 12q Duplication: A Case Report and Literature Review

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abstract

Inverse Marcus Gunn phenomenon is a rare form of congenital facial synkinesis in which jaw movement temporarily elicits ptosis, either unilateral or bilateral. This phenomenon is presumed to result from dysinnervation of facial muscles during development of the nervous system. We describe 2 brothers, both with inverse Marcus Gunn phenomenon in the context of multiple other congenital anomalies, all presumed secondary to a chromosomal abnormality involving 12q duplication and 1p36 deletion. Although a handful of familial cases of congenital facial synkinesis have been previously described, this is the first in which a genetic abnormality has been identified. Of the 4 genetic abnormalities previously described in association with congenital facial synkinesis (based on isolated case reports), 1 also involved duplication at the long arm of chromosome 12. We conclude that duplication of ≥1 of the roughly 44 protein-coding genes in the ~6.3-Mb overlap region between the previously published case and our 2 patients is a likely genetic cause of congenital facial synkinesis.

Congenital facial synkinesis is a rare entity resulting from aberrant facial muscle innervation. Jaw movement that improves congenital ptosis is the classic form, known as Marcus Gunn jaw-winking phenomenon.[1] Most instances are unilateral, although bilateral cases have also been reported.[2] Rarely, jaw movement provokes or worsens ptosis, an entity known as inverse Marcus Gunn or Marin–Amat syndrome.[3] Here, we present the first case of familial congenital facial synkinesis with an identified genetic abnormality and provide evidence that chromosome 12q24.1–q24.2 duplication is associated with this dysinnervation syndrome.

CASE PRESENTATION

The proband presented to the neurology service at 19 months of age with focal seizures, some of which had secondary generalization. During his neurologic examination, rhythmic right eyelid winking and more static ptosis of the left eye were noted, both observed only when the boy sucked on his bottle (Fig 1; video in Supplemental Information). These abnormalities were not elicited by jaw opening or other specific facial movements, and his parents confirmed that the noted features had been present since birth. Based on the apparent inhibition of Müller's muscle or levator palpebrae co-occurring with oromotor activity, a diagnosis of congenital facial synkinesis, specifically inverse Marcus Gunn phenomenon, was made.

The boy was born after an uncomplicated pregnancy via induced vaginal delivery at 42 weeks' gestation. He had multiple congenital anomalies including absent patellae,

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Dr Myers collected the data, prepared figures and tables, and drafted the initial manuscript; Dr Innes assisted with interpretation and description of the genomic abnormalities and reviewed and edited the manuscript; Dr Mah confirmed the clinical data and reviewed and edited the manuscript; and all authors approved the final manuscript as submitted.

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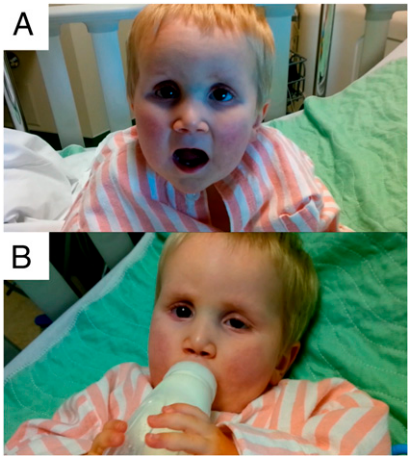

FIGURE 1
Bilateral inverse Marcus Gunn phenomenon. A, At baseline, the patient had no ptosis, even with jaw opening. B, When the patient was actively sucking on a bottle, rhythmic winking of the right upper eyelid occurred, in tandem with sucking, while the left eyelid became progressively more ptotic.

bilateral vertical tali, left iris coloboma, amblyopia, imperforate anus, low-lying conus medullaris with fatty filum terminale, and right hip dysplasia. His development was globally delayed, and at 19 months he could not stand independently, had no pincer grasp, and was not using any words with meaning. Achievement of early motor milestones was probably complicated by his musculoskeletal abnormalities and multiple hospitalizations. Aside from the previously mentioned musculoskeletal anomalies, his general examination was significant for a high arched palate and distinctive facial features, including thin upper lip, flattened philtrum, broad flat nasal bridge, and short, upslanting palpebral fissures (Fig 1). His neurologic examination was significant for axial hypotonia, but no focal deficits were identified. MRI of the brain showed a thin corpus callosum and no other abnormalities (Fig 2).

