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CLINICAL REPORT

A rare unbalanced translocation (trisomy 5q33.3-qter, monosomy 13q34-qter) results in growth hormone deficiency and brain anomalies

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Abstract

Background: Unbalanced translocations between the q arm of chromosomes 5 and 13 are exceedingly rare and there is only one reported case with distal trisomy 5q/monosomy 13q. In this report, we describe a second patient with a similar rearrangement arising from a paternal balanced translocation.

Methods: Karyotype analysis was performed on the proband and their parents. Microarray was also conducted on the proband.

Results: Our patient was found to have global developmental delay, distinct facial features, short stature, growth hormone deficiency, delayed puberty, and brain anomalies including a small pituitary. Karyotype and microarray analysis revealed a terminal duplication of chromosome regions 5q33.3 to 5qter and a terminal deletion of chromosome regions 13q34 to 13qter that resulted from a balanced translocation in her father. The endocrine abnormalities and neuroimaging findings have not been previously described in patients with either copy number change.

Conclusions: This case helps expand on the phenotype of patients with distal trisomy 5q/monosomy 13q as well as possibly providing useful information on the more common individual copy number changes.

KEYWORDS

brain anomalies, clinical genetics, endocrinology, growth hormone deficiency, unbalanced translocation

1 | INTRODUCTION

Rare unbalanced chromosomal translocations present a significant clinical challenge due to the often-complex phenotypes and lack of existing literature to guide management and counselling. Patients with distal trisomy 5q/monosomy 13q are very rare. Only one patient has been so far reported with this specific genetic complement (Shiihara et al., 2004). Much remains unknown about the phenotypic consequences of this rearrangement.

Alyssa C. M. Joynt and Ashish R. Deshwar contributed equally.

Multiple studies have reported patients with each respective copy number variant alone. Patients with distal trisomy 5q present with developmental delay/intellectual disability, growth restriction, distinct facial features, heart defects, limb anomalies, and craniosynostosis (Curry et al., 1979; Jones et al., 1979; Kumar et al., 1987; Osztovics & Kiss, 1975; Passarge et al., 1982; Shiihara et al., 2004; Zabel et al., 1978). Patients with distal deletions of 13q (starting at q33-q34) exhibit severe intellectual disability but do not tend to present with any other significant anomalies (Brown et al., 1993, 1995). The single patient reported with distal trisomy 5q/monosomy 13q was not described to have any unique features outside of those that could be explained by either copy number variant (Shiihara et al., 2004).

In this report, we described a patient with a terminal duplication of chromosome regions 5q33.3 to 5qter and a terminal deletion of chromosome regions 13q34 to 13qter that result from a balanced translocation in her father. She presents with similar features previously reported in the other patient with this rearrangement, including global developmental delay/intellectual disability, short stature, and distinctive facial features. Interestingly, the patient was found to have growth hormone deficiency and delayed puberty. A brain MRI revealed multiple anomalies, including gray matter heterotopia, a dysmorphic corpus callosum, and brainstem, and notably, a small pituitary. These features have not yet been reported in patients with either copy number variation. Our case expands on the phenotype of patients with this very rare rearrangement with implications for clinical management.

2 | CLINICAL DESCRIPTION

Our patient was born at 40 weeks (birth weight: 6 pounds, 11 ounces) to healthy non-consanguineous parents of Chinese descent. She first came to our attention at 6 months of age due to poor growth and feeding difficulties. At 6 months, her weight was 5.8 kg (3rd percentile) with a head circumference of 40 cm (2nd percentile) and a length of 65 cm (50th percentile). She was found to have very distinct facial features (Figure 1a). These included plagiocephaly, protruding ears that were over folded, low set, and posteriorly rotated, and the appearance of hypertelorism with telecanthus, proptosis, and significant hypoplasia of the supraorbital ridges. She had a low nasal bridge, broad root, anteverted nares, and a bulbous tip. She had the appearance of midface hypoplasia and a short philtrum and thin upper lip. At 6 months, she exhibited delays in development. She had poor head control, was not able to roll and had only minimal vocalizations.

