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Description of a patient with developmental delay and dysmorphic features caused by a novel SHANK2 deletion

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Abstract

Background The *SHANK* gene, located on chromosome 11q13.3-q13.4, encodes the SHANK2 protein with a function in neuronal synapses. An error in coding can alter the development of typical cognitive, linguistic and social skills. However, its alteration produces a phenotype that has yet to be fully defined.

Case presentation We present the case of a patient diagnosed with a deletion in the *SHANK2* gene as an infant and its subsequent evolution, including a description and iconography of the phenotype. Similar copy number variations (CNVs) are described in the literature, but none with the length of our patient's copy number.

Conclusions This work broadens the phenotypic and genotypic spectrum associated with the *SHANK2* gene, which promotes the genetic diagnosis of the disease.

Keywords Autism spectrum disorder, Comparative genomic hybridization array, Dysmorphic features, SHANK2

Background

The SHANK (multiple ankyrin repeat domains protein) family genes (including SHANK1, SHANK2 also known as ProSAP1 (OMIM: 603,290) and SHANK3 [1, 2]) encode synaptic structure proteins in the postsynaptic neuron, essential for synapse formation and stabilization, in addition to development and brain plasticity [1–5]. Deletions, duplications and mutations in the coding of these genes have been recurrently reported in patients with autism spectrum disorders (ASD) [3–8]. ASDs are characterized by impairments in social skills and stereotyped behaviours, as well as alterations in cognitive function and language [3, 4].

Several studies have shown the involvement of different genetic variants in ASDs such as chromosomal rearrangements or de novo variants, both in copy number and coding.

sequence [3]. More than 100 genes have been implicated [9], but each gene or genomic alteration usually accounts for less than 1% of cases. Many of these genes are involved in the development or function of neural circuits [3]. To date, no association of SHANK genes with Down syndrome has been reported.

The first pathology identified in patients affected by *SHANK* gene mutations was a deletion or other structural change of the terminal end of chromosome 22 in the 22q13 region or a disease-causing (pathogenic) variant of the SHANK3 gene, now known as Phelan McDermid syndrome, a form of intellectual disability caused by SHANK3 haploinsufficiency and often associated with ASD [8, 10]. These patients present with neonatal

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hypotonia, moderate-severe intellectual disability, significant speech impairment and minor dysmorphic features. ASD is present in approximately 80% of cases of alterations in the SHANK genes [3]. This makes autism spectrum disorders the main effect produced by the gene family on the clinical phenotype of the disease.

In recent years, extensive analyses of patients with ASD have shown a significant number of mutations not only in SHANK3, but also in SHANK1 and SHANK2 genes [3, 8, 11], strongly suggesting that SHANK proteins are involved in the regulation of a common molecular pathway associated with ASD: pathways controlling dendrite morphology and arborisation and spine morphology and growth [12, 13].

Although fewer studies describe the involvement of SHANK1 and SHANK2 in ASD, all agree that deleterious variants in these genes contribute to the disorder [1–4].

Variations in SHANK2 account for 0.17% of genetic causes of ASD and 0.33% of psychomotor developmental disorders [3]. Attention-deficit/hyperactivity disorder (ADHD) has also been linked to SHANK2 single-nucleotide polymorphisms, and previously with SHANK3 [7, 11, 14]. To date, there is no treatment for these disorders, however, some potential drug targets have been identified [8].

Case presentation and genetic findings

We reported a clinical case of a female 4-year-old girl diagnosed with *SHANK2* gene deletion at infant age. No family history of interest. Personal history: pregnancy and birth at full term without incident. Neonatal screening with no abnormalities. Anthropometry at birth (according to the charts of Fernández et al. 2011 [15]): weight 3175 g (P > 99); length (L): 49 cm (P 41); head circumference (HC): 33 (P 10).

