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A De Novo Microtriplication at 4q21.21-q21.22 in a Patient with a Vascular Malignant Hemangioma, Elongated Sigmoid Colon, Developmental Delay, and Absence of Speech

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The widespread application of array comparative genomic hybridization (aCGH) has provided new insights into the clinical significance of copy number variations (CNVs) in the human genome. Many microdeletion syndromes have recently been linked to corresponding reciprocal microduplication syndromes related to CNVs in the same chromosomal regions. However, the extent of CNVs may not be restricted to only microduplications but may also include microtriplications or even quadruplications. 4q21 microdeletion syndrome is one of these recently described syndromes. The phenotype includes growth restriction, neonatal hypotonia, severe developmental delay, absent or delayed speech, and distinct facial features. The minimal critical deleted region, which is 1.3 Mb in size, contains the *PRKG2*, *RASGEF1B*, *HNRNPD*, *HNRPDL*, and *ENOPH1* genes. Here, we report a 5.4-year-old girl with developmental delay, absence of speech, muscular hypertension, macrocephaly, a broad forehead, frontal bossing, relatively elongated extremities, a vascular malignant hemangioma in anamnesis, and elongated sigmoid colon. aCGH revealed a microtriplication at 4q21.21-q21.22 that was 1.61 Mb in size. This de novo microtriplication included nine genes (*BMP3*, *PRKG2*, *RASGEF1B*, *HNRNPD*, *HNRPDL*, *ENOPH1*, *TMEM150C*, *LINC00575*, and *SCD5*) and overlapped with the minimal critical region for 4q21 microdeletion syndrome. Some clinical features of the patient were similar to those of 4q21 microdeletion (macrocephaly, frontal bossing, developmental delay, absence of speech, and anxiety), whereas others were mirrored (elongated extremities and muscular hypertension). The first identified case of a de novo microtriplication at 4q21.21-q21.22 emphasizes the clinical significance of CNVs at 4q21 for patients with developmental delay and absence of speech.

Key words: 4q21 microtriplication; absence of speech; array comparative genomic hybridization; developmental delay; elongated sigmoid colon; mirrored phenotypes; vascular malignant hemangioma

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INTRODUCTION

The widespread application of array comparative genomic hybridization (aCGH) for genetic testing of patients with intellectual disability and developmental delay provides a powerful tool for identification of novel chromosomal regions associated with cognitive impairment and distinct clinical phenotypes [Vissers et al., 2016]. aCGH enables detection of both losses and gains throughout the genome, and its potential significantly surpasses those of targeted molecular cytogenetic

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technologies, such as fluorescence in situ hybridization (FISH) analysis. Therefore, it is not surprising that many previously known microdeletion syndromes have recently been linked to microduplication syndromes due to reciprocal copy number changes in the same chromosomal regions [Nevado et al., 2014]. However, the extent of CNVs may not only be restricted to chromosomal microduplications but may also include microtriplications [Yuan et al., 2015; Nimmo et al., 2016, Watanabe et al., 2016] or even quadruplications [Beck et al., 2015; Gu et al., 2016]. Moreover, recent data indicate that in addition to recombination-based processes, replication-based processes are also involved in the formation of structural variants at a given chromosomal locus [Carvalho and Lupski, 2016].

4q21 microdeletion syndrome (MIM 613509) is a recently described syndrome characterized by marked growth restriction, small hands and feet, severe developmental delay with absent or delayed speech, neonatal hypotonia, and distinct facial features. Twenty-one patients with this syndrome have been characterized using aCGH or FISH to date [Harada et al., 2002; Friedman et al., 2006; Dobyns et al., 2008; Bonnet et al., 2010; Dukes-Rimsky et al., 2011; Lipska et al., 2011; Bhoj et al., 2013; Bartnik et al., 2014; Komlósi et al., 2015; Yano et al., 2015]. The sizes of the deletions in these patients range from 2 to 20 Mb, with a 1.37 Mb minimal critical region containing five genes (*PRKG2*, *RASGEF1B*, *HNRNPD*, *HNRPDL*, and *ENOPH1*).