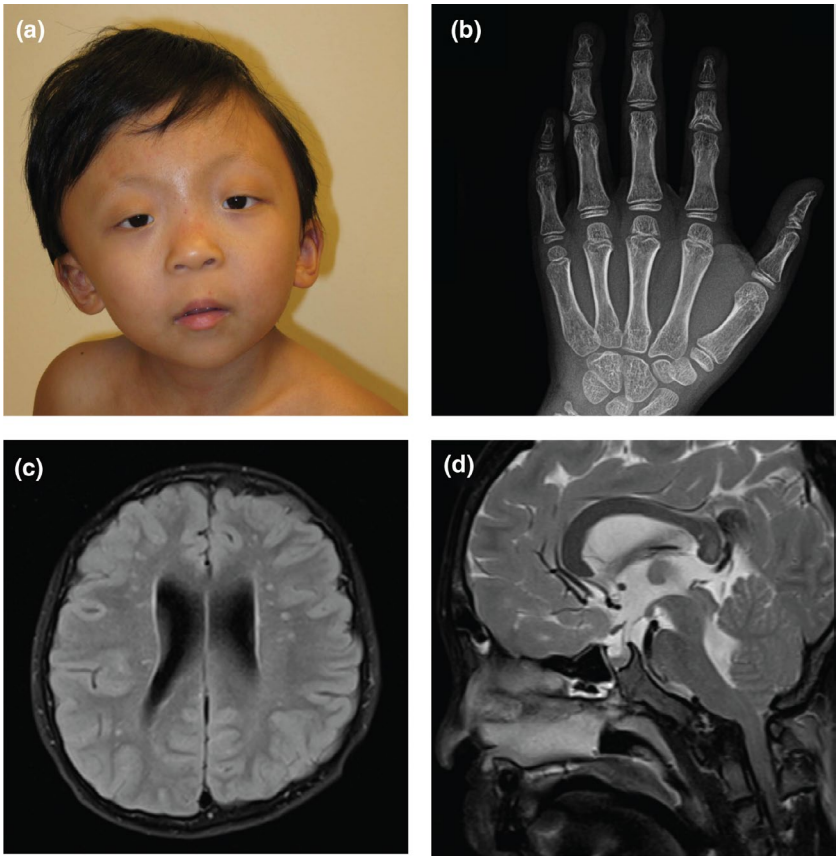

FIGURE 1 Facial features and clinical imaging of the proband. (a) Facial profile of the proband revealing distinct features. (b) Hand x-ray displaying delayed bone age. (c,d) Brain MRI revealing heterotopia, a dysmorphic corpus callosum and brainstem, and a small pituitary

Despite her normal length at 6 months, by 18 months old, she was below the 3rd percentile. She was last assessed in our clinic at 15 years of age where her weight was 33.5 kg (<1st percentile) and her height was 137.2 cm (<1st percentile). She exhibited mild fine and gross motor delay (she did not walk until 20 months) with significant language impairment. At nearly 3 years of age, she did not speak any words and was only able to babble. By 4 years of age, she had ~20 words and was unable to make any two-word sentences. At our last assessment at 15 years of age, she had a limited vocabulary of 50–100 words and was able to speak in simple sentences. A summary of our patients clinical features are provided in Table 1 and Table S1.

3 | RESULTS

After other investigations did not find a cause for her short stature and poor growth velocity, growth hormone stimulation testing was performed. Both arginine and clonidine stimulation tests revealed growth hormone deficiency with post-stimulation peak growth hormone levels below the expected range. Her peak GH level on the arginine stimulation test was 2.2 μg/L. Her clonidine stimulation test peak was 4.6 μg/L. A normal peak level after stimulation testing is >5.7 μg/L in our lab. Bone age at a chronological age of 12 years was 7 years and 10 months (Figure 1b). Other tests of pituitary function were normal aside from gonadotropins which were in the normal range for a prepubertal child as expected, but low for her chronologic age.

To further explore the etiology of her growth hormone deficiency an MRI brain was performed. This analysis revealed multiple focal subcortical and periventricular lesions, likely to represent grey matter heterotopia (Figure 1c). The corpus callosum and brainstem appeared dysmorphic. The pituitary gland had a concave upper margin and was small (Figure 1d). The posterior pituitary and pituitary stalk were normal. There was also a possible asymmetry of the intracranial vasculature, mucosal thickening of the paranasal sinuses, and a Chiari 1 malformation with pronounced stenosis of the foramen magnum.