During these four years, she has been monitored in multiple clinics of different specialities: nephrology for suspected tubulopathy in the context of altered weight development, which was ruled out and discharged, gastroenterology until the age of three for swallowing disorders and altered weight development (currently being monitored by the Dysphagia Unit for chewing problems), otolaryngology for suspected hypoacusis after alteration in the hearing screening at birth and subsequent language delay, rehabilitation due to a gait with platibasia and cephalic flexion and very pronounced talo valgus with hyperpronated flat foot, in treatment with DAFOS (dynamic ankle-foot orthosis), paediatric surgery due to the presence since birth of supraumbilical hernia which is maintained with expectant attitude and neurometabolism due to global delay in psychomotor development and microcephaly.

Follow-up in the neurometabolism unit began at 5 months of age due to the presence of psychomotor retardation and a peculiar phenotype. Physical examination revealed inconstant fixation and tracking, axial hypotonia and hypertonia of the four limbs with exaggerated osteotendinous reflexes. The phenotype showed microcephaly, elevated nasal root, narrowing of both temples, long philtrum and dysplasia of the left auricle. Anthropometric data at baseline were: HC 38.5 cm (< P1); weight 5085 g (P4); L 60.2 cm (P6).

The following complementary tests were performed: blood tests (including haemogram, liver, kidney and thyroid function, creatine phosphokinase, amino acids, ammonium, lactate, carbohydrate-deficient transferrin (CDT), copper and vitamin B12 metabolism, serum free fatty acids, beta hydroxybutyrate, homocysteine, long-chain fatty acid chromatography) and urine organic acids, transfontanellar ultrasound, abdominal ultrasound, ophthalmological and cardiological assessment and electroencephalogram, which did not detect any alterations.

In the genetic study performed by comparative genomic hybridization array (CGHa), a deletion 11q13.3-q13.5 (with *SHANK2* gene dosage alteration) was detected. The targeted variant is a likely pathogenic deletion of approximately ~5.6Mb in chromosome bands 11q13.3→q13.5, which alters the dosage of multiple reference genes, including the *SHANK2* gene (OMIM 603290), as well as the *DHCR7* morbid gene (OMIM 602858) (Fig. 1). Initially, as this was a pathogenic variant that appeared to clinically support the patient's phenotype, further genetic studies were not taken up.

However, apart from SHANK2 in the deletion, it is likely that more genes and/or genetic material are involved in the pathology but we do not currently know what role they play. This fact could explain why the clinical context of the patient was not exactly as expected in other children with alterations in the SHANK gene family. Thus, we have a coherent phenotype but with some peculiarities.

At the last visit, at the age of 4 years 9 months, she presented: She had a very severe neurodevelopmental disorder with severe cognitive deficit and special affectation in the area of communication (she uses a digital screen). No onset of purposeful language, no imitation or repetition. Frequent stereotypies. No symbolic play. However, he looks at the eyes and is aware of the environment, so no impression of ASD.

At a motor level, he has practically no use of his hands, he throws objects. No autonomy in eating or sphincter control. Dysphagia and constant drooling. Stable autonomous walking if the surface was safe and regular, with increased base of support, did not walk up and down stairs without assistance. No seizures or self-harm.

