Journal of the Neurological Sciences 401 (2019) 34–36

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Letter to the Editor

Exome sequencing identifies a recurrent *SOX2* deletion in a patient with gait ataxia and dystonia lacking major ocular malformations

ARTICLE INFO

Keywords:
Developmental disorders
Clinical genetics
Dystonia
Ataxia
SOX2

Dear Editor,

SOX2 (OMIM: 184429) encodes for a transcription factor of the SRY (sex-determining region Y)-related high-mobility-group box family which regulates pluripotency of human embryonic stem cells and is indispensable for coordinated embryogenesis. Pathogenic variants within this gene are associated with autosomal dominant syndromic forms of uni- or bilateral micro- or anophthalmia and a wide range of non-ocular features including neurological, gastrointestinal, genital, skeletal, cardiovascular, endocrine and renal anomalies [1]. Here, we describe a female child with a recurrent heterozygous 20 bp deletion within *SOX2* identified by whole exome sequencing who presented with gait ataxia, dystonia, and global developmental delay but without major ocular malformations. This case demonstrates that the use of exome sequencing in a genotype-first approach does not only improve the diagnostic yield of genetic testing for rare Mendelian disorders but also helps to refine the phenotypic spectra associated with known disease genes.

1. Case report

The 12-year-old female index case is the second child of a non-consanguineous couple of Caucasian ancestry and presented with profound global developmental delay as well as a complex movement disorder (II:2; Fig. 1A,B). She was born at 39 weeks after an uneventful pregnancy with a birth weight of 3900 g (91st percentile, z-value = 1.33), length of 52 cm (66th percentile, z = 0.41) and head circumference of 36 cm (86th percentile, z = 1.08). Developmental milestones were not reached at the appropriate age. She started walking three steps without support at the age of 30 months and had a delayed language development. At the age of 4 $^{11}/_{12}$ years, she used three-word sentences and presented a dystonic and ataxic gait with flinging movements. Her walking distance was limited to 500 m. Over the following years, she still had walking difficulties (Suppl. Videos 1–3) and special education needs because of persistent cognitive impairment. Various differential diagnoses, e.g. inborn errors of metabolism, congenital disorders of glycosylation or microdeletion syndromes, could not be confirmed. Repetitive magnetic resonance imaging of her brain and spinal cord, cerebrospinal fluid (CSF) analyses, neurophysiological examinations, a metabolic screen, and an array CGH analysis gave normal results. At the age of 11 $^{9}/_{12}$ years, she presented no clinical or paraclinical signs of puberty. Laboratory investigations demonstrated low estradiol, borderline low LH and FSH, as well as normal TSH, prolactin and thyroid function tests. Additionally, the index case reported symptoms of a vulvar lichen sclerosus without signs of a systemic autoimmune disease or pelvic organ prolapse that responded well to topical estrogen therapy. An ophthalmological examination revealed hypoplastic lacrimal ducts that had already caused recurrent eye infections in early childhood, bilateral scotomas, and macrodiscs with abnormal non-glaucomatous excavations but no other ocular malformations (Fig. 1C). No renal, cardiovascular, gastrointestinal, dental or skeletal anomalies had been documented. Both parents and siblings are healthy and reported no neurological or ophthalmological complaints.

The NucleoSpin Blood L kit (Machery-Nagel, Düren, Germany) was used to isolate genomic DNA from peripheral blood lymphocytes of the index case and her parents for trio-based whole exome sequencing. NGS target enrichment was performed with the SureSelect Human All Exon v6 kit (Agilent Technologies, Santa Clara, USA) and DNA libraries were sequenced on a HiSeq 4000 instrument (2 × 100 cycles, Illumina, San Diego, USA). The average exome coverages ranged from 132× to 141×, and > 98% of the target region was covered with at least 20×. Sequence analysis (https://ihg.helmholtz-muenchen.de/) revealed no rare variants in candidate genes upon the assumption of an autosomal recessive inheritance. In contrast, *de novo* variants were identified in three genes: *MORN1*, *CYSTM1,* and *SOX2*. Only the latter is listed in the OMIM database with an associated phenotype (OMIM: 206900). The recurrent 20 bp deletion in the *SOX2* gene [c.70_89del; p.(Asn24Argfs*65)] (Fig. 1D) that was found in a heterozygous state is listed in international mutation databases as pathogenic (HGMD Professional, ClinVar, LOVD *SOX2* MRC Human Genetics Unit) and had previously been described as one of the most frequently detected pathogenic *SOX2* variants in patients with severe micro- or anophthalmia. Sanger sequencing confirmed heterozygosity for proband II:2. Neither parent nor the older brother (II:1) did carry the *SOX2* frameshift variant (Fig. 1E). No inconsistencies with the paternity and maternity of the

