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Case Report

Solitary median maxillary central incisor syndrome caused by 22q11.2 microdeletion

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Highlights

- 22q11.2 microdeletion is clinically associated with SMMCI.
- NAHR is engaged even in deletions where breakpoints are not within typical LCRs.

Abstract. Solitary median maxillary central incisor (SMMCI) syndrome, the mildest form of the holoprosencephaly spectrum, is a rare anomaly characterized by the presence of a single midline central incisor in both the deciduous and permanent dentitions. Affected individuals can present with additional midline defects beyond dental findings. The 22q11.2 deletion syndrome (22q11.2 DS) arises from heterozygous microdeletions on chromosome 22q11.2, with breakpoints frequently located in eight clusters of low-copy repeats (LCR22A-H). Herein, we report an atypical case of 22q11.2 microdeletion in a male patient with SMMCI and additional features including hypothyroidism, ventricular septal defect, and several facial anomalies. The telomeric breakpoint was located in a segmental duplication 0.5 Mb distal to LCR22D, whereas the centromeric breakpoint was within LCR22C. Both segmental duplications shared a high level of sequence identity (97.2%), indicating the possibility of non-allelic homologous recombination (NAHR). This report supports the critical role of NAHR in the formation of rearrangements between regions other than LCR blocks and establishes a clinical association between 22q11.2 microdeletion and SMMCI.

Key words: solitary median maxillary central incisor (SMMCI) syndrome, 22q11.2 microdeletion syndrome, non-allelic homologous recombination (NAHR), hypothyroidism, growth retardation

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Introduction

Solitary median maxillary central incisor (SMMCI) syndrome (OMIM#147250) is a rare anomaly affecting 1 in 50,000 live births and characterized by the presence of a single midline central incisor in both the deciduous and permanent dentitions (1). The phenotypic spectrum of SMMCI ranges from isolated dental findings to multiple midline defects that affect the craniofacial bones, brain, maxilla, nasal airways, and other midline structures of the body (1). Moreover, GH deficiency, short stature, microcephaly, and intellectual disabilities have been reported in some cases (1). Owing to its clinical manifestations, SMMCI is considered the mildest form of the holoprosencephaly (HPE) spectrum, often referred to as microform HPE (1, 2). In general, HPE is a severe developmental disorder arising from the incomplete cleavage of the embryonic forebrain during early development (2, 3). As more HPE patient cohorts have accumulated, the genetic etiology of the HPE spectrum has been shown to encompass not only nucleotide-based variants in genes associated with 17 brain developmental pathways but also copy number variations (CNVs) dispersed across the human genome (3). Among the CNVs underlying the HPE spectrum, those located in the 22q11.2 region have been observed most frequently, with a prevalence of up to 18% (3).

The 22q11.2 deletion syndrome (22q11.2 DS), which affects 1 in 2,148 live births, arises from heterozygous microdeletions on chromosome 22q11.2 (4, 5). The 22q11.2 locus contains more than 100 genes, and haploinsufficiency may result in heterogeneous clinical presentations, regardless of deletion size. Multi-organ dysfunction is common in most cases, manifesting as cardiac and palatal abnormalities; immune and autoimmune dysregulation; endocrine, genitourinary, and gastrointestinal problems; and brain involvement encompassing developmental delays, cognitive deficits, and neuropsychiatric illnesses (4). The variable combination of these clinical manifestations has been described as different syndromes, including DiGeorge syndrome (DGS), velocardiofacial syndrome, conotruncal anomaly face syndrome, autosomal dominant Opitz G/BBB syndrome, Sedlackova syndrome, and Cayler cardiofacial syndrome (4–6). Recent advances in molecular analysis have revealed that these syndromes share a common genetic etiology and represent the phenotypic spectrum of 22q11.2 microdeletions. This heterogeneity is influenced by the eight clusters of low-copy repeats (LCRs) on chromosome 22q11.2, referred to as LCR22A–H, which mediate meiotic non-allelic homologous recombination (NAHR) (4, 8). Notably, the most frequently reported deletion spans a region of approximately 3 Mb and encompasses LCR22A–D (A–D). This deletion historically presents as DGS or velocardiofacial syndrome, with an incidence of approximately 1 in 4,000 live births (4, 8). Furthermore, advancements in molecular technology such as array-based comparative genomic hybridization (aCGH) have enhanced precise breakpoint identification in 22q11.2 microdeletions, revealing atypical deletions with at least one breakpoint beyond the LCR (8).