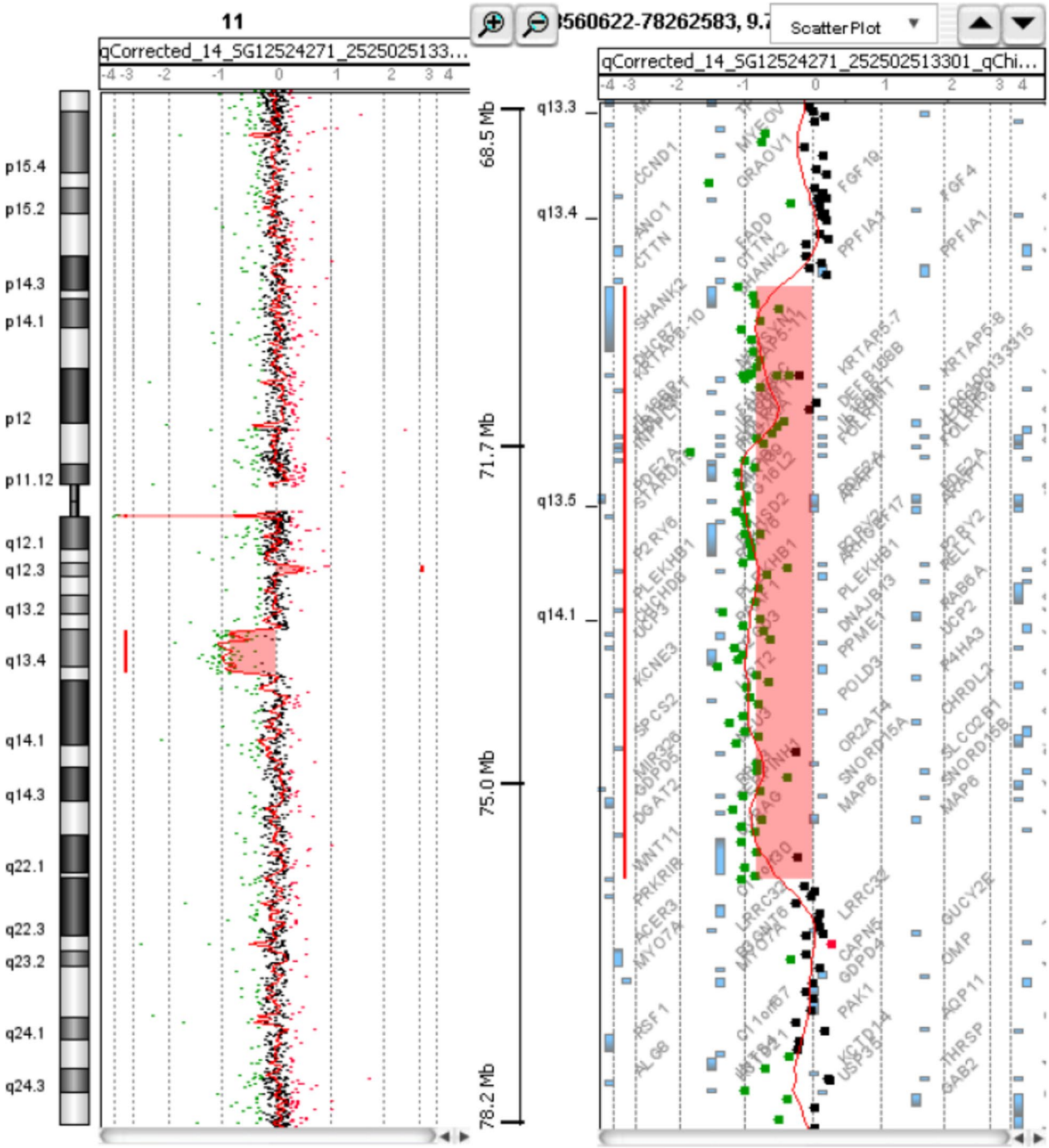

Fig. 1 Comparative genomic hybridization array (CGHa). Detail of the ~ 5.6 Mb interstitial deletion identified in the case presented

As for the phenotype (Figs. 2, 3), she had a flat profile, thick eyebrows, long eyelashes, bulbous nasal tip and prominent root, low-set and receding ears, with hypoplasia of the left auricle and generalized dental hypoplasia.