Here, for the first time, we report a 5.4-year-old girl with macrocephaly, distinct facial features, elongated extremities, developmental delay, and absence of speech who has a de novo 4q21.21-q21.22 microtriplication of 1.61 Mb in size detected by aCGH. The microtriplication contains nine genes and completely involves the minimal critical region for 4q21 microdeletion syndrome.

CLINICAL REPORT

The patient (Fig. 1) is a 5.4-year-old Russian girl born by caesarian section at the 37th week of gestation from a mother whose pregnancy was complicated by eclampsia. Intrauterine growth retardation was registered at the 32nd week of gestation. The patient is the second child of non-consanguineous healthy parents. The pedigree was unremarkable. The first son is healthy. Informed consent was obtained from the parents.

The patient's birth weight was 2970 g (10–25th centile), her birth length was 54 cm (97th centile), her head circumference was 36 cm (90–97th centile), and her chest circumference was 34 cm (50th centile). Her Apgar scores were eight and nine after 1 and 5 min, respectively. At birth, a 0.4–0.6 cm purple vascular hemangioma with black in the center was observed on the right shoulder, and it rose above the surface of the skin. At the age of 1 month, it increased in size up to 1.5 cm. A vascular malignant hemangioma was diagnosed as a result of biopsy, and it was then surgically removed with resection of the surrounding muscles. Elongated sigmoid colon was diagnosed at the age of 1 month. Muscular hypertension was pronounced at the age of 3 months. Calcaneovalgus foot was diagnosed at the age of 4 months. No heart defects were diagnosed by ultrasound examination during the first year of life. The girl was able to sit at the age of 5–6 months and stand independently at the age of 9–10 months. Her mental development slowed after the first

