Two de novo Overlapping Interstitial Duplications at 10q22 Associated with Speech Impairments, Behaviour Problems, Genital Anomalies, Developmental Delay and Intellectual Disability

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Abstract

Copy number variants (CNVs) involving the 10q22 chromosomal region are rarely reported. At present, only eight patients with deletions at this locus have been reported. The reciprocal duplications are rarer and have never been described. Here, we report two unrelated patients with de novo overlapping duplications at 10q22 detected by high-resolution chromosomal microarray analysis (CMA). CMA revealed two duplications: arr 10q22.1q22.3(7231092-78170233) × 3 dn and arr 10q22.1q22.3(70742930-80565963) × 3 dn. Speech impairments, behavior problems, genital anomalies, dysmorphic features, developmental delay and intellectual disability were observed in both patients. The shared genomic region and the similar clinical features suggest a novel contiguous gene duplication syndrome at 10q22. Based on all pathogenic CNVs delineated and candidate genes identified in this interval, the critical region for the novel genomic duplication syndrome is located on 10q22.2.

Keywords: Speech impairments; Behavior problems; Genital anomalies; Developmental delay; Intellectual disability; Intersitial duplication; 10q22

Abbreviations: CNVs: Copy Number Variations; CMA: Chromosomal Microarray Analysis; LCRs: Low Copy Repeats; MRI: Magnetic Resonance Imaging; DGV: Database of Genomic Variants; cnvDev-Delay: Copy Number Variation Morbidity Map of Developmental Delay; GPS: Genitopatellar Syndrome; SBBYSS syndrome; Say-Barber-Biesecker-Young-Simpson syndrome

Introduction

Chromosomal region 10q11q23.3 contains several Low Copy Repeats (LCRs) and is prone to non-allele homologous recombination. LCR1 and LCR2 are located at 10q11.22q11.23, and LCR3 and LCR4 are centered on 10q22.3q23.3. Each pair mediates reciprocal deletions and duplications. The recurrent deletions and reciprocal duplications within LCR1-LCR2 exhibit variable clinical features, and developmental delay and/or intellectual disability are the only features common to the majority of individuals [1]. Recurrent deletions at 10q22.3q23.3 mediated by LCR3-4 are associated with intellectual disability, developmental delay, dysmorphic features, behavior problems and other neurodevelopmental disorders, whereas reciprocal duplications are contributed to distinctive facial features, cognitive impairments, congenital heart disease, and delays in language and motor development. Intersitial deletions or duplications at 10q22.3q23.3 are infrequently reported, and a distinct clinically recognizable syndrome has not emerged [2-10].

However, interstitial deletions or duplications at 10q22 are rarer since this interval does not involve LCRs. To date, only eight patients with de novo deletions at 10q22 have been reported, and the main clinical features include speech impairments, dysmorphic features, genital anomalies, intellectual disability and developmental delay [7,11-15]. Dufke and Han each described a case with a de novo duplication at 10q22.2q22.3–23.1 and 10q22q24 detected by G-banding analysis respectively, whereas the two segments not only covered the 10q22 region but also LCR3-4 which was demonstrated to be clinically significant [8,10,16,17]. Here, we report two unrelated patients with de novo overlapping duplications at the 10q22 interval that are 6.4 Mb and 9.8 Mb in size separately, detected by high-resolution CMA. Clinical manifestations are characterized by speech impairments, dysmorphic features, behavior problems, genital anomalies, developmental delay and intellectual disability.

Patient data

Patient 1

The boy was the first child of healthy unrelated parents and the family history was unremarkable. He had two healthy sisters. There were signs of spontaneous abortion at early stages of pregnancy, and his mother underwent progesterone treatment for one week. Intrauterine growth retardation was noticed by ultrasound examination at 8 months of pregnancy. He was born by cesarean section at 38 weeks of gestation. Birth weight was 2.63 kg (<-1 SD), and length was 47.8 cm (<-1 SD). Apgar scores were all 9. He had hypotonia. No feeding difficulty was noted at all times.

