Received: 9 February 2022 | Revised: 30 June 2022 | Accepted: 18 August 2022

DOI: 10.1002/mgg3.2051

Molecular Genetics & Genomic Medicine Open Access WILEY

CLINICAL REPORT

Neurodevelopmental disorder with dystonia due to SOX6 mutations

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Abstract

Background: Mutations in SOX6 have recently been recognized as a new molecular cause of neurodevelopmental disorders characterized by intellectual disability, behavioral changes, and nonspecific facial and digital skeletal abnormalities. To date, <25 cases have been reported in the literature.

Methods and Findings: Here we report a new case of SOX6-associated neurodegeneration and expand the phenotype to include ceratoconus. The clinical picture consisted of early onset mildly reduced intellectual function, facial asymmetry, and dystonic tremor of hands and neck, substantially improved by levodopa. Skeletal abnormalities included scoliosis and hypertrophy of the mandibular coronoid process. A heterozygous de novo loss-of-function variant in SOX6 (c.277 C>T. p.Arg93*) was molecularly confirmed which leads to truncation of the SOX6 protein in its N-terminus, upstream of any known functional domain.

Conclusion: SOX6-associated neurodevelopmental delayis ultrarare with less than 25 cases described in the literature. We report a new case who presented with early-onset mildly reduced intellectual function, facial asymmetry, skeletal abnormalities and dystonic tremor of hands and neck, substantially improved by levodopa. Given the therapeutic implications, SOX6 mutations should be considered in patients with complex dystonia parkinsonism.

KEYWORDS

ceratoconus, dystonia, neurodevelopmental delay, SOX6

1 | INTRODUCTION

Recent advances in genetics including exome sequencing facilitate the identification of rare and ultrarare disorders. For example, we are seeing a growing number of molecular causes of neurodevelopmental disorders (Arnett et al., 2021; Dinneen et al., 2021; Kiser et al., 2015) which often present with a complex phenotype with overlapping clinical features such as intellectual disability, behavioral changes, or nonspecific facial and digital skeletal abnormalities. This includes mutations in SOX genes that produce Coffin-Siris-like syndrome-10 (OMIM: 618506; due to mutations in the SOX4 gene) (Zawerton et al., 2019), Lamb-Shaffer syndrome (OMIM: 616803; due to mutations

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in the SOX5 gene) (Zawerton et al., 2020), or Coffin-Siris-like syndrome-9 (OMIM: 615866; due to mutations in the SOX11 gene) (Hempel et al., 2016; Tsurusaki et al., 2014).

Most recently, the clinical phenotype associated with SOX6 genes has been delineated (OMIM: 607257) (Tolchin et al., 2020). Last year Tolchin and colleagues published a series of 19 individuals from 17 unrelated families harboring SOX6 gene mutations who presented with developmental delay and/or intellectual disability. Additional, inconsistant features included attention–deficit/hyperactivity disorder, autism, mild facial dysmorphism, craniosynostosis, and multiple osteochondromas. Beyond this, only a handful of cases have been reported (Ebrahimi-Fakhari et al., 2015; Scott et al., 2014; Tagariello et al., 2006), making this an ultrarare disorder.

Here we present the clinical features and investigational findings of a newly identified SOX6 patient and expand the phenotype to include ceratoconus.

2 | CASE REPORT

After an uneventful pregnancy and delivery, this German male patient of nonconsanguineous parents first came to medical attention at the age of 5 years because of delayed early motor and cognitive milestones. Early, a facial asymmetry was noted, which was, however, not typical of any of the common neurodevelopmental syndromes. At school age, dyslexia was diagnosed, and he was found to be generally slow, mainly because of a slow speech and reduced intellectual function (IQ not formally tested). He completed secondary school after 9 years of school. Around age 10 years, he developed atypical dystonia, primarily affecting the cervical region, with dystonic head and hand tremor and progressive scoliosis which was treated conservatively leading to a Cobb angle of 32° on the lumbar level and a counter swing of 27° of the thoracic spine at a postpubertal height of 185 cm. Around the same time, he experienced restrictions when trying to open his mouth which was found to be due to hypertrophy of mandibular processus coronoideii bilaterally. At age 15, a corneal ceratoconus bilaterally was diagnosed, and he was prescribed hard contact lenses.

His family history is presented in Figure 1. One brother has spina bifida, cognitive slowness, and depression. The father developed dystonic tremor with postural hand and head tremor, unresponsive to alcohol, but benefit from betablockers, at the age 47 years. The paternal great-grandfather also had tremor, and a paternal aunt had spina bifida. On the maternal side, several relatives were affected by legasthenia.