Karyotype analysis revealed a paternally inherited derivative chromosome 13 (der(13)t(5;13)(q33;34)pat) resulting in the gain of chromosome region 5q33 to 5qter, and a loss of chromosome region 13q34 to 13qter. Microarray analysis (Agilent Oligo Array) was later performed to better define the breakpoints and confirmed the above copy number change. The terminal duplication of chromosome region 5q33.3 to 5qter involved 340 oligonucleotide probes from position 157,434,338 to 180,629,553. The estimated size of the duplication was 23.20 Mb, resulting in a gain of one copy of ~170 coding genes including OMIM genes *IL12B* (OMIM: 161561), *GABRA1* (OMIM: 137160), *HMMR* (OMIM: 600936), *WWC1* (OMIM: 610533), *FOXI1* (OMIM: 601093), *KCNMB1* (OMIM: 603951), *NPM1* (OMIM: 164040), *NKX2-5* (OMIM: 600584), *MSX2* (OMIM: 123101), *SNCB* (OMIM: 602569), *FGFR4* (OMIM: 134935), *NSD1* (OMIM: 606681), *SLC34A1* (OMIM: 182309), *F12* (OMIM: 610619), *B4GALT7* (OMIM: 604327), *PROP1* (OMIM: 601538), *NHP2* (OMIM: 606470), *GRM6* (OMIM: 604096), *ADAMTS2* (OMIM: 604539), *LTC4S* (OMIM: 246530), *SQSTM1* (OMIM: 601530), and *FLT4*

TABLE 1 Clinical features of our proband, the patient described by Shiihara et al., and patients with individual distal trisomy 5q or distal monosomy 13q

Clinical features	Proband	Shiihara et al. (2004)	Distal trisomy 5q Patient count: 12	Monosomy 13q distal to 13q33 Patient count: 14
Microcephaly	Present	Present	7/12	5/14
Congenital heart defect	Small PFO only	Present (ASD, PDA)	10/12	2/14
Growth restriction/short stature	Present	?	8/12	/ (long bones were short) // 3/14
Developmental delay	Present	Present	6/12	1/14
Intellectual disability	Present	Present	5/12	7/14
Delayed bone age	Present	?	NR	NR
Delayed puberty	Present	?	2/12	NR
Growth hormone deficiency	Present	?	?	?
Structural brain anomalies	Present	?	?[a]	6/14

References: Shiihara et al., 2004; Kumar et al., 1987; Curry et al., 1979; Zabel et al., 1978; Osztovics & Kiss, 1975; Passarge et al., 1982; Jones et al., 1979; Wang et al., 2017; Quelin et al., 2014; Ballarati et al., 2007; Chen Chih-Ping et al., 2010; Kirchhoff et al., 2009; Brown et al., 1993

Abbreviations: N/D, not detected; NR, not reported.

[a]No intracranial malformation on CT (Kumar et al., 1987); necropsy showed no abnormalities of the CNS (Zabel et al., 1978); the brain of the fetus showed no macroscopic or microscopic abnormalities (Passarge et al., 1982).

(OMIM: 136352). The terminal deletion of chromosome region 13q34 to 13qter involved 37 oligonucleotide probes from position 112,345,947 to 114,110,891. The estimated size of the deletion was 1.765 Mb, resulting in the loss of one copy of ~24 coding genes including OMIM genes *F7* (OMIM: 613878), *F10* (OMIM: 613872), and *GRK1* (OMIM: 180381).

4 | DISCUSSION

In this case report, we describe a patient with a terminal duplication of chromosome regions 5q33.3 to 5qter and a terminal deletion of chromosome regions 13q34 to 13qter. This is the second reported patient in the literature with a similar chromosomal abnormality. We report several aspects of our patient's phenotype that appear to be novel including growth hormone deficiency and brain anomalies including a small pituitary. A comparison of our patient's clinical features to the patient described by Shiihara et al. and previously described patients with distal trisomy 5q and monosomy 13q are summarized in Table 1 and Table S1.

