Unusual de novo Partial Trisomy 17p12p11.2 due to Unbalanced Insertion into 5p13.1 in a Severely Affected Boy

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Abstract

Keywords

- ▶ Charcot-Marie-Tooth disease type 1A
- ▶ Potocki-Lupski syndrome
- ▶ insertion
- ▶ molecular cytogenetics
- ▶ genotype-phenotype-correlation

Gain of copy numbers can be due to different chromosomal rearrangements such as direct or indirect duplications, translocations, small supernumerary marker chromosomes, or insertions. In a 3-year-old boy with dysmorphic features and developmental delay, chromosome analyses revealed a derivative chromosome 5. Microdissection and reverse fluorescence in situ hybridization identified the in 5p13.1 inserted part as 17p12-p11.2 material. Thus the patient suffered from a rare combination of genomic disorder, that is, Charcot-Marie-Tooth disease type 1A and Potocki-Lupski syndrome. Parental studies indicated that the abnormality was de novo in origin. As the question how this rearrangement arose cannot be answered conclusively, formal genetic counseling is warranted, which includes a discussion regarding the possibility of gonadal mosaicism. In conclusion, this case highlights that chromosome 17p is genetically relatively instable, and thus it can lead to rare chromosomal conditions.

Introduction

Several common contiguous gene syndromes arise from nonallelic homologous recombination (NAHR). This can cause a reduction or increase in copy numbers of genes within the affected region. It can also contribute to the copy number variation seen in some gene clusters.¹ Besides direct or indirect duplications, gain of copy numbers can also be caused by unbalanced rearrangements, such as insertions,² translocations,³ complex rearrangements,⁴ or small supernumerary marker chromosomes (sSMC).⁵

The proximal short arm of chromosome 17 is a genetically relatively unstable region, as it is particularly rich in region-specific low-copy repeats (LCRs) (also known as “segmental duplications”).⁶ Thus it is not surprising that four genomic disorders⁷ are located here in close proximity, including Charcot-Marie-Tooth disease type 1A (CMT1A [MIM 118220]),⁸ hereditary neuropathies with liabilities to pres-

sure palsies (HNPP [MIM 162500]),⁸ Smith-Magenis syndrome (SMS [MIM 182290]),⁶ and the Potocki-Lupski syndrome (PLS [MIM 610883]).⁹

These syndromes are caused predominately due to NAHRs favored by the human genome architecture in this region.¹⁰ The SMS common deletion includes the disease causing gene retinoic acid-induced gene 1 (*RAI1*); the corresponding region is flanked by large (200 kb), highly homologous LCR gene clusters termed “SMS-REPs.”^{9,11} The proximal and distal SMS-REPs likely act as substrates for NAHR, resulting in both, common deletions leading to SMS and reciprocal duplications associated with PTLs.^{6,9,12} The 17p12 locus, distal to the SMS/PTLS critical region, presents with two other LCR clusters (termed “CMT1A-REPs”). NAHR between the two CMT1A-REPs results in the common recurrent 1.4 Mb duplication, associated with CMT1A.¹³ The dosage-sensitive gene *PMP22* ([peripheral myelin protein 22] [MIM 601097]) is included in the CMT1A duplication and has

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been shown to be responsible for CMT1A as well as the genetically reciprocal disease HNPP.¹⁴

The architecture of this genomic region can also trigger nonrecurrent constitutional chromosomal rearrangements that cause chromosomal deletions and duplications,^{10,15} translocations,¹⁶ sSMCs,¹⁷ and somatic rearrangements; the latter are not associated directly with NAHR and are less frequent.¹⁸

Commonly, the recurrent PTLS and the CMT1A duplications are independent genomic rearrangement events, because they are mediated by different and nonhomologous LCR pairs. *RAI1* and *PMP22*, associated with PTLS and CMT1A respectively, are in close physical proximity in the human genome; the distance between them is approximately 2.5 Mb. As a result, duplications encompassing both genes have already been observed.^{18,19}

In this paper, we report the clinical and cytogenetic features of a boy with an unusual duplication of 17p12-p11.2 region, due to unbalanced insertion in 5p13.1. To the best of our knowledge, this is the first case report describing partial trisomy 17p due to insertion of another autosome.

Material and Methods

Patient

A male patient with delayed neurologic development presented at the age of 3 years (►Fig. 1A). He was the first child of healthy nonconsanguineous parents without any remark-

able family history. He was born at 38th week of pregnancy by cesarean section due to fetal distress. His birth weight was 3,000 g (3rd–15th percentile), length 50 cm (50th percentile), and head circumference 34 cm (15th–50th percentile).

Physical examination demonstrates at 3 years hypotonia, brachycephaly, developmental delay of locomotion and in acquiring skills, and tonic-clonic seizures. His weight is 12 kg (3rd–15th percentile), height 87.8 cm (10th percentile), and head circumference 47 cm (10th–25th percentile). Other dysmorphic features in this patient are malformed ears, narrow forehead with low hairline, flattened nasal bridge, anteverted nostrils, midface-hypoplasia, umbilical hernia, and widely placed nipples. Additionally the hands show brachydactyly, clinodactyly of fifth finger, and nail hypoplasia. Finally the genitals present with left cryptorchidism and hypospadias grade 1. The child also has cranial cortical atrophy of frontal region of the brain as detected by magnetic resonance imaging. No other external or internal clinical signs and symptoms were detected.

Cytogenetics

Samples for chromosomal analyses were collected in the National Center of Medical Genetic of Havana, Cuba, in accordance with the institutional review board for quality control. Peripheral blood samples of the patient's parents were acquired, and high-resolution metaphase chromosomes were prepared using standard cytogenetic methods and analyzed at the 550 band level.