https://doi.org/10.1016/j.jns.2019.04.007
Received 18 January 2019; Received in revised form 15 March 2019; Accepted 5 April 2019
Available online 08 April 2019
0022-510X/

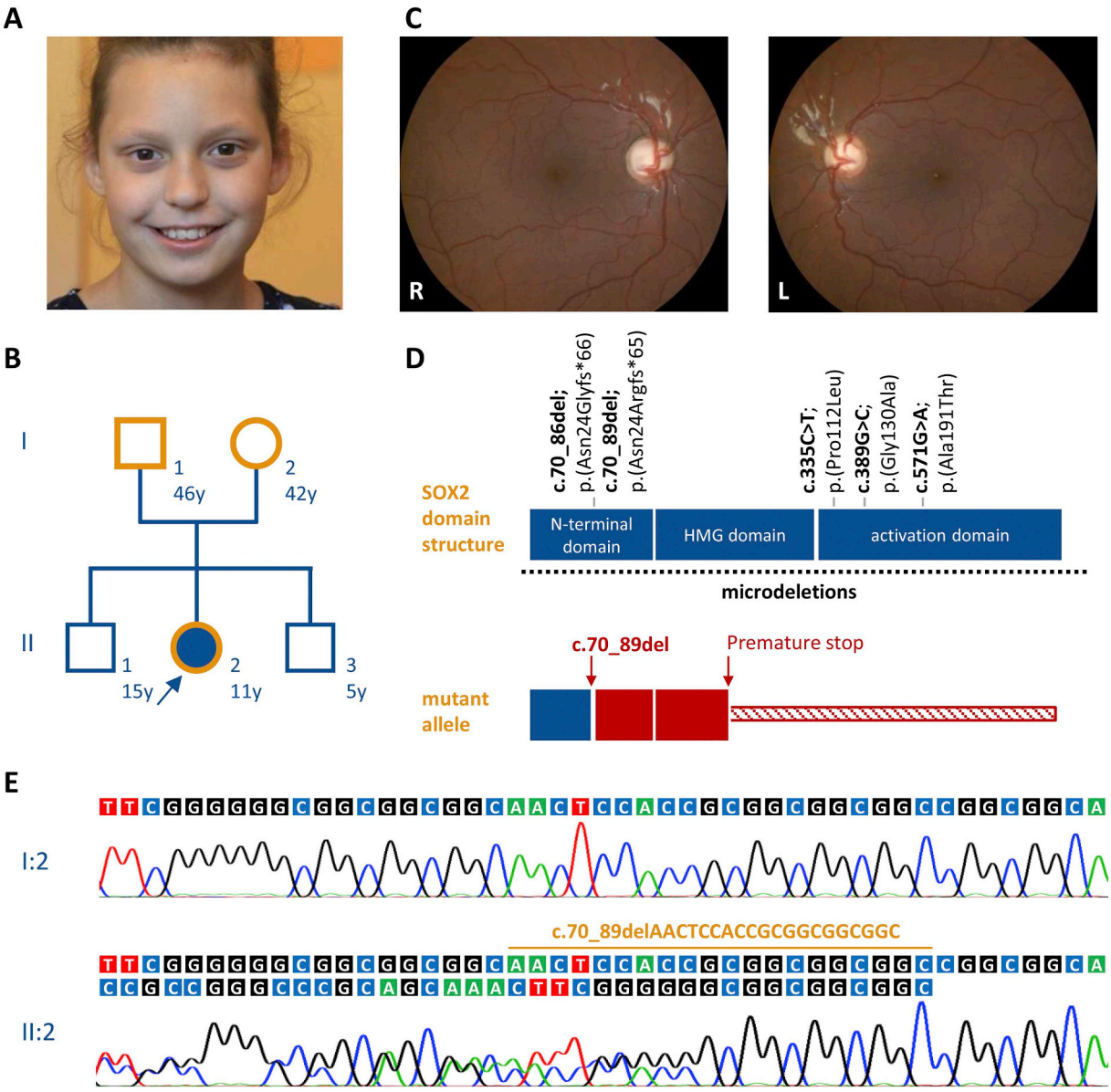

Fig. 1. (A) Photograph of the index patient at the age of eleven showing sparse eyebrows but no ocular malformations. (B) Pedigree of the index case (II:2, blue arrow). Whole-exome sequenced probands are marked with orange circles. (C) Fundus photographs showing bilateral macrodiscs with abnormal non-glaucomatous excavations. R = right eye, L = left eye. (D) Pathogenic *SOX2* variants that have previously been identified in patients without major eye malformations [1–3,5] (upper panel). The 20 bp deletion [c.70_89del; p.(Asn24Argfs*65)] identified by whole exome sequencing in II:2 is predicted to cause premature protein truncation (lower panel). (E) Validation of the frameshift variant in II:2 and exclusion in her mother's DNA sample (I:2) by Sanger sequencing.

parents were detected in a multiplex short tandem repeat analysis (PowerPlex 16, Promega, Germany). As intellectual disability, movement disorders, and delayed puberty belong to the spectrum of symptoms observed in patients with SOX2-related ocular malformations, the identified variant was classified as pathogenic for the phenotype of our index case.

2. Discussion

To the best of our knowledge, we here report only the second carrier of the most common *SOX2* mutation c.70_89del with an ataxic gait and merely the fourth patient with this specific variant without major ocular malformations [2–4]. Micro- and anophthalmia are by far the most frequently observed symptoms of *SOX2* mutation carriers. Since its identification as a disease-associated gene for severe structural eye malformations in 2003 more than 90 pathogenic variants have been discovered in *SOX2,* and only fifteen *SOX2* mutation carriers without micro- or anophthalmia have been reported so far [1–3,5].

