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De novo 393 kb microdeletion of 7p11.2 characterized by aCGH in a boy with psychomotor retardation and dysmorphic features

Konstantinos Varvagiannis [a], Ioannis Papoulidis [b], Theodora Koromila [c], Konstantinos Kefalas [d], Monika Ziegler [e], Thomas Liehr [e], Michael B. Petersen [a], Yolanda Gyftodimou [a], Emmanouil Manolakos [b,f,*]

[a] *Department of Genetics, Institute of Child Health, Athens, Greece*
[b] *Eurogenetica S.A., Laboratory of Genetics, Athens–Thessaloniki, Greece*
[c] *Laboratory of Human Genetics, Department of Biology, University of Athens, Athens, Greece*
[d] *Bioiatriki S.A., Laboratory of Genetics, Athens, Greece*
[e] *Institute of Human Genetics Anthropology, Jena University Hospital, Jena, Germany*
[f] *Cattedra di Genetica Medica, Ospedale Binaghi, Cagliari, Italy*

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ABSTRACT

We report on a 27 month old boy presenting with psychomotor delay and dysmorphic features, mainly mild facial asymmetry, prominent cup-shaped ears, long eyelashes, open mouth appearance and slight abnormalities of the hands and feet. Array comparative genomic hybridization revealed a 393 kb microdeletion in 7p11.2. We discuss the possible involvement of *CHCHD2*, *GBAS*, *MRPS17*, *SEPT14* and *PSPH* on our patient's phenotype. Additionally, we studied the expression of two other genes deleted in the patient, *CCT6A* and *SUMF2*, for which there is scarce data in the literature. Based on current knowledge and the *de novo* occurrence of this finding in our proband we presume that the aberration is likely to be pathogenic in our case. However, a single gene disorder, elsewhere in the genome or in this very region cannot be ruled out. Further elucidation of the properties of this chromosomal region, as well as of the role of the genes involved will be needed in order to draw safe conclusions regarding the association of the chromosomal deletion with the patient's features.

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* Corresponding author at: Eurogenetica S.A., Laboratory of Genetics, Michalakopoulou 125, 11523 Athens, Greece. Tel.: +30 210 7474904; fax: +30 210 7474908.
E-mail address: emanolakosgr@yahoo.gr (E. Manolakos).

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Introduction

Intellectual disabilities represent an important cause of disease with an estimated global prevalence of 1–3% (Maulik et al., 2011; Roeleveld et al., 1997). The advent of array comparative genomic hybridization (array-CGH) has revolutionized the investigation of such patients, particularly those with dysmorphic features where a diagnostic yield of about 10% can be achieved (Sagoo et al., 2009). Recently, the International Standards for Cytogenomic Arrays (ISCA) Consortium has published its consensus statement, suggesting that array-based copy number analyses may have an even higher diagnostic rate and recommending their use as a first-tier diagnostic test for the evaluation of this patient group (Miller et al., 2010). Several strategies and guidelines have been developed for the interpretation of the results (Gijsbers et al., 2009; Hanemaaijer et al., 2012; Koolen et al., 2009; Lee et al., 2007; Miller et al., 2010; Poot and Hochstenbach, 2010). Yet, understanding the functional impact of the reported alterations remains often troublesome (Tsuchiya et al., 2009; Vermeesch et al., 2011).

We report here on the clinical and cytogenetic findings of a 27-month old male who presented with psychomotor delay as well as dysmorphic features. A submicroscopic deletion of 393 kb size was detected at the proximal part of chromosome 7p. After careful investigation of the corresponding genes, we hypothesize that the finding is likely to be causal in our patient. However, the possibility of a single gene disorder in the specific region or elsewhere in the genome cannot be excluded.

Clinical report

The proband was born to 35 year old parents, both healthy and unrelated. Family history was insignificant except for paternal infertility secondary to varicocele and oligospermia. The couple underwent five cycles of in vitro fertilization, the latter leading to the conception of the patient. The boy was delivered by emergency cesarean section at 34 weeks of gestation, due to placental abruption. Birth weight was 2200 g (40th centile), length 40 cm (90th–97th centile) and head circumference (OFC) 31 cm (45th centile). The early neonatal period was complicated by episodes of tachypnea with decreased oxygen saturation during feedings, and by hyperbilirubinemia, the latter treated with phototherapy.