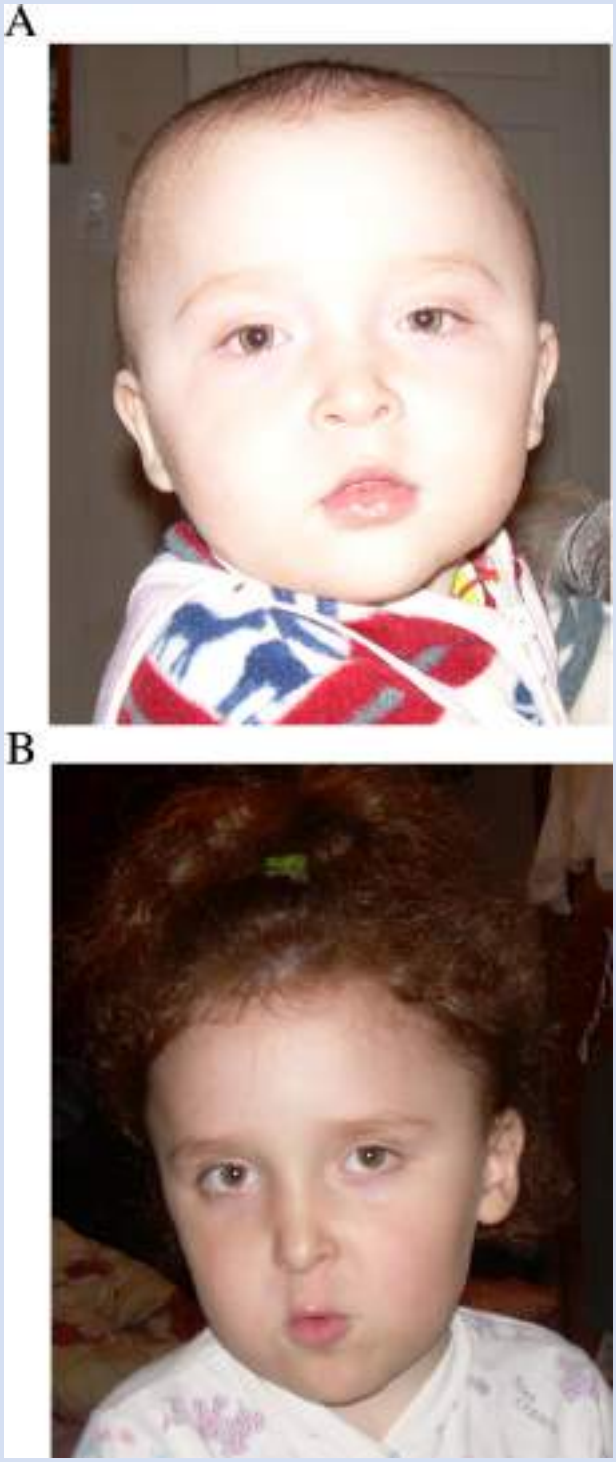

FIG. 1. The patient at the ages of 2 years (A) and 4.4 years (B), with distinct facial features (macrocephaly, broad forehead, frontal bossing, widely spaced eyes, a narrow mouth, thin upper vermilion, and thick lower vermilion). [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga].

year of life. She was unable to walk independently until 1 year and 10 months of age. The girl did not speak and was unable to pronounce even syllables. Cerebral magnetic resonance tomography (MRT) was unremarkable. The results of audiological examination were normal.

At the age of 4.4 years, her weight was 20 kg (75–90th centile), her height was 110 cm (75–90th centile), and her head circumference was 53 cm (97th centile). The patient had a broad forehead, frontal bossing, copper-colored hair, widely spaced eyes, attached earlobes, underdeveloped alae nasi, low hanging columella, a long philtrum, a narrow mouth, thin upper vermilion, thick lower vermilion, and a short neck.

At the age of 5.4 years, her height was 113 cm (50–75th centile), and her head circumference was 54.2 cm (>97th centile). The head circumference-to-height ratio of the patient was 0.48 (75–90th centile). The patient's increased head circumference and frontal bossing may be due to hyperplasia of osteoid tissue. Elongated upper and lower extremities in relation to the patient's body size were noted. Significantly, the arm-span of the patient was 127.5 cm, which is 14.5 cm longer than her height. The patient's upper arm length was 23 cm, which is in agreement with the mean value for the 5.0 to 5.9-year-age group (22 ± 1.4 cm) and falls within the 50th centile. The patient's shoulder width (22.6 cm) and upper arm length (23 cm), as wells the length of her hand (12 cm), corresponded to normal values. Therefore, her increased arm-span may be due to her elongated forearm (19.5 cm). The girl's sitting height was 58 cm, which is between the −2 and −1SD values for 5- to 6-year-old girls. The length of her legs was 63 cm, which is a slightly above the 1SD value. The patient's sitting height/height ratio was 0.513, which is between the −2 and −1SD. The index of Manouvrier was 91.4 %, and the index of Pierce was 95%.

Radiographs of the wrist and hand revealed foci of ossification in the capitate, hamate, triangular, lunate, trapezoid, trapezium, and scaphoid bones. Epiphyses of the radial and metacarpal bones, and phalanges developed with a slight increase in age. Mild pronounced deformation and restructuring of the cellular character of the V metacarpal bones was observed. Monostotic fibrous dysplasia was suggested.

This patient developed frequent infections of the upper respiratory airway up to 4 years of life and suffered from pneumonia two times. Atopic dermatitis on the back was evident. Biochemical blood testing conducted at the age of 4.4 years revealed decreased serine (35 μM/L), glycine (65 μM/L), histidine (15 μM/L), lysine (50 μM/L), and methionine levels (10 μM/L) compared with the standard levels for patients of her age. The aspartic acid, glutamic acid, arginine, proline, tyrosine, valine, cysteine, β-alanine, taurine, leucine, and isoleucine levels were within the normal ranges. At the age of 5.4 years, decreased levels of serine (40 μM/L), glycine (105 μM/L), and methionine (13 μM/L) were still observed, whereas all other previously measured biochemical markers were within the normal range.