His psychomotor development was delayed: he raised his head at 5 months, sat alone at 8 months and independently walked at 1 year 8 months. Language development was significantly delayed and he began to talk at the age of 2 years. Cryptorchidism was noticed. The patient was 8-year-old at the time of molecular evaluation. Upon physical examination, his growth development was within the normal range: his height was 125 cm (-1 SD), weight 36 kg (>1 SD) and head circumference 50 cm, indicating catch up growth. He had mild intellectual disability, and his Intelligence Quotient was 71 using the Wechsler Intelligence Scale. His abnormal behavior included tongue stretching, anxiety...
and irritation. His distinctive facial features were characterized by flattened midface, broad forehead, low nose bridge, short philtrum, teeth dysplasia and downturned mouth (Figures 1a and 1b). Inguinal hernia was observed, and surgical repair was performed at 8 years of age. Brain Magnetic Resonance Imaging (MRI) and echocardiography were normal. No additional abnormalities were detected.

**Patient 2**

The female patient was the third child of healthy unrelated parents without any family history of congenital malformations or genetic disorders. Her siblings were all healthy. Developmental milestones were delayed: she raised her head at 6 months, sat alone at 10 months, walked without assistance at 1 year 9 months, and spoke her first words at 2 years 8 months. She had hypotonia and hypotonia persisted all the time. She had mild intellectual disability and did not finish primary school education.

The patient was 24-year-old at the time of molecular evaluation. At her last physical examination, her height was 160 cm, and her weight was 64.5 kg. She could merely speak and understand simple sentences. She had behavior problems including irritable, easily frustrated, solitary and aggressive behaviors. Her distinctive facial features included flattened midface, broad forehead, low nose bridge, teeth dysplasia, downturned mouth and immobile mask-like face (Figures 1c and 1d). She had genital anomalies and suffered from infertility after marriage. Shoulder asymmetry, limb contracture, large toes and clinodactyly of the fifth fingers were observed. No additional abnormalities were detected.

**Methods**

**Chromosomal microarray analysis**

Chromosomal microarray analysis was employed for our patients and both parents using the Affymetrix Cytoscan HD Array (Affymetrix, Santa Clara, CA, USA). Genomic DNA was extracted from peripheral blood using a commercial kit (Qiagen). The labeling and hybridization procedures were performed according to the manufacturer’s instructions. The raw data of the chromosomal microarray were analyzed by Affymetrix Chromosome Analysis Suite Software.

**Results**

High-resolution CMA demonstrated that the 10q22 duplication of patient 1 had a proximal border at genomic position chromosome 10:72331092, and the distal breakpoint was at chromosome 10:78710233. Thus, the duplication was 6.4 Mb. In patient 2, the proximal breakpoint was located at chromosome 10:70742930, and the distal breakpoint was at chromosome 10:80565963. The size of the duplication was 9.8 Mb. Parental CMA tests were all normal. Therefore, both patients carried an apparently de novo duplication. The involved segment in patient 1 was completely within the one in patient 2 (Figure 2).

**Discussion**

The long arm of chromosome 10q11q23.3 involves several LCRs. LCR1 and LCR2 are centered on 10q11.21q11.23, and LCR3 and LCR4 are located at 10q22.3q23.3, resulting in chromosomal rearrangements through non-allelic homologous recombination. Several recurrent
deletions and reciprocal duplications involving these LCRs have been reported. However, CNVs at 10q22 are rare given that no LCRs are located in this interval. Only eight patients with de novo deletions at 10q22 have been delineated [7,11-15], whereas the reciprocal duplications have never been described to date. In this study, we reported two unrelated patients with de novo overlapping duplications at 10q22 separately, who presented with similar clinical features including speech impairments, behavior problems, dysmorphic features, genital anomalies, developmental delay and intellectual disability. No other clinical significant CNVs were detected in our patients. No duplication at this interval was reported in the Database of Genomic Variants (DGV). The two duplications involved were relatively large sizes and occurred in gene-rich regions. Therefore, we concluded that these de novo duplications at 10q22 were pathogenic and most likely to be responsible for our patients’ clinical phenotypes.

