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Identification of a de novo microdeletion 1q44 in a patient with hypogenesis of the corpus callosum, seizures and microcephaly – A case report

Dominik S. Westphal [a,b,*], Stephanie Andres [a], Kirsten I. Beitzel [c], Christine Makowski [d], Thomas Meitinger [a,b], Julia Hoefele [a]

[a] Institute of Human Genetics, Technical University Munich, Munich, Germany
[b] Institute of Human Genetics, Helmholtz Zentrum Munich, Neuherberg, Germany
[c] Department of Diagnostic and Pediatric Radiology, Schwabing Hospital, Munich, Germany
[d] Department for Pediatrics, Technical University Munich, Munich, Germany

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ABSTRACT

Microdeletion 1q44 on the long arm of chromosome 1 leads to a phenotype that includes microcephaly, seizure, agenesis or hypogenesis of the corpus callosum, polydactyly, congenital heart defects and severe developmental delay along with characteristic facial dysmorphic signs. Until today, the distinct genetic causes for the different symptoms remain unclear.

We here report a 1.2 Mb *de novo* microdeletion 1q44 identified by performing a SNP array analysis. The female patient presented with microcephaly, seizure, hypogenesis of corpus callosum, postaxial hexadactyly, an atrial septal defect, a ventricular septal defect, hypertelorism, a long and smooth philtrum, thin vermilion borders, and micrognathia, all common features of microdeletion 1q44. An additionally performed chromosome analysis excluded any chromosomal rearrangements. The deleted region included the genes *ZBTB18* as well as *HNRNPU* amongst others. Both are possibly candidate genes for the dysgenesis of the corpus callosum. *AKT3*, another candidate gene, was not affected by the deletion in this patient.

Thus, the genetic findings in this case report spotlight *ZBTB18* and *HNRNPU* in the genesis of the typical microdeletion 1q44 symptoms, especially concerning the dysgenesis of the corpus callosum, and therefore could help to unveil more of the genetic background of this syndrome.

1. Introduction

In the last ten years, a few patients have been identified carrying a microdeletion 1q44.(Cho et al., 2014; Thierry et al., 2012; Caliebe et al., 2010; Ballif et al., 2012) It is already well documented that alterations in this critical region on the long arm of chromosome 1 cause the symptoms of the so called 1q44 microdeletion syndrome, characteristically presenting with microcephaly (MIC), seizures (SZR) and malformations of the corpus callosum, *i.e.* agenesis (ACC) and hypogenesis (HCC). However, the distinct genetic cause for the different symptoms or a defined genotype-phenotype correlation has not been unveiled so far. Furthermore, contradicting data concerning the genotype-phenotype correlation can be found in the literature. A study by Ballif et al. 2012 describing 22 patients affected by a heterozygous microdeletion 1q44 proposed the heterozygous loss of *AKT3* as causative for microcephaly, *ZBTB18* (syn. *ZNF238*) for ACC and the region containing *FAM36A* (syn. *COX20*), *C1ORF199* (syn. *HNRNPU-AS1*), and *HNRNPU* for SZR with *HNRNPU* as the most likely candidate.(Ballif et al., 2012) In a case report published by de Munnik et al. (2014) a patient with a single nonsense mutation in *ZBTB18* showed signs and symptoms of the microdeletion 1q44 syndrome including microcephaly but without ACC. The authors explained this finding with reduced penetrance of ACC. (de Munnik et al., 2014) Additionally, *AKT3* (Boland et al., 2007; Andrieux et al., 2008) and *HNRNPU* (Caliebe et al., 2010) are still possible candidate genes for ACC/HCC. Here we present an additional female patient with a *de novo* 1.2 Mb microdeletion in 1q44, spanning *ZBTB18* and *HNRNPU* but not *AKT3* presenting with the clinical features of

Abbreviations: ACC, agenesis of the corpus callosum; ASD, atrial septal defect; AV, atrioventricular; bpm, beats per minute; Chas, Chromosome Analysis Suite Software; HCC, hypogenesis of the corpus callosum; IUGR, intrauterine growth retardation; MIC, microcephaly; MRI, magnetic resonance imaging; RefSeq, reference sequence; pLI, probability of loss of function intolerance; SD, standard deviation; SNP, single nucleotide polymorphism; SZR, seizure; VSD, ventricular septal defect.