At the age of 4.4 years, the girl still did not speak. She was able to pronounce only several simple words, such as "mama" and "give." However, she was able to say a whole sentence while sleeping (for example, "do you really remember?"). She demonstrated good receptive language. She began to show improvement in activities related to fine motor skills (modeling and drawing). She demonstrated remarkable anxiety, especially while walking or coming into contact with hot items. At the age of 5.4 years, the patient's vocabulary consisted of only approximately 20 words.

MATERIALS AND METHODS

Cytogenetic Studies

Conventional cytogenetic analysis was performed with GTG-banded metaphases of peripheral blood lymphocytes from the patient, her brother, and her parents at a 400-band resolution.

aCGH Studies

aCGH was performed using a Human Genome G3 SurePrint 8×60 K Microarray (Agilent Technologies) according to the manufacturer's recommendations. Labeling and hybridization of the patient's DNA, her parents' DNA, and reference DNA (#5190-3796, Human Reference DNA, Agilent Technologies) were performed based on the supplied protocols for Enzymatic Labeling and Hybridization (v. 7.3 Agilent Technologies). Array images were acquired using an Agilent SureScan Microarray Scanner (Agilent Technologies). Data analysis was performed using Cytogenomics Software (v. 3.0) (Agilent Technologies), and the publicly available Database of Genomic Variants (DGV) and Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER). The annotations of genes located within the region of genomic imbalance were retrieved from databases such as NCBI Gene Database and OMIM, in addition to the literature.

Real-Time PCR Studies

Specific target sequences for the *PRKG2*, *RASGEF1B*, *HNRNPD*, and *SCD5* (exons 1 and 5) genes were selected for real-time quantitative PCR assay using Primer 3 software. The presence of a microtriplication was checked in genomic DNA isolated from peripheral blood lymphocytes from the patient, her brother, and her parents using an AriaMX thermocycler (Agilent Technologies).

SNP Analyses

Twelve SNPs (rs2071559, rs6841086, rs11133482, rs4073, rs56061981, rs4256246, rs4386624, rs958617, rs11728697, rs10005603, rs3733619, rs1996546) located at 4q12-q35.1 were selected to exclude uniparental inheritance in the patient, to allow discrimination between microtriplications and duplications on a single homologue in the case of uniparental disomy (UPD) of chromosome 4. SNP analyses were performed via real-time PCR with TaqMan probes, through high-resolution melting analysis or using the restriction fragment length polymorphism (RFLP) technique.

RESULTS

Metaphase analysis of G-banded chromosomes from peripheral blood lymphocytes showed normal karyotypes for the patient, her healthy brother, and her parents. Microarray analysis

revealed a 1.61 Mb 4q21.21-q21.22 microtriplication: arr[hg18] 4q21.21q21.22(82,189,943–83,801,062) × 4 (Fig. 2A and B). This microtriplication involved nine genes (*BMP3*, *PRKG2*, *RASGEF1B*, *HNRNPD*, *HNRPDL*, *ENOPH1*, *TMEM150C*, *LINC00575*, and *SCD5*), five of which (*PRKG2*, *RASGEF1B*, *HNRNPD*, *HNRPDL*, and *ENOPH1*) are considered part of the 1.37 Mb minimal critical region for 4q12 microdeletion contiguous gene syndrome (MIM 613509). Two borderline genes, *BMP3* and *SCD5*, were interrupted, in introns 2 and 3, respectively. The microtriplication and its borders were confirmed by quantitative real-time PCR to examine four genes within or outside (*SCD5*, exon 1) of the triplicated region (Fig. 2C). The results of the aCGH analysis of both parental DNA samples were normal. Thus, the observed microtriplication had a de novo origin, which was confirmed via real-time PCR. SNP analysis revealed biparental inheritance of chromosome 4, excluding the possibility of duplication due to UPD(4) (data not shown).