At 2 months, he was admitted to the hospital because of vomiting, poor feeding and diarrhea. Intussusception was diagnosed on abdominal ultrasound and was further confirmed by barium enema. Surgical reduction was achieved after failure of all conservative measures.

The patient was re-hospitalized at 21 months, for evaluation of global developmental delay. According to his prior medical records, he was able to sit steadily at the age of 11 months. He began physiotherapy at 15 months, stood up at 16 months, and at 17 months he was still crawling and could only make a few steps when held by both hands. With regard to his language development, he was able to use one or two single words with meaning at 18 months.

On admission, a detailed neurological examination was conducted. Cranial nerves were intact, though he had a tendency to keep his mouth open leading to drooling. Normal tone was present in the upper part of the body, while a mild hypertonia was evident in the lower extremities. Deep tendon reflexes were brisk and bilaterally symmetrical. Head circumference (OFC) was 46.5 cm (3rd–10th centile). A brain magnetic resonance imaging (MRI) and routine electroencephalogram revealed no abnormalities. Laboratory investigations including complete blood count, serum biochemistry (including glucose, electrolytes, urea, creatinine and liver enzymes), iron, folate, ammonia, lactic acid, thyroid function tests, plasma amino acids, and urine mucopolysaccharides were all within normal limits apart from a mild hypochromic microcytic anemia attributed to iron deficiency. An ophthalmology consultation was obtained, with no findings on slit-lamp examination. Cardiology evaluation with electrocardiography (ECG) and echocardiography was unremarkable. Otolaryngology exam documented the presence of otitis media with effusion along with purulent rhinitis. Otoacoustic emission (OAE) tests, following therapy, were normal.

At 26 months, despite continuation of physical therapy, the lower limb hypertonia persisted. Botulinum toxin A was administered intramuscularly at the gastrocnemius muscles of the patient, at a total dose of 360 units divided equally between the two limbs. The boy responded well with improvement of his muscle tone. He walked independently a few months after this intervention.

He was referred to our genetic department at the age of 27 months because of the above problems and his facial dysmorphism. On physical examination his weight was 12 kg (10th–25th centile), length 88 cm (25th centile) and head circumference (OFC) 48.5 cm (10th–25th centile). Clinical features included:

dolichocephaly with a prominent occiput, ridged metopic suture and apparently closed fontanelles, high forehead and thick eyebrows. A mild hypertelorism was evident with straight palpebral fissures and long curly eyelashes. The nasal bridge was somewhat broad. He presented with a mild facial asymmetry, with his nasal tip, his deep philtrum and open mouth deviating to the right. He had thick lips, with the lower one being everted. A labial frenulum of the lower lip had been surgically corrected. One of the most striking characteristics of our proband was however the presence of prominent, large and cup-shaped ears. The extremities did not exhibit any remarkable anomaly apart from the squared fingertips and the presence of slightly aberrant palmar creases. The boy demonstrated truncal hypotonia with peripheral hypertonia. His parents noted that he used to have an aggressive behavior when associating with others, though he had a relatively happy demeanor throughout the examination.

Materials and methods

Chromosome analysis was carried out on phytohaemagglutinin (PHA) stimulated lymphocytes with standard GTG-banding technique (G-banding using trypsin treatment and giemsa staining). Array comparative genomic hybridization (a-CGH) analysis was performed using the Agilent 60 K oligonucleotide array, according to the manufacturer's protocol (Agilent Technologies, Santa Clara, CA). Fluorescent in situ hybridization (FISH) testing was done according to a previously described protocol (Liehr et al., 2002). Chromosome 7 was characterized by FISH employing whole chromosome 7 paint probe WCP7 and bacterial artificial chromosome (BAC) probe RP11-769B4 in 7p11.2. Analysis was performed using a Zeiss epifluorescent Axioskop 2 plus microscope, and images were captured, enhanced and analyzed using Cytovision (Applied Imaging) software. Both the conventional cytogenetics and FISH results were described according to the 2009 International System for Human Cytogenetics Nomenclature (ISCN) (International Standing Committee on Human Cytogenetic Nomenclature et al., 2009).