* Corresponding author at: Institute of Human Genetics, Technical University Munich, Trogerstr. 32, 81675 Munich, Germany.
E-mail address: dominik.westphal@mri.tum.de (D.S. Westphal).

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HCC, seizures and microcephaly along with dysmorphic signs, cardiac septal defects, muscular hypotonia, and developmental delay.

2. Case report

The female patient is the second child of healthy parents. The older sister is also healthy. The patient was born at a gestational age of 41 weeks. The measurements at birth were too small in relation to her gestational age (birth weight: 2720 g (−2.01 SD), birth length: 46 cm (−2.82 SD), head circumference at birth: 33 cm (−1.71 SD)). At birth, she showed a postaxial hexadactyly of her left hand. She also suffered from obstipation since birth. On the eleventh day of life poor feeding and somnolence due to paroxysmal supraventricular tachycardia (heart rate max. 280 bpm) with AV nodal reentrant tachycardia as a differential diagnosis were noted along with an atrial septal defect (ASD) and a ventricular septal defect (VSD). Although the cardiac problems were treated, the symptoms of poor growth and feeding remained. An epileptic seizure was suspected at the age of 2 months. Since the age of 10 months seizures have been occurring more frequently. Therefore, the patient was initially treated with levetiracetam and medication was then changed to valproate because of worsening of the frequency of seizures. A MRI of the brain revealed microcephaly, HCC (Fig. 1A) and polymicrogyria affecting the right hemisphere (Fig. 1B). At the age of 1 year and 3 months her weight was 8050 g (−1.79 SD), her length 71 cm (−2.53 SD) and her head circumference 41 cm (−5.34 SD). At the age of 1 year and 6 months the girl was presented at our genetic department. At this time she showed facial dysmorphic signs such as hypertelorism, long and smooth philtrum, thin vermilion borders, and micrognathia (Fig. 2). She also had muscular hypotonia and severe global developmental delay. Mutations causing Smith-Lemli-Opitz syndrome had already been excluded before. At the age of 1 year and 8 months her poor feeding improved and she advanced in her motoric and linguistic skills while receiving additional supportive care early on.

3. Methods

Blood samples from the patient for molecular karyotyping were collected after written informed consent. DNA was extracted from peripheral blood using the Gentra Puregene Blood Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. DNA samples of the patient and her parents were analyzed by using the SNP-Array Affymetrix® CytoScanTM 750 K Array (Affymetrix® Inc., Santa Clara, USA) with an average space between two oligonucleotides of 4 kb. Scanning was performed by the Affymetrix® GeneChip Scanner 3000 7G (resolution 0.51 to 2.5 μm). The data analysis was conducted using the Affymetrix® Chromosome Analysis Suite Software (ChAS), version 3.0, hg19.

Additionally, chromosome analysis of peripheral blood lymphocytes was performed in the patient according to standard procedures for cultivation and GTG banding.

4. Results

SNP-Array analysis revealed a 1.2 Mb microdeletion in the chromosomal region 1q44 including six OMIM genes (*ZBTB18*, *ADSS*, *DESI2*, *COX20*, *HNRNPU*, and *KIF26B*) out of 11 RefSeq genes (Fig. 3). Following SNP array analyzes of the parents revealed the *de novo* status of the patient's microdeletion. Chromosome analysis of the patient was additionally performed in order to rule out any chromosomal rearrangements. It resulted in a normal female karyotype (46,XX; data not shown).