A common feature of patients with terminal 5q duplications (and observed in our patient) is growth restriction. An obvious candidate gene which may explain this presentation is *NSD1*. *NSD1* is commonly known as the gene responsible for Sotos syndrome, where loss of function variants result in overgrowth with macrocephaly and advanced bone age (Chen et al., 2006; Novara et al., 2014). Patients with duplications in *NSD1* have been reported to have short stature, microcephaly and delayed bone age, suggesting that a gene dosage effect causes a reciprocal syndrome (Chen et al., 2006; Novara et al., 2014; Sachwitz et al., 2017). These patients also present with intellectual disability and distinct facial features, some of which overlap with our patient (smooth philtrum and thin upper lip; Dikow et al., 2013). Overexpression of *NSD* in *Drosophila* has been shown to result in increased apoptosis and downregulation of the mTOR pathway, suggesting a possible mechanism for the undergrowth phenotype seen in patients with duplications of *NSD1* (Quintero-Rivera et al., 2021). Interestingly, growth hormone deficiency and/or pituitary anomalies have not been reported in patients with *NSD1* duplication, suggesting that there are likely additional mechanisms responsible for our patient phenotype (Novara et al., 2014).

It is difficult to determine whether growth hormone deficiency is a common feature across all patients with terminal 5q duplications or is unique to our patient's specific genetic complement. Although growth restriction is a common characteristic of terminal 5q duplications, none of the previous descriptions report growth hormone levels (Curry et al., 1979; Jones et al., 1979; Kumar et al., 1987; Osztovics & Kiss, 1975; Zabel et al., 1978). An intriguing candidate for this is the gene *PROP1*, where loss of function variants cause growth hormone deficiency. However, there are several reported duplications in ClinVar that are reported as benign (Bertko et al., 2017; Cohen & Radovick, 2002; Correa et al., 2019; de Graaff, 1993; Maghnie et al., 2006). More detailed phenotyping of patient with distal trisomy 5q will be required to better understand the etiology of the short stature in these patients.

Our patient was found to have multiple brain anomalies for which the etiology is unclear. These anomalies were not reported in the case of the only other patient described with a similar rearrangement and have not been reported in patients with distal 5q trisomy (Shiihara et al., 2004). One limitation is that many of these patients did not have reported neuroimaging although in cases where brain imaging or necropsy was completed, there was an absence of macroscopic or microscopic abnormalities (Curry et al., 1979; Jones et al., 1979; Kumar et al., 1987; Osztovics & Kiss, 1975; Passarge et al., 1982; Zabel et al., 1978). Whereas brain anomalies including heterotopia and agenesis of the corpus callosum have been reported in patients with larger 13q terminal deletions, those with deletions of similar size to our patient have not been reported with these same anomalies (Ballarati et al., 2007; Brown et al., 1993, 1995; Chen Chih-Ping et al., 2010; Kirchhoff et al., 2009; Quelin et al., 2014; Wang et al., 2017). Altogether, a more detailed brain imaging is required in patients with both copy number variants to better understand the etiology of these malformations.

Of note is that three of the genes present in the chromosome 5 duplication (*GABRA1*, *GABRB2*, and *GABRG2*) are associated with epileptic encephalopathy. No seizures were observed in our patient and an EEG was never pursued. Other genes present in the duplication such as *FGFR4* and *MSX2* have been implicated as candidate genes for limb malformations; however, our patient did not exhibit any overt limb defects other than the fifth fingers appearing subjectively short at one clinical visit (Jamsheer et al., 2013).

In summary, we present the second case of very rare chromosomal translocation with novel clinical features. These features highlight a lack of detailed phenotypic characterization of previously reported patients with each individual copy number variation. Further investigations of patients with these more common variants will be informative and will provide useful information for the management of these patients.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

AUTHOR CONTRIBUTION

Alyssa C. M. Joynt, Ashish R. Deshwar, Jessica Zon, Lucie Dupuis, Diane K. Wherrett, and Roberto Mendoza-Londono were involved in acquisition of the data, analysis and interpretation of the data, and drafting or revising the article. Ashish R. Deshwar and Roberto Mendoza-Londono were involved in the study conception and design.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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