In order to quantify chaperonin containing TCP1, subunit 6A (zeta 1) (*CCT6A*) and sulfatase modifying factor 2 (*SUMF2*) mRNA transcripts, we developed and evaluated real-time fluorescence PCR assays for the Roche LightCycler (LC; Roche Diagnostics, Mannheim Germany). Total RNA was extracted from peripheral blood samples using the RNeasy Mini Kit (Qiagen, Hilden, Germany). RNA quality was determined by electrophoresis and absorbance spectrophotometry. Reverse transcription was performed with Avian Myeloblastosis Virus Reverse Transcriptase (AMV-RT) (Roche Diagnostics, Mannheim, Germany) and random hexamers as primers. DNA oligonucleotide primers and hybridization probes were synthesized by TIB Molbiol (Berlin, Germany) for each target gene as well as for the housekeeping gene glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*). The sequences of the primers used for *CCT6A* quantification were forward primer: 5′-TAGATGCT CTTTCAAAAGAAGGCA-3′ reverse primer: 5′-AAGGTAAACTTCTCTTCTCCCAATG-3′ and for *SUMF2* forward primer: 5′-ACCACCAGGATGGGCAA-3 reverse primer: 5′-GCCATCGTCAACACACATTG-3′. The adjacent ends of the hybridization probes were labeled with fluorophores. The 5′ end of the first probe was labeled with the acceptor fluorophore LC Red 640 and the 3′ end of the second probe with the donor fluorescein (FITC, 3FL). The 5′ labeled probes were 3′-phosphorylated to block polymerase extension during PCR. For quantification, LightCycler® FastStart DNA Master HybProbe (Roche) was used. The sequences of the probes used for *CCT6A* quantification were: 5′-LC640-TGTGGTGGGGTAGCCCTGAATTCTT—PH, 5′-AGGAGAAATATGGAGAGGCTG ACTCTTGC—FL and for *SUMF2*: 5′-LC640-TCCCCTTCCCTGTCTCCCATCC—PH, 5′-GAGAGCTTCAGCCTCAGGAAAG AAC—FL.

Results

The G-banding analysis of the proband revealed a normal karyotype (550 band level). Consequently, a-CGH testing revealed a 393 kb heterozygous interstitial deletion in 7p11.2 (Chr7: 55,874,388-56,267,502 — NCBI Build 37 Hg19). Subsequent a-CGH analysis of the parents yielded normal results, suggesting that the aberration had arisen *de novo* in the proband.

The metaphase chromosomes were subjected to FISH for further confirmation of the finding. The deletion was confirmed in the proband but not in his parents (Fig. 1). The patient's karyotype was thus defined to be 46,XY,ish del(7)(p11.2p11.2)(wcp7+,RP11-769B4-)dn. The deleted region contained the following 11 RefSeq genes: Septin 14 (*SEPT14*), Zinc finger protein 713 (*ZNF713*), mitochondrial ribosomal protein S17 (*MRPS17*), glioblastoma amplified sequence (*GBAS*), phosphoserine phosphatase (*PSPH*),

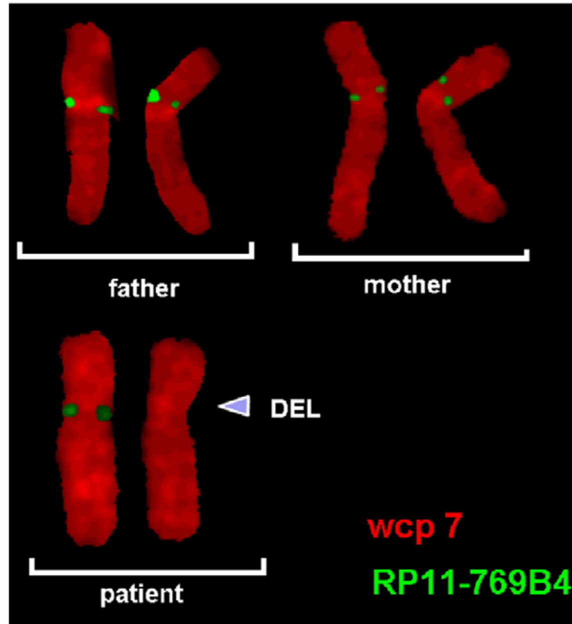

Fig. 1. FISH analysis for the confirmation of the observed deletion. Whole chromosome 7 paint probe WCP7 (red) and BAC probe RP11-769B4 (green) were used. Notice the absence of the RP11-769B4 probe in the patient's chromosome (arrowhead) but not in the parental chromosomes.

CCT6A, small nucleolar RNA, H/ACA box 15 (*SNORA15*), *SUMF2*, phosphorylase kinase, gamma 1 (*PHKG1*), coiled-coil-helix-coiled-coil-helix domain containing 2 (*CHCHD2*), and nuclear protein, transcriptional regulator, 1-like (*NUPR1L*).