5. Discussion

The microdeletion 1q4 is known to cause a broad spectrum of symptoms like congenital heart defects, hypotonia, seizures, developmental delay, short stature, microcephaly, ACC/HCC, anomalies of the hands and feet as well as distinct facial features.(Thierry et al., 2012; Caliebe et al., 2010; Shaffer et al., 2007; Hiraki et al., 2008) Although ACC was also found in a patient suffering from a microdeletion 1q41q42 (Filges et al., 2010) a critical region was identified in 1q43q44 by some authors before.(Boland et al., 2007; Hill et al., 2007; van Bon et al., 2008; Poot et al., 2007)

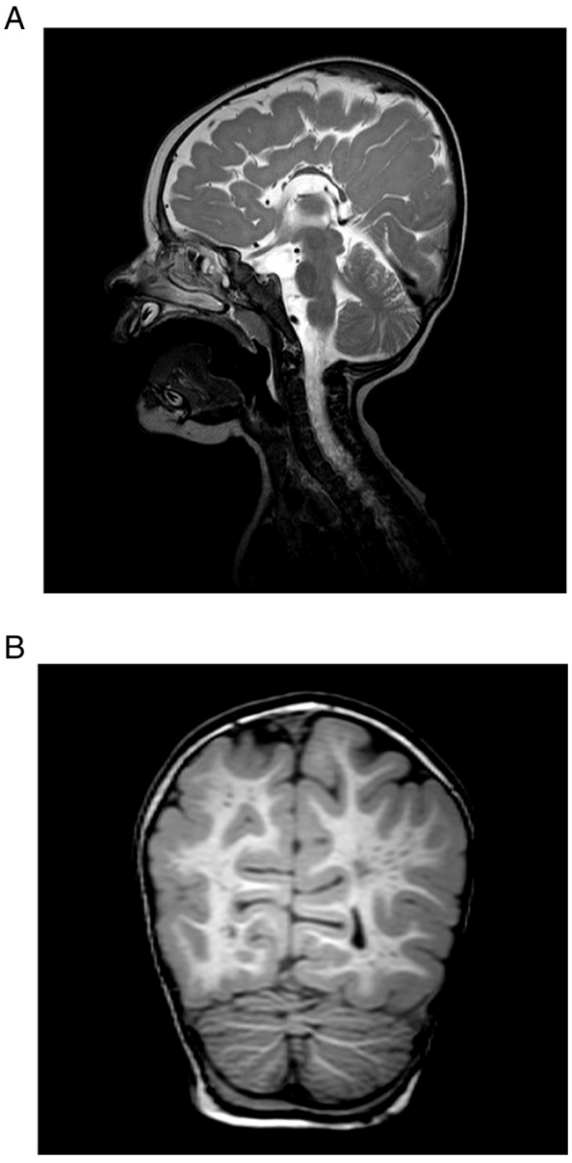

Fig. 1. MRI of the patient showing signs of microcephaly, HCC (A) and polymicrogyria affecting the right hemisphere (B).

AKT3 which was not affected by the microdeletion in our case is suspected to cause ACC/HCC in microdeletion 1q44 patients. It encodes a serine/threonine-kinase and was found to be involved in brain development in mice. (Easton et al., 2005) Boland et al. and Poot et al. proposed this gene as one of the first candidate genes related to ACC in patients with microdeletion 1q44. (Boland et al., 2007; Poot et al., 2008) However, its role in the microdeletion 1q44 phenotype spectrum changed gradually after a patient had been published showing ACC besides other symptoms with a terminal microdeletion of 1q44 that did not include *AKT3*.(Poot et al., 2007) Furthermore van Bon et al. reported 13 patients with microdeletions in the chromosomal region 1q43q44 indicating a critical region for ACC/HCC that did not include *AKT3*. (van Bon et al., 2008) Nevertheless, Orellana et al. (2009) reported a patient that showed no sign of MIC or ACC and was carrier of a deletion that