The detected microtriplication has not been previously reported in publicly available databases (DGV and DECIPHER) or in the literature. Three patients with duplications involving 4q21 are included in DECIPHER (patients IDs 248919, 283964, and 256563), all of whom exhibited significantly larger duplications involving genes both within and outside of the minimal critical regions for 4q21 microdeletion syndrome. One patient with myoclonic astatic epilepsy and a de novo 4q21.22q21.23 microduplication was recently reported [Ottaviani et al., 2015]. The 778 kb microduplication affected 11 genes and was close to but did not overlap with the microtriplication in our patient. Six other cases of 4q21 duplications involving chromosomal regions from 4q13.1 to 4qter detected through conventional cytogenetics have been reviewed by Schinzel [2001]. However, comparison of the phenotypes of patients with these chromosomal abnormalities with that of our patient is unreasonable due to large differences in the sizes of the affected regions and the extent of the copy number gains.

DISCUSSION

The growing list of chromosomal syndromes has revealed the association of several already known microdeletion syndromes with novel reciprocal microduplication syndromes involving copy number changes in the same chromosomal regions [Nevado et al., 2014]. These so-called "genomic sister disorders" provide new insights into the clinical consequences of CNVs in the human genome. According to Golzio and Katsanis [2013], different genotype-phenotype correlations are possible for reciprocal microdeletions and microduplications that result in mirrored, similar, overlapping, identical, or unique phenotypes. However, the extent of CNVs may be much higher and may include not only chromosomal microduplications but also microtriplications and even quadruplications. Therefore, it is important to trace the dose-dependent phenotypic changes in patients with a higher degree of chromosomal segment amplifications.