Among the genes deleted in our patient, we chose to study the expression of *CCT6A* and *SUMF2* because of their high expression levels in human blood and the scarce literature information concerning them. Results were presented as absolute number of target cDNA molecules for each target gene (*CCT6A* and

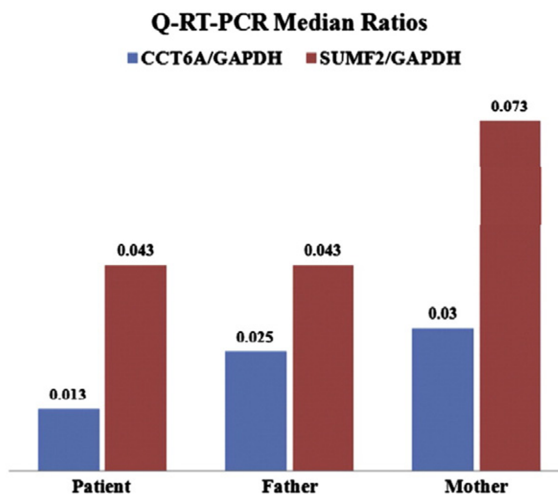

Fig. 2. Quantitative RT-PCR analysis of CCT6A and SUMF2 for patient's family members. The graph shows the median ratios of triplicate experiments for *CCT6A* and *SUMF2* mRNA levels, divided by the *GAPDH* mRNA levels.

SUMF2) divided by the number of target cDNA molecules for *GAPDH* gene in the same sample to give a *ratio*. The values shown in Fig. 2 are the median values of triplicate experiments that we performed for each examined gene. The *SUMF2* expression levels were found higher than *CCT6A*, while expression patterns were different among samples. Specifically, the median *CCT6A*/*GAPDH* ratios were higher in both parents (mother's median: 0.030, father's median: 0.025) than in the patient (median: 0.013). The standard deviation values (SD) were 0.002082, 0.001528 and 0.001 respectively. The median *SUMF2*/*GAPDH* ratios were lower in the father and patient (father's median: 0.043, patient's median: 0.043) than in the mother (median: 0.073). The SD values were 0.002082 for both the parents and 0.001528 for the patient.

Discussion

We describe here a patient with global developmental delay, moderate facial dysmorphism and a 7p11.2 submicroscopic deletion demonstrated by a-CGH. Unfortunately, most cases of 7p11.2 deletion published to date are rather unsuitable for comparison, being rather poorly characterized as to their breakpoints, with the aberration extending also to other cytogenetic bands. Coulter et al. (2011), reported on a patient (Supplementary material, patient VPS-25) with a minimal 47 kb deletion of this region, known to have developmental delay and mild intellectual disability. The chromosomal imbalance found in this patient was assumed to be a variant of possible significance (Coulter et al., 2011). Review of the cases reported in the Database of Genomic Variants (DGV) revealed that similar aberrations have been found in otherwise healthy individuals. Specifically, variants esv2734447 and dgv1201e199 have been recently described by two different whole-genome sequencing studies (Genomes Project, C., et al., 2012; Wong et al., 2013) (Fig. 3). These two variants encompass almost the same region and are reported as deletions. In two relevant cases submitted by the International Standards for Cytogenomic Arrays (ISCA) Consortium, patients nssv584505 and nssv582021, the deletions have been characterized as of uncertain significance and benign respectively. It is however noticeable that both these cases present with a neurological phenotype (seizures). Finally, our case shows partial overlap with patient 255179 in the DECIPHER database (The Centre for the Development and Evaluation of Complex Interventions for Public Health Improvement), for whom no phenotypical information is available (Fig. 3).

Interestingly, proximal 7p has been extensively studied in the past, in an attempt to find genes subject to imprinting. Cases of Silver–Russell syndrome (OMIM #180860) due to maternal uniparental disomy of chromosome 7 (Eggermann et al., 1997; Kotzot et al., 1995), and cases due to segmental duplications of this chromosome have led to the narrowing of the imprinted candidate region to 7p11.2–p13 (Joyce et al., 1999; Monk et al., 2000). Monk et al. (2002) studied the expression pattern of *PHKG1*, *CCT6A*, *GBAS*, and *PSHP* in human fetal tissues. The authors demonstrated a biallelic expression of *PHKG1*. Unfortunately, imprinting studies for *CCT6A* were non-informative while expression of *GBAS* and *PSPH* was undetectable in all tissues (Monk et al., 2002). We however consider an imprinting effect in our case rather unlikely, given that the genomic region in our case is orthologous to a respective of mouse chromosome 5 devoid of imprinted genes, whereas both the distal parts of 7p11.2 and 7p12.1 are orthologous to a highly imprinted region of mouse chromosome 11 (Scherer et al., 2003).