The potential association between SMMCI and 22q11.2 microdeletions was first suggested in 1997 by Hall *et al.*, who reported a case of SMMCI with a chromosomal deletion within this region. This was followed by three additional cases in which deletions were identified using fluorescence in situ hybridization, as reported by Oberoi *et al.* and Yang *et al.* in 2005 (9–11). In some of these studies, it remained unclear whether SMMCI, the mildest form of the HPE spectrum, and 22q11.2 DS were coincidentally associated (9, 11). Recent advances in understanding the overlapping clinical manifestations in patients with 22q11.2 DS and the HPE spectrum have suggested that 22q11.2 microdeletions may be an underlying cause of SMMCI; however, the impact of these deletions on the clinical phenotype of patients with SMMCI remains unclear. Herein, we report the case of a patient clinically diagnosed with SMMCI with an atypical heterozygous 22q11.2 deletion spanning from LCR22C to the segmental duplication approximately 0.55 Mb distal to LCR22D.

Patient and Methods

The patient was born at 36 wk of gestation with a weight of 1,852 g (–2.25 SD) and a length of 44.0 cm (–1.08 SD) and was diagnosed with intrauterine growth retardation at 30 wk of gestation. He was the third child of a non-consanguineous, phenotypically normal 38-yr-old father and 33-yr-old mother. Their first child was healthy with no abnormalities, whereas their second child had micrognathia that required orthodontics. No notable events were reported during pregnancy. At birth, he presented with hypoglycemia (21 mg/dL) and mild respiratory distress, requiring admission to the neonatal intensive care unit. Cardiac ultrasonography revealed a ventricular septal defect (VSD) in the muscular septum and a small patent foramen ovale, which were asymptomatic and underwent spontaneous closure within 5 mo.

At 7 mo of age, the patient was referred to our clinic because of prenatal and postnatal growth retardation. He presented with short stature (59.1 cm, –4.2 SD), low weight (5,274 g, –3.7 SD), and several dysmorphologic features, including flat facial appearance, microcephaly, high forehead, long eyelashes, ptosis, blepharophimosis, closely spaced eyes, depressed nasal bridge, long philtrum, thick lower lip, and narrow mouth. He did not eat sufficient amounts of weaning food because of unbalanced food preferences. External genitalia were unremarkable. At his first visit, laboratory results showed an elevated TSH level as high as 5.110 μIU/mL but normal fT_4 (1.65 pg/mL) and fT_3 (4.61 ng/dL) levels. At 8 mo of age, the repeated evaluation showed a gradual elevation in TSH level (10.840 μIU/mL) and the patient was diagnosed with subclinical congenital hypothyroidism. Levothyroxine replacement therapy (25

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μg/d, 4.74 μg/kg/d) was subsequently initiated. Abundant secretion of GH was recorded during the arginine loading test at 10 mo of age (peak GH: 45.2 ng/mL), whereas the IGF-1 level was as low as 23 ng/mL (–1.47 SD). On follow-up after tooth eruption at 1 yr and 7 mo, we observed a single central incisor in the maxilla positioned centrally at the midline (**Fig. 1A**). Magnetic resonance imaging (MRI) confirmed the presence of a single midline central incisor; however, no abnormalities were found in the hypothalamus, pituitary gland, olfactory bulbs, ocular bulbs, or optic nerves (**Fig. 1B**). In addition, G-banding analysis revealed a 46,XY karyotype. At 9 yr and 7 mo of age, the onset of puberty was first noted, with an enlarged testicular volume exceeding 3 mL and elevated gonadotropin levels (LH 0.41 mIU/mL, FSH 1.60 mIU/mL, and testosterone < 3 ng/dL). During his follow-up, he required a gradual increase in the dose of levothyroxine to 50 μg/d (1.1 μg/kg/d). On his latest follow-up at 10 yr of age, the patient exhibited normal stature (137.3 cm, –1.0 SD) (**Fig. 1C**), normal thyroid function under levothyroxine replacement therapy, and appropriate pubertal development (LH 3.02 mIU/mL, FSH 1.95 mIU/mL, and testosterone 71 ng/dL). Serum calcium and phosphorus levels remained within age-matched reference intervals at all points evaluated. Frequent infectious episodes suggestive of immune deficiency were not observed. However, he displayed mildly restricted intellectual development and required special educational support in elementary school.