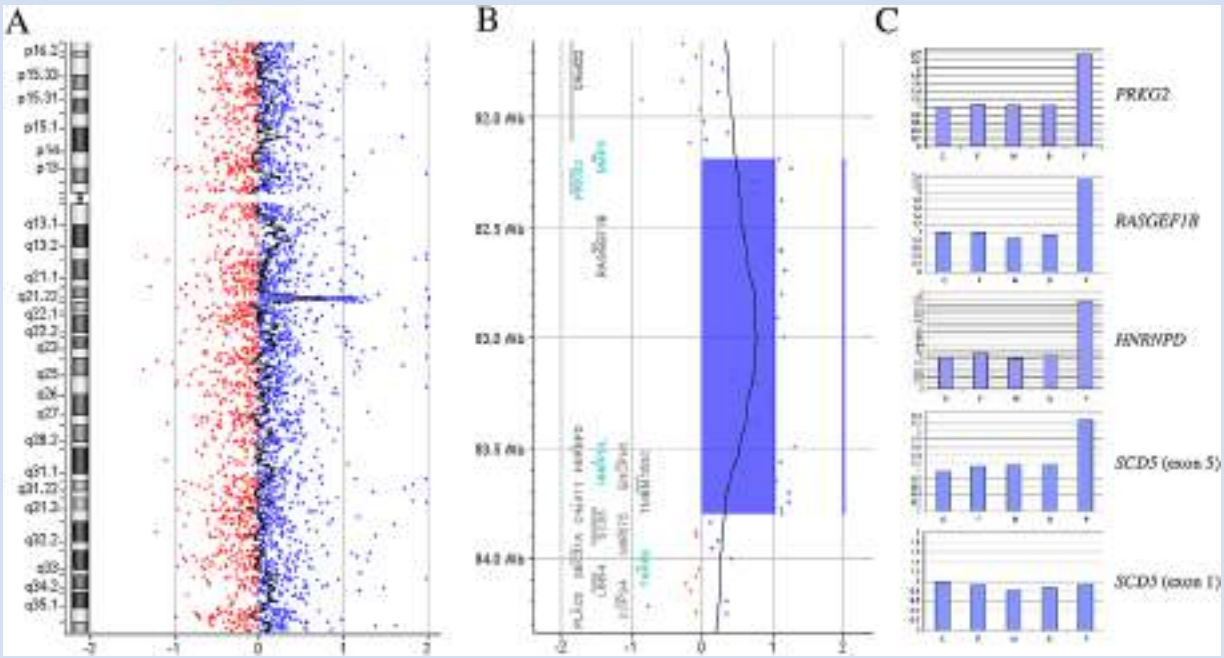

FIG. 2. aCGH image of chromosome 4 (A); aCGH image of the triplicated 4q21.21-q21.22 region, including the involved genes (B); the results of quantitative real-time PCR analysis. C, control; F, father; M, mother; B, brother; P, proband (C). [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga].

Some of the clinical features observed in our patient, such as macrocephaly, a broad forehead, frontal bossing, developmental delay, absence of speech, and anxiety, were similar to those of patients with 4q21 microdeletions, whereas others, such as muscular hypertension and elongated upper and lower extremities were mirrored. Additionally, unique overgrowth phenotypes, such as vascular malignant hemangioma and elongated sigmoid colon, were noted.

The mirrored and similar phenotypes are of particular interest for analysis of the clinical effects of differentially directed changes in gene copy numbers. However, the absence of reported cases of 4q21 microduplication with involvement of only the minimal critical region for 4q21 microdeletion syndrome in the literature complicates this analysis due to the impossibility of distinguishing the phenotypic effects of duplications and triplications. Only three patients with 4q21 microduplications are included in DECIPHER. One of these patients (ID 248919), who exhibited intellectual disability, finger joint hypermobility, knock-knee, obesity, and enuresis, harbored a de novo microduplication at 4q21 with a size of 5.65 Mb and a de novo microduplication at 16q22 (1.07 Mb in size). All of the genes in the triplicated region of our patient were also present in the duplicated area of this DECIPHER patient (ID 248919). Another patient (ID 283964) with a global developmental delay carried a de novo 4q21 microduplication with a size of 2.89 Mb and a 286.4 kb 16q22 microduplication inherited from the father. All of the triplicated genes observed in our patient except for *BMP3* were involved in the 4q21 microduplication of this patient (ID 283964). The third patient (ID 256563), who showed profound intellectual disability, an absence of speech, moderate postnatal growth retardation and coloboma, harbored a large 4q21 duplication (36.41 Mb) arising from a balanced parental rearrangement.

A 15-year-old patient with myoclonic astatic epilepsy and a de novo 4q21.22q21.23 microduplication was recently reported [Ottaviani et al., 2015]. This 778 kb microduplication entirely encompasses the following genes: *LIN54*, *COPS4*, *PLAC8*, *COQ2*, *HPSE*, *HELQ*, *MRPS18C*, *FAM175A*, and *AGPAT9*, whereas *THAP9* and *BC005018* are only partially interrupted. This microduplication is close to but does not overlap with the microtriplication observed in our patient or with the minimal critical region for 4q21 microdeletion syndrome.

Two bone-related genes, bone morphogenetic protein 3 (*BMP3*, OMIM 112263), and cGMP-dependent protein kinase type II (*PRKG2*, OMIM 601591), are considered candidates for severe growth retardation, delayed bone age, and small hands and feet in patients with 4q21 microdeletions. BMP3 is one of the bone morphogenetic proteins (BMPs), which are the multifunctional growth factors originally identified for their contributions to cartilage and bone formation [Lipska et al., 2011]. BMP signaling is also involved in shaping the limb interdigital mesenchyme. Consequently, mutations in BMP signaling genes are involved in various types of brachydactyly, and a missense mutation in *BMP3* (F452L) is fixed among extreme brachycephalic canine breeds [Schoenebeck et al., 2012]. The most recent finding is highly remarkable because another candidate gene for intellectual disability and autism (*CNTN6*) [Kashevarova et al., 2014; Hu et al., 2015] that is known to be responsible for face shape modifications in humans was recently associated with brachycephalic face in Persian cat breeds [Bertolini et al., 2016].