As the exact function of many genes within this 393 kb interval remains to be elucidated, only speculations can be made as to their contribution to our patient's phenotype. The region of imbalance, however, encompasses three genes postulated to be important for mitochondrial function, namely *CHCHD2*, *GBAS* and *MRPS17*. For both *CHCHD2* and *GBAS*, it has been suggested that they play a role in oxidative phosphorylation (OxPhos). Baughman et al. (2009) illustrated that *CHCHD2* is consistently co-expressed with other nuclear-encoded structural OxPhos subunits (Baughman et al., 2009). shRNA-induced silencing of *CHCHD2* in human fibroblasts led to considerable reduction of oxygen consumption rate. Knockdown of this gene reduced both complex IV and complex I activity. *GBAS*, glioblastoma amplified sequence, has previously been reported to have a high expression in brain, skeletal muscle and heart (Seroussi et al., 1998; Wang et al., 1998). Martherus et al. (2010) found a similar expression profile for *GBAS* and *COX6A2* encoding cytochrome c oxidase subunit VIa polypeptide 2. HELA-cells transfected with siRNA against *GBAS* displayed a significant reduction in total cellular ATP level. The authors concluded that *GBAS* is involved in OxPhos (Martherus et al., 2010). Finally, *MRPS17* encodes mitochondrial ribosomal protein S17, thus has an indirect role in the mitochondrial translation system

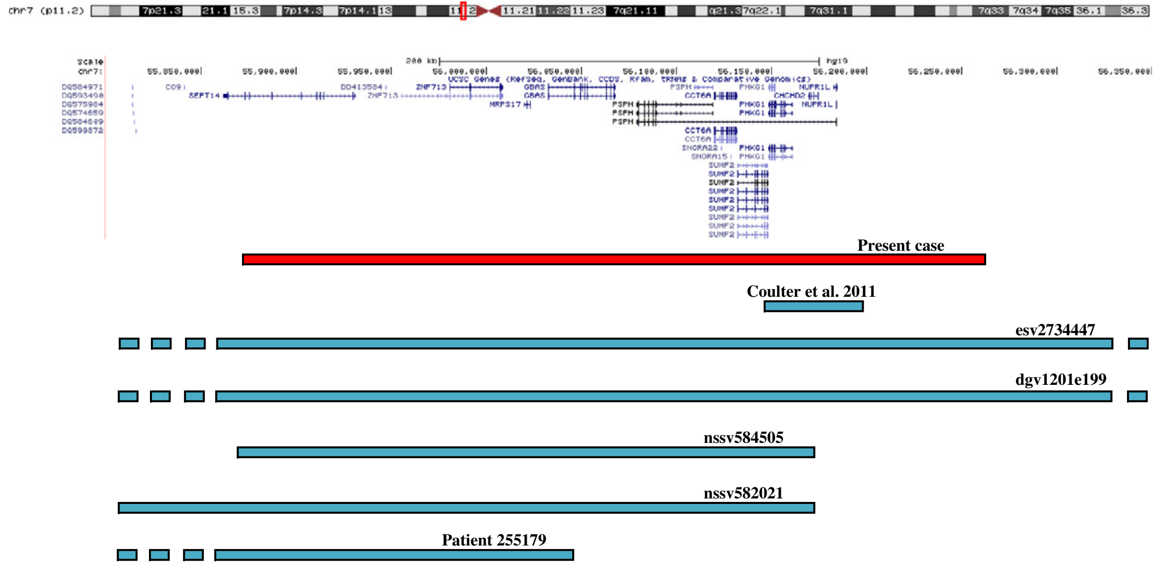

Fig. 3. Schematic view of the 393 kb deletion region in this case and other reported cases. Information for the patient reported by Coulter et al. (2011) and the case in the DECIPHER database (https://decipher.sanger.ac.uk/) (patient 255179), the ISCA database (https://www.iscaconsortium.org/index.php/search) (patients nssv584505, nssv582021) as well as the Database of Genomic Variants (http://projects.tcag.ca/variation/) (patients esv2734447, dgv1201e199) are also included.