An initial karyotype and subsequent array comparative genomic hybridization showed an unbalanced translocation resulting in a 1.2-Mb deletion of chromosome 1p36 and a

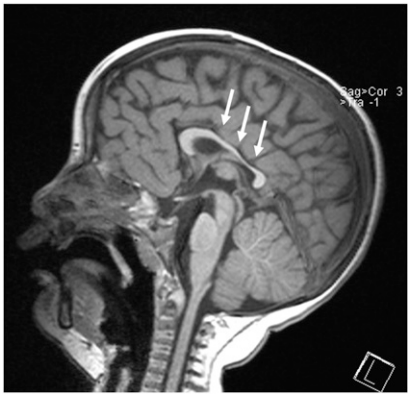

FIGURE 2
Brain MRI. Midline sagittal T1 view demonstrates corpus callosum dysgenesis with thinning of the body and relative sparing of the genu and splenium. The remainder of the midline structures have normal appearance.

12q24.1-ter duplication of 18.82 Mb (46,XY,der(1)t(1;12)(p36.3;q24.21).arr 1p36.33(120 840–1 361 776)x1, 12q24.21–q24.33(114 948 776–133 773 393)x3; NCBI/Hg19). The duplication of chromosome 12 includes ~270 genes. A balanced translocation in 1 of the parents was suspected but not confirmed because additional genetic testing was declined.

Family history revealed that similar eyelid abnormalities provoked by sucking, as well as a nearly identical pattern of congenital anomalies, were present in the proband's younger brother. That boy had a routine karyotype showing the same unbalanced chromosomal translocation as the proband. Although array comparative genomic hybridization could have confirmed that the precise breakpoints were the same in this boy as in his brother, the test was not performed. The karyotype was thought to be sufficient evidence that the same genomic anomaly was present, and parents had declined additional genetic testing in any case.

DISCUSSION

Congenital facial synkinesis is a poorly understood phenomenon, presumed secondary to maldevelopment of cranial nerve pathways leading to dysinnervation of facial muscles. One or both of the levator palpebrae and Müller's muscle are presumably influenced by the trigeminal nerve in our proband and his brother. In such young children, electrophysiological techniques are invasive and impractical, so we were unable to more precisely elucidate the complex dysinnervation patterns, but the presentations are consistent with bilateral inverse Marcus Gunn phenomenon.

Genetic causes are often suspected when congenital facial synkinesis is observed, and ≥10 familial cases, including both classic and inverse Marcus Gunn, have been reported (Table 1).[4–11] The underlying genetic cause was not identified in any of those cases, and the 4 known genetic associations are based primarily on individual case reports (Table 2).[12–16]

The only genetic anomaly that has been associated with >1 case of congenital facial synkinesis is mutation of *KIF21A*.[16] This gene is mutated in the majority of cases of congenital fibrosis of the extraocular muscles 1 (CFEOM1), an autosomal dominant inherited disorder involving extensive cranial dysinnervation resulting in bilateral ophthalmoplegia and ptosis,[16] neither of which was present in our patients. Five reported cases of CFEOM1 due to *KIF21A* mutation had unilateral Marcus Gunn phenomenon.[13,16]

Of the 3 remaining reports of congenital facial synkinesis with an identified genetic anomaly, 1 involves a patient with 12q24.1–q24.2 duplication and unilateral Marcus Gunn phenomenon.[12] Rhythmic winking of 1 eye was seen in that patient, as in our proband, but because the patient had a baseline ptosis in the same eye, the abnormality was classified as classic Marcus Gunn. That patient had only unilateral eyelid abnormality,

TABLE 1 Familial Cases of Congenital Facial Synkinesis

Reference	Clinical Syndrome	Number Affected	Suspected Inheritance Pattern	Genetic Abnormality
Current article	Bilateral inverse Marcus Gunn	2	Unbalanced chromosomal translocation secondary to parental balanced translocation	1p36 deletion, 12q24.1-ter duplication
Sundareswaran et al 2015	Unilateral Marcus Gunn	2	Unclear	None identified
Conte et al 2012	Unilateral Marcus Gunn	4	Autosomal dominant with incomplete penetrance	None identified
Oh et al 2003	Inverse unilateral Marcus Gunn	3	Autosomal dominant	None identified
Mrabet et al 1991 (1)	Bilateral Marcus Gunn	4	Autosomal dominant with incomplete penetrance	None identified
Mrabet et al 1991 (2)	Unilateral Marcus Gunn	3	Autosomal dominant with incomplete penetrance	None identified
Kirkham 1969	Unilateral Marcus Gunn	2	Unclear	None identified
Laska 1965	Unilateral Marcus Gunn	2	Autosomal dominant with incomplete penetrance	None identified
Kanter 1955	Unilateral Marcus Gunn	2	Autosomal dominant with incomplete penetrance	None identified
Falls et al 1949	Unilateral Marcus Gunn	3	Autosomal dominant with incomplete penetrance	None identified