Discussion

We present the case of a patient with a probably pathogenic interstitial deletion of 5.6Mb in chromosome bands 11q13.3 → q13.5, which alters the dosage of multiple reference genes. Partially overlapping deletions (although

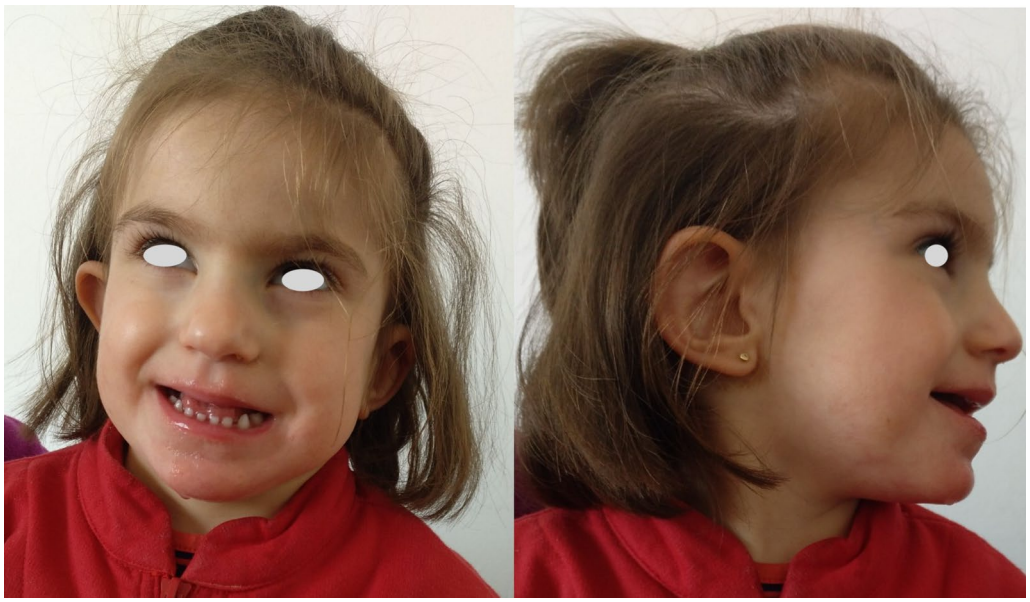

Fig. 2 Front and profile facial phenotype. Flat profile, thick eyebrows, long eyelashes, bulbous nasal tip and prominent root, low-set and receding ears, hypoplasia of the left auricle and generalized dental hypoplasia

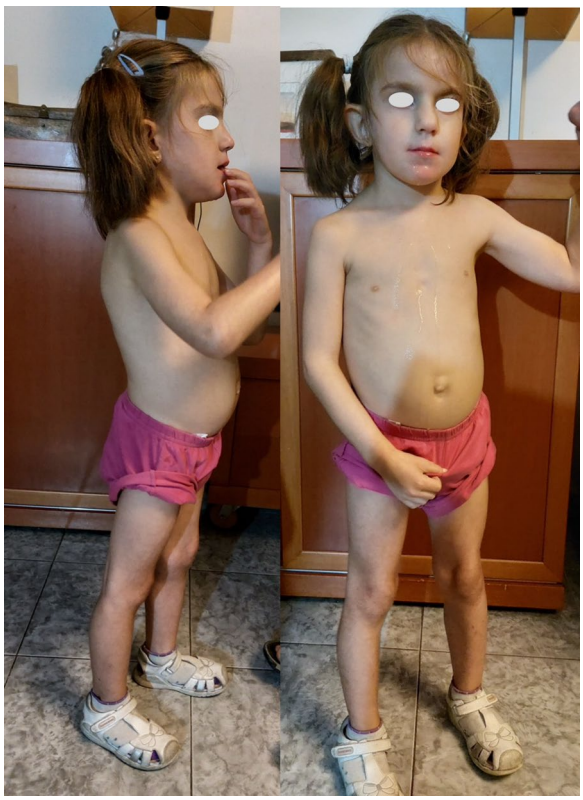

Fig. 3 Front and profile full body phenotype

none identical) have been described in the literature in patients with variable phenotypes, including neurocognitive disorders, among other manifestations.