Fig. 1 (A) The patient is 2 years and 10 months old. (B) Both chromosomes 5 of the patient after high-resolution GTG banding; the derivative chromosome 5 (der(5)) presents with two unusual additional bands in 5p (arrow). (C) Results of reverse FISH after microdissection of the short arm of the der(5) from ►Fig. 1B. The obtained der-5p-probe gave signals on chromosomes of a normal male in 5p and 17p. (D) Here the reverse FISH result for chromosome 17 is shown in a larger magnification.

Fluorescence in situ Hybridization

Fluorescence in situ hybridization (FISH) was done according to standard procedures. Besides a commercially available probe for the Smith-Magenis region in 17p12 with control probe (Abbott/Vysis), also homebrewed probes were applied. The latter were produced by glass needle-based microdissection as reported previously.²⁰ A previously established, whole chromosome painting probe for #5 (wcp5) was used, and for the present study, a DNA-probe was acquired from the short arm of the derivative chromosome 5 (der-5p-probe). Wcp5 was applied on the patient's chromosomes, whereas the der-5p-probe was used for reverse FISH and mapping of the position of the inserted material on normal male control metaphases.

Results

The patient's chromosomes were assessed first with high-resolution karyotyping, and a derivative chromosome 5 was found (► Fig. 1B). The high-resolution karyotypes from blood cells of both parents were normal. Subsequent FISH applying a probe for the Smith-Magenis region in both parents also was normal (results not shown).

FISH in the patient applying a wcp5 probe revealed an unstained gap in 5p (results not shown). Thus the patient's chromosome 5p on the der(5) was microdissected and reverse

FISH was done. As shown in ► Fig. 1C, reverse FISH revealed that the extra material on the der(5) was derived from 17p12 to 17p11.2. As the orientation of the inserted piece could not be determined by locus-specific probes due to its small size, the final karyotype is 46,XY,der(5)(5pter->5p13.1::17p12->17p11.2 or 17p11.2->17p12::5p13.1->5pter)

A comparison of clinical features of our and 17 previously published comparable cases¹⁸ is given in ► Table 1. The most consistently reported clinical features were feeding difficulties, global developmental delay, behavioral difficulties, and language delay.

Discussion

Here we describe a male patient with a severe syndrome characterized by multiple congenital malformations and developmental delay. The cytogenetic findings show a chromosome 17p12p11.2 duplication involving both the SMS- and CMT1A-critical region, resulting from insertion of this region in 5p13.1. The 5p13.1 region, where the 17p11.2-p12 segment is inserted, is a region deserted for protein-encoding genes.^{21,22} Thus, it can be speculated that most likely this region does not contribute to the observed phenotype. However, only sequencing of the breakpoint could answer whether there is some genetic material lost or a gene has been disrupted in the breakpoint region.

Table 1 Comparison of clinical features of 17 previously published individuals with *PMP22-RAI1* contiguous gene duplications¹⁶ with the present case

Clinical features		Subjects with <i>PMP22-RAI1</i> contiguous gene duplication given in %	The present case
Development	Developmental delay	100	+
	Age at walking	18 mo–11 y	No walking at 3 y
	Unusual gait/dropped foot	64.7	n.a.
	Behavioral difficulties	58.8	+
	Language delay	82.4	+
Nutrition	Feeding difficulties	70.6	+
	Failure to thrive	64.7	+
Neurologic features	Infantile hypotonia	88.2	+
	Clinical neuropathy	76.5	+
	Sleep disturbance	64.7	+
	Distal extremity weakness or atrophy	82.4	+
Other physical features	Facial dysmorphism	88.2	+
	Foot deformities	70.6	–
	Sensory loss	64.7	–
	Reduced or absent ankle deep tendon reflexes	64.7	–
Additional findings	Magnetic resonance imaging abnormality of the brain	58.8	+
	Syringomyelia	11.8	–
	Congenital heart defect	47.1	–
	Renal abnormality	23.5	–

Abbreviation: n.a., not applicable.

Infantile hypotonia, failure to thrive, and developmental delay are common features of PTLs,^{6,9,23,24} whereas the clinical manifestations of CMT1A do not present during infancy, yet develop gradually during the first two decades of life. Delayed walking is seen in the vast majority of persons with PTLs, while individuals with CMT1A typically reach early developmental features without difficulty. The present patient demonstrates 12/19 features listed in ▶Table 1 concordance with comparable cases from the literature.¹⁸ In 4 of 19 features from ▶Table 1, our patient was not in concordance with previously reported cases, partly because he was not walking yet and/or these features were also rare in the other similar cases. Thus, overall, clinically the present patient shows typical signs of SMS/PMP22 gene duplications.

Regarding how the rearrangement arose is only a possible speculation. An involvement of NAHR can be suggested but cannot be proven. Parental studies demonstrate that the rearrangement is de novo. Additionally nonpaternity and gonadal mosaicism cannot be excluded. The latter is still possible in this case—especially as similar cases with de novo unbalanced insertions are rarely seen but can be found in the literature.²⁵

Overall, the present report underlines the fact that chromosome 17p is genetically instable, due to regions prone to NAHR, and can also lead to rare chromosomal conditions, such as an insertion of #17-material into another autosome in the present case. Banding cytogenetics gave the important advice what was the underlying mechanism and reason for clinical problems in that specific case, that is, additional chromosomal material in 5p. In the end, a combination of banding cytogenetics, molecular cytogenetics, and microdissection, together with clinical genetic analyses, provided to the correct diagnoses for the family.

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