Molecular analysis was approved by the Institutional Review Board Committee of the Tohoku University School of Medicine and was performed after obtaining written informed consent from the parents. DNA samples were extracted from the peripheral leukocytes of the patient and his parents, and CNVs were examined in the genome using aCGH with a catalog human array (SurePrint G3; 8 × 180 K format, Agilent Technologies, Santa Clara, CA, USA) when the patient was one year old. Deletion size, genomic sequence characteristics around the breakpoints, and genes affected by CNVs were analyzed using the UCSC Genome Browser data (https://genome.ucsc.edu/; GRCh37/hg19) and DECIPHER v11.26 (https://www.deciphergenomics.org/) (12).

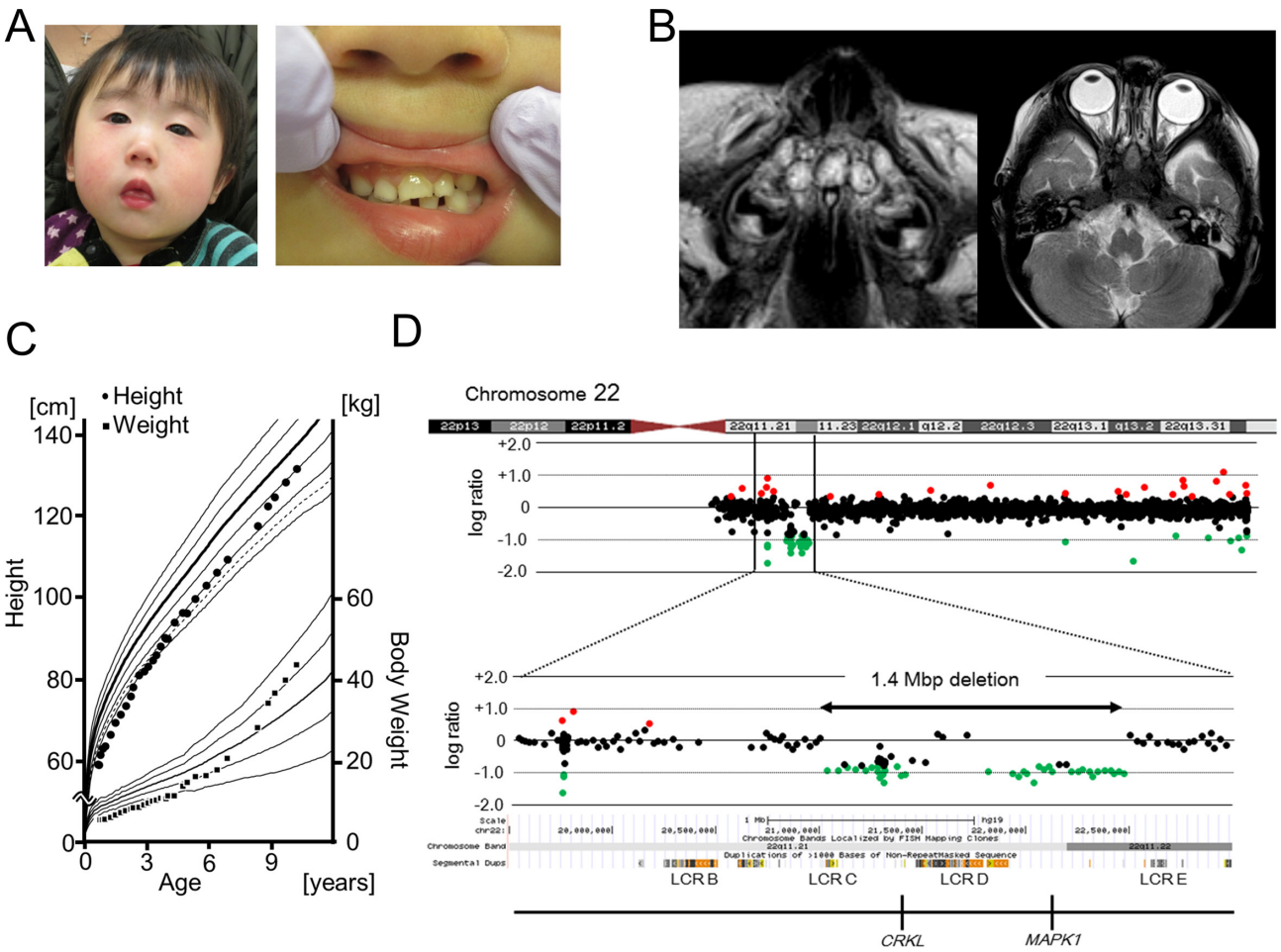

Fig. 1. A: Clinical photographs of the patient. B: Magnetic resonance imaging (MRI) findings of the patient. C: Growth chart of the patient. D: Results of comparative genomic hybridization analysis. The black, red, and green dots denote signals indicative of normal, increased, and decreased copy numbers, respectively. The black arrow indicates the deleted genomic region. A schematic diagram of low-copy repeats (LCRs) was made using the UCSC Genome Browser Build 37/hg19 (http://genome.ucsc.edu/).

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Results

Our analysis revealed a heterozygous deletion spanning approximately 1.4 Mb at 22q11.2 (arr[GRCh37]22q11.2(20992641x2, 21025654_22467751x1, 22495022x2)). The deleted region encompassed 24 known protein-coding genes, including *CRKL* and *MAPK1* (Supplementary Table 1). The aCGH analysis revealed that the proximal breakpoint was located in the region between the probes designed on chromosomes 22:20,992,641–20,992,700 and 22:21,025,654–21,025,713 (Supplementary Fig. 1A). Twelve paired segmental duplications in this region were registered in the UCSC Genome Browser (Supplementary Fig. 1A and Supplementary Table 2). In contrast, the distal breakpoint was located between the probes designed on chromosomes 22:22,467,692–22,467,751 