BMP signaling pathways are involved in the formation of the bony structures of the ear and membranous labyrinth, and *BMP3* is, therefore, considered a deafness candidate gene. *BMP3* inactivation is also reported in various types of cancer, including biliary, gastric, and colorectal cancers [Loh et al., 2008; Kisiel et al., 2013; Liu et al., 2014], highlighting its tumor suppressor function. Notably, in our patient with vascular malignant hemangioma and elongated sigmoid colon, the *BMP3* gene was interrupted by the microtriplication.

PRKG2 encodes cGMP-dependent protein kinase type II (cGKII), which is expressed abundantly in the intestinal mucosa, kidney, lung, brain, and cartilage. *cGKII*$^{-/-}$ mice develop postnatal dwarfism caused by a severe defect in endochondral ossification at the growth plates and impaired chondrocyte hypertrophy [Bonnet et al., 2010]. The Komeda miniature rat Ishikawa, which is a naturally occurring mutant caused by an autosomal recessive mutation *mri*, exhibits longitudinal growth retardation and expanded growth plates. Chikuda et al. [2004] identified the *mri* mutation as a deletion in cGKII.

The mechanism underlying cGKII-mediated chondrocyte hypertrophy was revealed in studies by Kugimiya et al. [2005] and Kawasaki et al. [2008]. It was shown that cGKII phosphorylates glycogen synthase kinase-3b (GSK-3b). Phosphorylation inactivates GSK-3b, which is a negative regulator of b-catenin through its phosphorylation and degradation. When GSK-3b is phosphorylated and inactivated, b-catenin levels increase, and b-catenin can enter the nucleus to enhance chondrocyte hypertrophy. cGKII also phosphorylates Sox9, an inhibitor of chondrocyte hypertrophy, and suppresses its nuclear entry, leading to the enhancement of chondrocyte hypertrophy. Chondrocyte hypertrophy of the growth plates is a rate-limiting step in longitudinal skeletal growth. In cGKII$^{-/-}$ mice, chondrocyte hypertrophy and growth plate elongation are impaired, resulting in postnatal dwarfism. These experimental data provide support for the hypothesis that haploinsufficiency of *PRKG2* could explain the severe growth delay observed in the patients with 4q21 microdeletions [Bonnet et al., 2010]. In our patient with fibrous dysplasia, frontal bossing and elongated extremities, the *PRKG2* gene was triplicated according to aCGH analysis.

The cGKII transcript has also been shown to be abundant in the brain. cGKII can phosphorylate an integral membrane protein belonging to the glutamate-gated ion channel family (GluR1), leading to an increased surface GluR1 level and to the surface expression of ionotropic transmembrane α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors for glutamate at extrasynaptic sites. This mechanism plays important roles in synaptic plasticity and long-term potentiation in hippocampal neurons, a critical step in learning and memory [Bonnet et al., 2010]. Therefore, changes in the *PRKG2* dose could also play a role in the cognitive impairments reported in patients with 4q21 microdeletion and in our patient with 4q21 microtriplication. Finally, *PRKG2* activation is observed in some cancers, including gastric cancer and myeloproliferative disorders [Gallagher et al., 2008; Wang et al., 2014].