In contrast, ataxia seems to be a rather rare feature in patients with pathogenic *SOX2* variants. We are aware of only twelve published cases with *SOX2* mutations or microdeletions who presented with truncal or gait ataxia [1,3,6–9]. Notably, three of these patients had no micro- and/or anophthalmia (Suppl. Table S1). Prenatal ablation of *Sox2* in mice has recently been reported to induce severe Bergmann glia dysfunction, abnormalities of cerebellar morphology and defects in fine motor coordination [10]. As ataxic features have also been observed in oligodendroglial SOX2-deficient mice [11], ataxia can be considered as part of the phenotypic spectrum of SOX2-related disorders. Thus, the case presented here supports the hypothesis that the expressivity of this long-known Mendelian disorder is more variable than previously thought [1,3]. Furthermore, it exemplifies that exome sequencing is often indispensable for the diagnosis of rare genetic diseases in patients who do not present all key features.

In summary, our findings demonstrate that a heterozygous *SOX2*

mutation can be a rare cause of developmental delay and complex movement disorders. Even if there is no micro- or anophthalmia, a SOX2-related disease may be included in clinical differential diagnostic considerations and patients should be examined for minor ocular malformations.

Ethical standards

All family members gave their written informed consent and the study protocol was approved by the local ethics committee (University Medicine Greifswald; BB 047/14).

Conflicts of interest

None.

Funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Patient consent

The authors obtained informed consent of the patient for publication.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.04.007.

Acknowledgements

We thank the patient and her family for granting permission to publish this information.

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