Among them, the presence of the *SHANK2* morbid gene (OMIM 603290), whose haploinsufficiency has been associated with susceptibility to autism and cognitive disorders [4]; as well as the *DHCR7* morbid gene (OMIM 602858), whose loss-of- function mutations in homozygosis are associated with Smith-Lemli-Opitz syndrome [16, 17]. Notably, the deletion identified in the present case partially overlaps with 3.5Mb recurrent deletions (flanked by segmental duplications and including *SHANK2* and *FGF3* candidate genes, the latter not included in the present case deletion) previously described in the literature in patients with developmental and language deficits, intellectual disability, microcephaly and craniofacial dysmorphies [1–10, 14, 18, 19]. The DECIPHER database describes a patient with feeding problems, short stature, small for gestational age, hypotonia, intellectual disability, aphasia, cardiovascular anomalies and dysmorphias, carrier of a 5.14Mb de novo deletion partially overlapping the one identified in the present case, also affecting the *SHANK2* candidate gene.

To date, only 15 patients with pathogenic variants in the SHANK2 gene worldwide have been described in the literature, so the phenotypic spectrum is only partially described.

One of the peculiarities of this case is that although similar copy number variations (CNVs) have been described in the literature, but none with the length of

our patient's copy number. Furthermore, in Spain there is no case described in the literature with alterations in SHANK2 and CNVs. Among these patients, all individuals carried de novo variants (premature stop codons or single-nucleotide variants and microdeletions) resulting in SHANK2 haploinsufficiency. However, cases with rare nonsense SHANK2 variants inherited from unaffected parents have been reported, suggesting the presence of alleles with low penetrance [1–4, 18].

The clinical features associated with SHANK2 haploinsufficiency lead to a varied phenotype, dominated by autism spectrum disorder, language delay and intellectual disability. However, it has been associated with a broader clinical phenotype: verbal dyspraxia, absence of signalling, variable eye contact, repetitive and stereotyped behaviour, sleep disturbances, contact-anxious features (such as aggression or self-injury) limiting performance on objective standardized tests, attention deficit, hyperactivity, limited autonomy (in basic activities such as eating or dressing), and hypotonia which is very rare [3, 8, 18, 19].

Despite the previously described association of SHANK2 with ASD, Doddato et al. described a patient with no signs of ASD (he had a pathogenic de novo variant c.334C > T, p.(Gln112)). This finding increases the phenotypic spectrum associated with SHANK2 mutations [1].

Marcou et al. described a girl with *SHANK2* gene deletion presenting with microcephaly as in our case, associated with other dysmorphic features and global developmental delay [2].

Conclusion

The present study detected a female with a probably pathogenic interstitial deletion of 5.6Mb in chromosome bands 11q13.3 → q13.5 which alters genes such as *SHANK2* (OMIM 603290), whose haploinsufficiency has been associated with susceptibility to autism and cognitive disorders as well as the *DHCR7* morbid gene (OMIM 602858). We describe the phenotype of our patient supported by images. This work contributes to broadening the phenotypic and genotypic spectrum associated with the *SHANK2* gene, which remains partially described in the current literature. It is important to report clinical cases for a complete description.

Abbreviations

ASD	Autism spectrum disorders
ADHD	Attention-deficit/hyperactivity disorder
DAFOS	Dynamic ankle-foot orthosis
CGHA	Comparative genomic hybridization array
P	Percentile
L	Length
HC	Head circumference

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Author contributions

DMH, RPD and SIA drafted and critically reviewed the manuscript. RPD was the principal physician in the patient's case. AMH, GCM and BSS contributed to data collection, literature search and helped to draft the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

The authors confirm that the journal's ethical policies have been respected. We do not attach the report of the local ethics committee. The reason for this is that our committee refers that in case report an informed consent from the parents or legal guardians is already included and that should be sufficient.

Consent for publication

Written informed consent was obtained from the parents of the patient.

Competing interests

The authors declare that they have no competing interests.

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