On neurological examination at age 21, he had a leptosomic appearance (height 91st percentile, body mass index

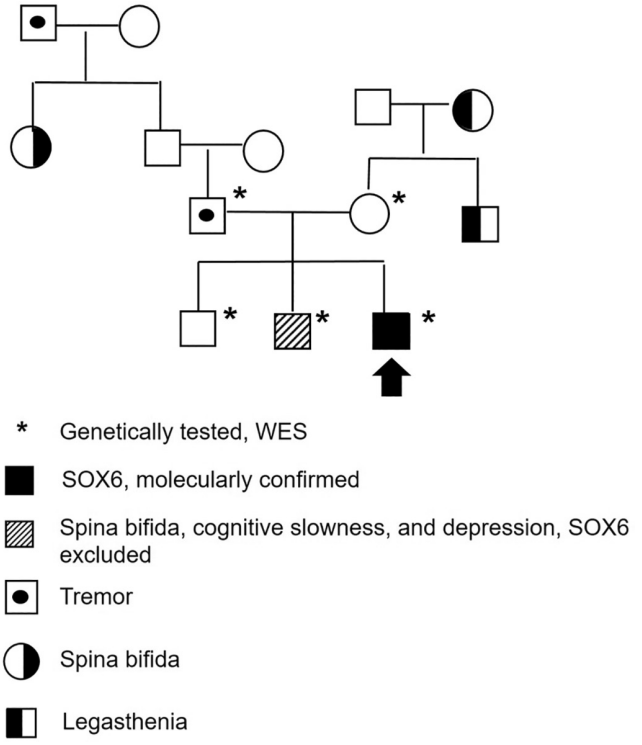

FIGURE 1 Pedigree

18.9). There was facial asymmetry, slow speech, mild rest, postural and kinetic tremor of the hands, left more than right, neck dystonia with mild dystonic head tremor, and asymmetry of the shoulders with scoliosis. The tone was increased in the legs; reflexes were reduced in the upper and brisk in the lower extremities. There were no cerebellar signs. Postural stability and gait were unremarkable. There was no sensory disturbance. He had a skin rash on the left middle back of unexplained etiology. He was graded 0 on the Walton-Gardner-Medwin Scale (a generic clinical tool used to assess weakness). He scored 1 for the upper and lower extremities bilaterally on the Vignos scale (used to evaluate the functional abilities of patients with muscle weakness). He was referred with a suspected diagnosis of Lujan-Fryns syndrome, that is, X-linked syndromic intellectual disorder.

Diagnostic work-up then revealed normal myosonographic echointensity and structure of proximal and distal upper and lower limb muscles as well as ventral and dorsal trunk muscles (Heckmatt Score I). This included normal findings of the masseter muscle. Sensory and motor nerve conduction velocities were generally normal. Electrophysiology showed mild slowing of the sural nerve. Electrocardiogram and echocardiography were normal. Neuropsychological testing was not performed (according to the parents' wishes).

Chromosomal analysis and an array of chromosomal microarray testing were unremarkable. Subsequent targeted genetic testing was negative for mutations in MED12, UPF3B, and ZDHHC9 (associated with the

Lujan-Fryns type and nonsyndromic X-linked intellectual developmental disorder (Shimell et al., 2019)), FBN1 (including copy number variations, associated with classic Marfan syndrome (Milewicz et al., 2021)), and FMR1 (Fragile X syndrome). Exome sequencing with trio analysis eventually identified a heterozygous mutation in SOX6 (c.277 C>T. p.Arg93*) in the index case. In addition an independent from trio exome filtering procedures, a comprehensive gene panel was evaluated regarding dystonia in the index patient, whereby causal variants in the respective analyzed gene were excluded (see supplement). This additional analysis was independent of inheritance pattern and/or penetrance of the included genes.

All other family members tested (i.e., the parents and both brothers) were negative for the SOX6 mutation in blood, sputum, and urine. The diagnosis of a de novo mutation was made.

Treatment with botulinum toxin produced only minor temporary benefits of cervical and facial dystonic symptoms and was discontinued after five sessions using various approaches and dosing regimens. Hypertrophic processus muscularis mandibulae were resected in 2018 leading to improved mouth opening.

Based on the pathophysiology of SOX6-associated disorders, a trial of levodopa (375 mg/day) was initiated which substantially ameliorated dystonic hand and head movements and improved his handwriting as well as his concentration and thereby school performance.