necessary for the production of the 13 proteins essential for OxPhos (Kenmochi et al., 2001). Mutations of *MRPS16*, another component of the mitochondrial ribosomes, are known to result in combined oxidative phosphorylation deficiency type 2 (OMIM #610498). Mitochondrial and particularly OxPhos disorders can lead to developmental delay and intellectual disability along with other neurological or muscular manifestations (Berdanier, 2005). These diseases may present at any age and with a considerable clinical variability. Our patient presented with psychomotor delay and spasticity of the lower limbs. Cases reported by the ISCA consortium with similar deletions, present with epilepsy, another feature of mitochondrial disorders. Even though plasma lactic acid was normal in our case, it is well established that normal concentrations do not exclude the presence of a mitochondrial disease (Chinnery, 1993). Finally, several clinical features of these disorders, such as diabetes or retinopathy, appear later in life and thus an incomplete mitochondrial disorder phenotype, due to our patient's small age cannot be ruled out.

Additionally, *SEPT14*, the gene coding for septin 14 presents an interesting profile. Septins are a family of heteropolymeric filament-forming GTP-binding proteins that perform diverse functions depending on their tissue localization and their interacting partners. Cell division, cytokinesis, plasma membrane compartmentalization as well as the assembly of diffusion barriers and scaffolds appear to be some of the cellular processes in which the 14 members of this highly conserved family are involved. Several septins have a brain-specific expression, while many members have been implicated in many neurological disorders, as outlined in a detailed review by Peterson and Petty (2010). Although it was initially demonstrated that human Septin 14 is a testis-specific protein (Peterson et al., 2007), a recent study showed that Septin 14 is highly expressed in the developing mouse cerebral cortex and testis and regulates the proper positioning of cortical neurons during corticogenesis (Shinoda et al., 2010). The authors suggested that Septin 14 is involved in neuronal migration and possibly neuronal maturation. It was underscored that disruption of the migration process can lead to the misplacement of neurons and disorganized cortical lamination, clinically evident as mental retardation (Clark, 2002).

It would also be of value to note that the deletion in our patient also spans *PSPH*, the gene for phosphoserine phosphatase. *PSPH* catalyzes the final step of L-serine biosynthesis, a process substantial for the development and function of the central nervous system (Tabatabaie et al., 2010). Deficiency of this enzyme (OMIM #614023) as well as the other serine synthesis disorders is predominantly complicated by neurological symptoms including developmental delay and seizures (de Koning, 2006). Quantitative plasma aminoacid analysis in our patient did not demonstrate deficiency of this aminoacid. Nonetheless, this does not deviate from the autosomal recessive inheritance mode proposed for this disorder by Veiga-da-Cunha et al. (2004).

Expression of two deleted genes (*CCT6A* and *SUMF2*) was studied in our patient as well as in his parents. For *CCT6A* we were able to demonstrate lower expression in the patient compared to his parents. To our knowledge, the function of this gene has not been associated to a specific phenotype to date. Expression of *SUMF2* was rather uninformative, being similar in the patient and his father but lower compared to the patient's mother. The protein encoded by *SUMF2*, is known to form homodimers and heterodimers with the respective encoded by *SUMF1* (sulfatase-modifying factor 1) and to associate with sulfatases. The interaction between *SUMF1* and *SUMF2* is presumed to regulate the sulfatases' catalytic activities (Zito et al., 2005). Homozygous or compound heterozygous mutations of *SUMF1* are known to result in multiple sulfatase deficiency (OMIM #272200), characterized by delay in psychomotor development (Diez-Roux and Ballabio, 2005).

Conclusions

Small copy number changes detected by a-CGH are difficult to evaluate. We postulate that the aberration in our proband is likely to be pathogenic. The *de novo* occurrence of this finding and the hemizygosity for genes relevant to our patient's phenotype support this argument. However, it would be important to acknowledge the possibility that this finding may be coincidental, and the patient's phenotype is due to a single gene disorder elsewhere in the genome. Taking in consideration the existence of benign CNVs reported in DGV, we cannot exclude the latter assumption. Nonetheless, we also can postulate, that a single point mutation in the respective region of the normal homologue chromosome 7 is likely the causative factor in our case. Of course, this possibility may be proven only by sequencing the whole respective area. Further reports of similar cytogenetic alterations, as well as understanding of the

region's properties and the involved genes will be needed to shed light on the pathogenicity or not of the current deletion.

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