TABLE 2 Genetic Anomalies Associated With Congenital Facial Synkinesis

Reference	Syndrome	Genetic Anomaly	Locus
Kaçar Bayram et al 2015	Unilateral Marcus Gunn (* with CFEOM)	*KIF21A*	12q12
Cordovez et al 2014	Unilateral Marcus Gunn	22q11.2 duplication	22q11.2
Basu et al 2012	Unilateral Marcus Gunn	*PHOX2B*	4p13
Doco-Fenzy et al 2006	Unilateral Marcus Gunn	12q24 duplication	12q24
Yamada et al 2005	Unilateral Marcus Gunn (* with CFEOM)	*KIF21A*	12q12
Yamada et al 2005	Unilateral Marcus Gunn (* with CFEOM)	*KIF21A*	12q12
Yamada et al 2005	Unilateral Marcus Gunn (* with CFEOM)	*KIF21A*	12q12
Yamada et al 2005	Unilateral Marcus Gunn (* with CFEOM)	*KIF21A*	12q12

CFEOM, congenital fibrosis of the extraocular muscles.

suggesting synkinesis was less extensive than in our patients.

The duplicated 12q24.1–24.2 region in that case overlaps with the duplicated 12q24.1-ter region in our proband (Fig 3). We thus hypothesize that duplications involving the ~6.3-Mb 12q24.1–q24.2 overlap region[17] are a genetic cause of congenital facial synkinesis. At this point it is not clear whether this is caused by disruption of ≥1 of the estimated 44 protein-coding genes in that region.

There are 25 other clinical reports involving liveborn, nonmosaic individuals with 12q duplications involving our identified overlap region.[18–37] Although none of these reports identified classic or inverse Marcus Gunn, this phenomenon is easily missed on routine examination because the abnormalities are evoked only by oromotor activity. Interestingly, some of these patients may have shown other subtle signs of abnormal neuronal development, including 2 who were noted to have congenital ptosis.[19,27] An additional patient had asymmetric facial movement, although it was unclear whether this asymmetry was secondary to dysinnervation or congenital absence of the depressor anguli oris muscle, also known as asymmetric crying facies syndrome.[38] Of those who underwent brain

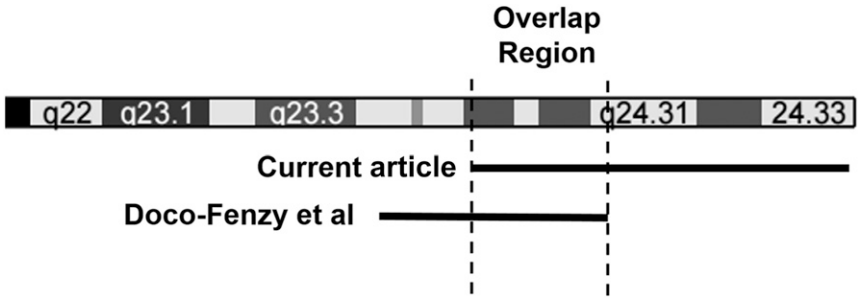

FIGURE 3
12q duplications with congenital facial synkinesis. The duplicated region in our patients and that described by Doco-Fenzy et al (clones RP11-256L11 → RP11-665J20). The overlap region is ~6.3 Mb in size and contains an estimated 44 protein-coding genes. Figure includes a screenshot from the University of California Santa Cruz genome browser (http://genome.ucsc.edu).

imaging, 6 were found to have corpus callosum dysgenesis,[19,21,24,25,34] also present in our patient. The only other significant radiologic abnormality was Dandy–Walker malformation, reported in 2 patients.[34,37]

Our proband also carries a 1p36 deletion (OMIM 607872), which has been associated with a syndrome most commonly involving characteristic facial features, intellectual disability, and congenital malformations. This common copy number variant is not thought to contribute to the patient's inverse Marcus Gunn phenomenon because congenital facial synkinesis has not previously been reported with monosomy 1p36, and our proband's 1.2-Mb deletion is small.[39] Nevertheless, the deletion is probably at least partially responsible for some of the other features of these patients' complex phenotypes.

In summary, this is the first report of familial congenital facial synkinesis with an identified genetic abnormality. Based on this family and a previous report, the most likely genetic cause of these patients' complex cranial dysinnervation is duplication of the 12q24.1–12q24.2 chromosomal region. More research is needed to clarify the apparently complex role of the long arm of chromosome 12 in cranial innervation during brain development.

ABBREVIATION

CFEOM: congenital fibrosis of the extraocular muscles

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