and 22:22,494,963–22,495,022 (Supplementary Fig. 1B). Twelve paired segmental duplications were registered around the distal breakpoint. Among them, only one paired segmental duplication, located on chromosomes 22:21,021,885–21,025,627 and 22:22,469,043–22,472,748 (**Fig. 1D**), was located within both the proximal and distal breakpoint-flanking regions. Both segmental duplications shared a high level of similarity, exhibiting a sequence identity of 0.9720 (alignment bases 3,773 bp; matching bases 3,573 bp). Genetic testing of the parents confirmed that they did not carry the deletion.

Discussion

We identified a 22q11.2 submicroscopic deletion in a male patient with SMMCI who exhibited additional clinical features, including hypothyroidism, VSD, and several facial anomalies. Although four cases of SMMCI were previously reported to carry a 22q11 microdeletion using conventional techniques, precise mapping of breakpoints has not been performed, and no patients have been examined for brain malformations (9–11). Similar to the findings of our study, Rump *et al*. reported the case of a 31-yr-old female patient with a *de novo* deletion spanning 1.4 Mb from LCR22C to beyond LCR22D (8). She also had short stature, intrauterine growth retardation, microcephaly, a high forehead, droopy eyelids, and a thick lower lip similar to the present case; however, her dental symptoms were unknown (8). To the best of our knowledge, our study is the first to suggest that a deletion spanning 1.4 Mb from LCR22C to beyond LCR22D can be an underlying cause of SMMCI. The dysmorphic manifestations of the patient were consistent with the well-described phenotypes of 22q11.2 DS. In addition, the severe postnatal growth retardation could be explained by unbalanced dietary behavior, a frequently observed neurodevelopmental problem associated with 22q11.2 DS (4, 6, 7). In fact, the patient had a relatively low IGF-1 level despite the absence of GH deficiency. These observations suggested that his clinical manifestations could be ascribed to 22q11.2 DS.