Next, we searched databases for duplications overlapping with this region. One case nssv 3448244 was identified from Copy Number de novo duplications at 10q22 were pathogenic relatively large sizes and occurred in gene-rich regions. Therefore, we concluded that these de novo duplications at 10q22 were pathogenic and most likely to be responsible for our patients’ clinical phenotypes.

Table 1: Genomic and clinical information of patients with duplications or deletions at 10q22. The genomic coordinates are based on GRCH37/hg19.

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Phenotypes

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The KAT6B (OMIM 605880) gene maps in 10q22.2 region. KAT6B-related disorders include Genitopatellar syndrome (GPS) and the Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS syndrome). Features present exclusively in GPS are contractures, anomalies of the spine, ribs and pelvis, renal cysts, hydropnephrosis and corpus callosum agenesis. Major features for SBBYSS include immobile mask-like face, blepharophimosis/ptosis, long thumbs/great toes, lacrimal duct anomalies and lower extremity joint stiffness. Both disorders are characterized by developmental delay/intellectual disability, congenital heart defects, dental anomalies, hearing loss, hypotonia, genital anomalies in males (cryptorchidism) and ptellar hypoplasia \[18,19\]. Numerous studies have shown that KAT6B-related disorders are mainly caused by either nonsense or frameshift mutations in the KAT6B gene that lead to premature truncation of the protein \[20-24\]. It is noted that individuals with larger 10q22 deletions involving KAT6B gene do not appear to have classic facial feautres of SBBYSS, but present with some features overlapping those of SBBYSS \[7,11-14\]. Furthermore, Preiksaitiene et al. reported a female patient carrying a de novo deletion at 10q22.1q22.3, who presented with immobile mask-like face, blepharophimosis/ptosis, hypotonia, congenital heart defect, developmental delay and intellectual disability which were major features for SBBYSS. It was likely that haploinsufficiency of the KAT6B gene involved in this region was responsible for the main clinical phenotypes, which further broadened our knowledge regarding the clinical consequences of haploinsufficiency of the KAT6B gene \[15\]. In this study, we observed that the phenotypes of our patients partly overlapped with the ones of SBBYSS, including dental dysplasia, hypotonia, genital anomalies, long thumbs/great toes, clinodactylly, developmental delay and intellectual disability. Therefore, it was speculated that the KAT6B gene could be a triplosensitive gene responsible for dysmorphic features and neurodevelopmental anomalies in our patients.

Additionally, the ADK (102750) gene at 10q22.2 is an interesting candidate gene. The ADK gene encodes adenosine kinase, an abundant enzyme in mammalian tissues that catalyzes the transfer of the gamma-phosphate from ATP to adenosine, thereby serving as a potentially important regulator of concentrations of both extracellular adenosine and intracellular adenine nucleotides. Adenosine has widespread effects on the cardiovascular, nervous, respiratory and immune systems \[25\]. Transgenic animal models indicate that overexpression of ADK in brain is associated with adenosine deficiency, seizures, cognitive impairments and neurodevelopmental disorders \[26-29\]. Thus, it is also possible that ADK gene duplication may play a role in our patients’ clinical features. The CNVs at 10q22 region are non-recurrent and has been rarely reported. Currently, the physiological function of other genes at this interval remains largely unknown and there is no evidence to date supporting the direct involvement in human developmental disorders, which are yet to be discovered.

**Conclusion**

In conclusion, we reported two unrelated patients with de novo overlapping duplications at 10q22 detected by CMA who shared similar clinical features especially speech impairments, dysmorphic features, behavior problems and genital anomalies. We proposed that KAT6B and ADK are possible triplosensitive genes which are likely responsible for the shared clinical features. The reported 10q22 duplication cases may represent a novel contiguous gene duplication syndrome that will require further delineation.

**Acknowledgments**

We would like to express our gratitude to the patients and their families for their cooperation.

**References**