3 | DISCUSSION

Here we report a new case of SOX6-associated neurodevelopmental delay broadening the clinical phenotype. Most reported cases in the literature arose de novo, however, autosomal-dominant fashion with inheritance from a mosaic father has also been reported. In our patient, extensive genetic work-up of the family excluded the mutation in other family members (including a neurologically affected brother), so a de novo mutation is assumed.

Clinically, in view of the tall, marfanoid habitus, distinct facial dysmorphism, and behavioral problems, a diagnosis of Lujan-Fryns syndrome or X-linked mental retardation (XLMR) had been made. However, common genetic causes including MED12 (Xq13), UPF3B (Xq25-q26), ZDHHC9 (Xq26.1), and differential diagnoses including Fragile X syndrome were excluded. Subsequent exome sequencing led to unraveling the final diagnosis: a soxopathy due to SOX6 mutations located at 11p15. Like in our case, SOXopathies in general result from de novo heterozygous loss-of-function mutations (Angelozzi & Lefebvre, 2019).

A variety of bone abnormalities have been observed in SOX6 cases including craniosynostosis (Tagariello et al., 2006). Our case had hypertrophy of the mandibular coronoid processes which may be associated with the limited buccal opening (Mazzetto & Hotta, 2007). His scoliosis remained stable with conservative management up to date. Our patient also had bilateral ceratoconus, another cause of which could not be established. To our knowledge, this is the first report of ceratoconus in SOX6 mutation.

Overall, sophisticated genetic methods and increasing availability of genetic testing have led to improved diagnostic accuracy. However, only for a fraction of patients, this has direct therapeutic implications. In our patient, given the role of *SOX6* in the development of dopaminergic neurons (Panman et al., 2014), a trial of levodopa was initiated. This resulted in substantial improvement of dystonia, which had previously failed to respond to botulinum toxin injections. Similar observations of SOX6-associated dopa-responsive dystonia (Ebrahimi-Fakhari et al., 2015) and parkinsonism (Scott et al., 2014) in SOX6 have been reported. Notably, other SOX genes, i.e. SOX2 (Pilz et al., 2019) andSOX9 (Choi et al., 2018) link to dystonia, sometimes in the absence of typical clinical features (Pilz et al., 2019), and parkinsonism has also been established based on clinical or basic research grounds.

SOX6 belongs to the SOX gene family encoding proteins of the HMG box superfamily of DNA-binding proteins, which are involved in diverse developmental processes. Specifically, SOX6, together with SOX5 and SOX13, is a member of the SOXD subgroup (Angelozzi & Lefebvre, 2019). These genes encode proteins that homodimerize through coiled-coil domains and bind target genes preferentially to pairs of SOX sites (Angelozzi & Lefebvre, 2019). Sox6 single-null mice are born with discrete skeletal malformations, and double-null fetuses die in utero with severe chondrodysplasia in line with clinical observations (Tagariello et al., 2006). The nonsense variant detected in our patient truncates the SOX6 protein in its N-terminus, upstream of any known functional domain, thus almost undoubtedly a loss-of-function variant. The same mutation was observed in a previous patient (#10, UK2) (Tolchin et al., 2020).

In conclusion, this SOX6 patient is able to live an independent life with respect to all domains of the WHO International Classification of Functioning, however, requiring continuous medical monitoring of potential secondary complications (including vision and spine). Treatment with levodopa led to substantial improvement.

AUTHOR CONTRIBUTIONS

Susanne A. Schneider: conceptualization, writing of the first draft; Christine Mueller: clinical input, critical review; Saskia Biskup: genetic analysis, critical review; Urban M. Fietzek: clinical input, critical review; Andreas Sebastian Schroeder: clinical input, critical review.

ACKNOWLEDGMENTS

We would like to thank the family for permitting to report their case. We thank Dr Veronique Lefebre for the insightful discussion and Britta Pauli for assistance with sample handling. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

SAS and ASS are supported by the LMU Clinician Scientist Excellent Programme.

ETHICS STATEMENT

All persons described gave their informed consent prior to inclusion into the study. The study conforms to regular standards and policies aimed to protect human subjects.

CONFLICT OF INTEREST

None of the authors has any conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Schneider, S. A., Mueller, C., Biskup, S., Fietzek, U. M., & Schroeder, A. S. (2022). Neurodevelopmental disorder with dystonia due to SOX6 mutations. *Molecular Genetics & Genomic Medicine*, *10*, e2051. https://doi.org/10.1002/mgg3.2051