Another gene from the minimal critical region is a highly conserved guanine nucleotide exchange factor for Ras superfamily proteins (*RASGEF1B*, OMIM 614532) that functions as a molecular switch in signal transduction, cytoskeleton dynamics, and intracellular trafficking. RASGEF1B is expressed at a high level in the central nervous system and is therefore a good candidate for cognitive impairment [Bonnet et al., 2010]. Two other genes are heterogeneous nuclear ribonucleoproteins, *HNRNPD* (OMIM 601324) and *HNRPDL* (OMIM 607137), whose products are known to be involved in the regulation of mRNA decay [Bhoj et al., 2013]. *Hnrnpd*-null mice exhibit a dysregulated immune response to endotoxins, which causes chronic pruritic inflammatory skin dermatitis. Atopic dermatitis was evident in our patient. Heterogeneous nuclear ribonucleoprotein D-like protein (HNRPDL) may play roles in the stress and inflammatory responses, and it has been shown to be an important regulatory modulator of NK-kB-repressing factor and to bind to an upstream element in TNF-a. There are currently no animal or human phenotypes associated with this gene, and its complete function remains to be elucidated. At the same time, the frequent respiratory infections in our patient and in some patients with 4q21 microdeletions allow for consideration of *HNRPDL* as a candidate for the immune system deficiency. The last gene from the critical region is enolase-phosphatase I (*ENOPH1*, Gene ID: 58478), which is a bifunctional enolase/dephosphorylase enzyme in the methionine salvage pathway. Notably, our patient had a decreased methionine level. Recent studies of mice have shown that the *Enoph1* gene is differentially expressed in paternal strains, which have different spermidine levels and show distinct anxiety- and depression-related phenotypes [Barth et al., 2014]. Anxiety is a remarkable feature of patients with 4q21 microdeletion, and it was noted in our patient.

The functions of two other genes, encoding transmembrane protein 150C (*TMEM150C*, Gene ID: 441027) and long intergenic non-protein coding RNA 575 (*LINC00575*, Gene ID: 439934), which are located outside of the minimal critical region, remain unclear. The last gene disrupted by the microtriplication is stearoyl-CoA desaturase 5 (*SCD5*, OMIM 608370). The product of this gene is an integral membrane protein of the endoplasmic reticulum that catalyzes the formation of monounsaturated fatty acids from saturated fatty acids. SCD may be a key regulator of energy metabolism, with roles in obesity and dyslipidemia. However, obesity has been documented in only one patient with a 4q21 microdeletion [Bartnik et al., 2014] and in a DECIPHER patient (ID 248919) with 4q21 and 16q22 microduplications. No signs of obesity were noted in our proband.

To the best of our knowledge, there are no universal molecular mechanisms leading to microtriplication. Both recombination- and replication-based processes are considered candidate mechanisms [Carvalho and Lupski, 2016]. There is no evidence of segmental duplications in the 4q21 chromosomal region, which can serve as a molecular substrate for non-allelic homologous recombination. However, pathogenic deletions at 4q21.21-q21.22 were previously bioinformatically predicted using a sliding window analysis [Cooper et al., 2011]. Moreover, one case of a de novo 4q21.22q21.23 microduplication has been reported [Ottaviani et al., 2015] in which the microduplication is close to but does not overlap with the minimal critical region for 4q21 microdeletion syndrome. One prenatally detected case of directly transmitted benign 4q12-q13.1 quadruplication associated with tandem segmental amplifications of the *LPHN3* gene has been described [Chen et al., 2011]. A three-step process combining *Alu*-mediated replicative repair-based mechanism(s) and intergenerational, intrachromosomal non-allelic homologous recombination was also proposed recently to explain the origin of quadruplication [Gu et al., 2016]. However, intergenerational recombination-based mechanisms are unlikely involved in the origin of the de novo microtriplication observed in our patient because of the normal 4q21 copy number present in the parents according to aCGH results. Further studies are required to determine the molecular mechanisms related to chromosomal copy number changes in the 4q21 region.

In conclusion, we report the first case of a de novo 4q21.21-q21.22 microtriplication, emphasizing the clinical significance of CNVs in 4q21 for patients with developmental delay and absence of speech. It is evident that polar changes in the doses of genes within affected chromosomal regions may be responsible for similar and mirrored phenotypes.

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DATABASES

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