Twenty-four genes were affected within the identified range of deletions (Supplementary Table 1). Because SMMCI is at the mild end of the HPE spectrum, heterozygous *CRKL* deletions are expected to be responsible for the presence of a single central incisor (2, 3, 13). Animal models have demonstrated that a decreased dosage of *Crkl* affects *Fgf8* cell signaling via Fgfr1/2, resulting in inappropriate organogenesis and increased neural crest cell apoptosis (13). The significance of this pathway in HPE has recently been reinforced by the identification of *FGF8* and *FGFR1* variants (3, 14). Moreover, a mouse model showed that inadequate epithelial *Fgf8* signaling results in the formation of fused supernumerary incisors (15). This result is consistent with those of human studies, as among 1,420 HPE probands, *FGF8* and *FGFR1* variants were detected in 2.5% and 2.0% of patients, respectively (3). In addition, abnormal FGF signaling is not only known to cause pituitary hypothyroidism, including combined pituitary hormone deficiency (16), but may also be associated with relatively mild primary hypothyroidism. Chemical suppression by blocking FGF receptors has been reported to affect thyroid development in zebrafish (17). Nevertheless, considering that genes associated with FGF signaling are not responsible for congenital hypothyroidism (18), their role in primary hypothyroidism is likely minimal, if present at all. In fact, the patient maintained normal thyroid function with a relatively lower dose of levothyroxine (1.1 µg/kg/d) than the replacement dose required for patients with congenital hypothyroidism and thyroid aplasia (2.5 ± 0.5 µg/kg/d at 10 yr) (19). Mild congenital cardiac malformations, a core symptom of 22q11.2 DS, have also been attributed to *LZTR1* and *MAPK1*. These genes, along with CRKL deficiencies, have been reported to be responsible for Noonan syndrome, which is characterized by cardiac anomalies (4, 7, 20). The normal calcium metabolism and immune episodes of the patient could be explained by the fact that the deleted region did not affect the *TBX1* gene, which is responsible for parathyroid and thymic hypoplasia (4, 6, 7). However, the marked postnatal growth retardation observed in the patient, with a lower height SD value in infancy (–4.2 SD) compared with the height SD value at birth (–1.08 SD), could not be directly explained by genetic defects. However, this growth retardation may have been influenced by a developmental disorder resulting in low and unbalanced dietary intake. Furthermore, *SNAP24*, *PI4KA*, and *MAPK1* have been reported to be associated with impaired intellectual development and behavioral problems (4, 6, 7). However, considering the young age of our patient, follow-up studies are necessary to evaluate the clinical consequences of this deletion.

The breakpoint on the telomere side was located approximately 0.55 Mb distal to the LCR22D blocks, whereas that on the centromere side was located within the LCR22C blocks (7). Notably, the breakpoint-flanking regions contained highly similar segmental duplications

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with a sequence identity rate of 97.2%. This strongly suggests that NAHR plays a vital role in the formation of rearrangements between regions other than the LCR blocks, further highlighting its potential contribution to the heterogeneous presentations of 22q11.2 DS (7, 21). Importantly, the aCGH analysis revealed that only one paired segmental duplication exhibited sequence homology in both the proximal and distal regions between the two probes denoting one or two copies. The breakpoint is reasonably likely to lie within this segmental duplication, suggesting that the aCGH analysis had sufficient power to detect the breakpoint precisely in this case. Our findings emphasize the utility of systemic screening for CNVs using aCGH in diagnosing heterogeneous endocrine disorders with anomalies. Prior to performing the aCGH analysis at one year of age, we were unable to narrow down the location of the expected CNVs. As a result, the diagnosis of 22q11.2 DS in our patient was made exclusively through the aCGH analysis. Although 22q11.2 DS is a major genetic cause of HPE, responsible CNVs can be detected globally in the human genome (3, 4). However, further studies are necessary to clarify the precise deletion and phenotypic spectrum of 22q.11.2 microdeletion syndrome.

Conclusion

This study broadens the clinical spectrum of 22q11.2 DS by establishing its association with SMMCI. Systemic screening for CNVs using aCGH and detailed evaluation of minor orthodontic changes may help identify 22q11.2 microdeletions in patients with growth retardation.

Conflict of interests: The authors have nothing to declare.

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