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Further Characterization of Microdeletion Syndrome Involving 2p15-p16.1

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Abstract

We report on a patient presenting with cognitive delay, prenatal and postnatal growth deficiency, microcephaly, ptosis of eyelids, high and broad nasal root and camptodactyly. Analysis of a dense whole genome SNP array showed a *de novo* 3.35Mb deletion on 2p15-p16.1. In order to study the parental origin of the deletion we analyzed selected SNPs in the deleted area in the proband and her parents showing Mendelian incompatibilities suggesting a *de novo* deletion on the chromosome of paternal origin. Based on the five cases described previously in the literature, we have narrowed the critical region responsible for the 2p15-p16.1 microdeletion syndrome phenotype. The critical region does not include the *VRK2* gene that had been speculated to have a role in cortical dysplasia. However, the association of the *VRK2* gene with cortical dysplasia remains to be determined, as MRI imaging of the brain and gene content of the 2p15-16 deletion becomes established in more patients.

Keywords

microdeletion; chromosome 2; paternal origin

INTRODUCTION

It has been recognized that a considerable proportion of patients with multiple congenital anomalies and learning disability/mental retardation (MCA/MR) have chromosomal abnormalities. Many of these are detected by routine cytogenetic analysis; however, its resolution is limited to 5 to 10 Mb. The broad use of technologies such as fluorescent *in situ* hybridization (FISH) allowed the characterization of many microdeletion syndromes, and probes for the subtelomeric regions have been used to identify submicroscopic abnormalities in 5% of subjects with MCA/MR [Knight et al., 1997; Koolen et al., 2004]. More recently screening of the whole genome for submicroscopic abnormalities in patients with idiopathic intellectual disability using new technologies such as array comparative genomic hybridization (array-CGH) or single nucleotide polymorphism (SNP) arrays has increased the number of previously unrecognized cytogenetic abnormalities [Hoyer et al., 2007; Menten et al., 2006; Shaw-Smith et al., 2004; Vissers et al., 2003]. Based on several published studies using different resolution arrays a recent meta-analysis estimated the average diagnostic yield of 10% (95% CI: 8–12%). This analysis suggested that a resolution better than 1Mb will have the greatest diagnostic yield [Sagoo et al., 2009]

The use of array CGH has contributed to the description of a new microdeletion syndrome involving the region 2p15-p16 [Rajcan-Separovic et al., 2007]. The authors described two unrelated patients with 4.5 and 5.7 Mb deletions respectively presenting with microcephaly, ptosis, short palpebral fissures, broad and high nasal root, camptodactyly, cortical dysplasia and intellectual disability. Three additional patients were reported narrowing down the critical region [de Leeuw et al., 2008; Chabchoub et al., 2008; Liang et al., 2009].

We report on an additional case of the 2p15-p16.1 microdeletion syndrome and discuss the critical region responsible for the clinical phenotype by comparison with cases previously reported in the literature.

CLINICAL REPORT

The patient is a 4-year-old girl born to nonconsanguineous, 28- and 30-year-old parents of European descent. At 28 weeks of pregnancy intrauterine growth retardation was detected by ultrasound. She was born preterm (34 weeks) by cesarean. Birth weight was 1520g (below 10 centile), birth length 39 cm (below 10 centile) and OFC was 28.5 cm.(below 10th centile). She was admitted to the neonatal intensive care unit and was discharged weighing 1930g (below 10th centile) at one month of age. She had difficulty in gaining weight and a poor suck. Lactose intolerance and gastro-esophageal reflux were diagnosed at 6 months of age. At 18 and 28 months of age she had a febrile seizure. She was noted to have developmental delay and sat at 1 year, walked unsupported at 3 years and has only a few spoken words at 4 years of age. She has been on physiotherapy and in special education with good improvement. The child does not display autistic behaviour.

At 38 months old, physical examination showed length of 87 cm (3rd–10th centile), weight of 10.9 Kg (below 3rd centile), OFC of 43 cm (below 3rd centile), microcephaly, micrognathia, high nasal root, ptosis of eyelids, long eyelashes, a smooth philtrum, high palate, dimple on the shoulders and elbows, and camptodactyly of the digits 2–5 bilaterally (Fig 1).

The investigations included a normal cranial magnetic resonance imaging (MRI), normal echocardiogram and normal abdominal ultrasound. Eletroencephalography was performed showing disorganized background activity. Karyotype showed 46,XX (500 bands) and analysis of 7-dehydrocholesterol was normal.

METHODS

Blood was obtained from the proband and her parents after signed informed consent. DNA was isolated using standard procedures. We used 1.5µg of DNA from the proband to perform a genome wide copy number scan using Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA).). The results were analyzed using the Partek Genomics Suite software (<http://www.partek.com/software>). This array provides good genome coverage with almost 2 million SNPs and copy number variation probes and makes possible an excellent assessment of possible breakpoints of deletions to assess copy gains or losses.

RESULTS

Our analysis showed a stretch of homozygosity of 3.35 Mb suggestive of a deletion in the region 2p15-p16.1. The deleted area encompassed the position 59,139,200 to 62,488,871 (according to the UCSC Genome Browser on Human February 2009 Assembly) showing 934 contiguous homozygous SNPs.

In order to investigate the parental origin of the deletion, we sequenced selected SNPs including the target deleted area using the proband and her parents DNA. We designed primer sets of including approximately 400 bp around 10 selected SNPs (rs991964, rs10169462, rs17050238, rs1013344, rs11125832, rs10490071, rs766448, rs6705537, rs6715590, rs7601770). Sequence was carried out using BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystem, Foster City, CA) according to the manufacturer's instructions. Cleanup was performed by standard protocols and the samples were resuspended in ddH₂O and analyzed in an Applied Biosystems 3730 sequencer.

Selected sequenced SNPs on the deleted region showed heterozygous parents and a miscalled homozygous proband for the same allele, suggesting the proband was hemizygous on that region. Using the method of classification of transmission pattern [Conrad et al., 2006] several SNPs were informative for Type I Mendelian incompatibilities confirming a *de novo* deletion on the chromosome of paternal origin.

DISCUSSION

We report here on a patient with a microdeletion of 2p15-p16.1. The clinical features are very similar to the subjects reported by Rajcan-Separovic et al. [2007], including intellectual disability, pre and postnatal growth retardation, microcephaly, high and broad nasal root, long eyelashes, and camptodactyly (Table I). The patient presented with a *de novo* 3.35 Mb deletions which occurred on the paternal chromosome 2.

The child reported here had dysmorphic facial features associated with camptodactyly and pre and post natal growth retardation. The clinical findings are similar to the cases reported by Rajcan-Separovic et al. [2007]. Liang et al. [2009] suggest that the critical region for the 2p15-p16.1 microdeletion syndrome phenotype is between the position 59,000,000 and 61,500,000. Our patient has a similar breakpoint region. The common deleted area includes several known genes with different functions including B-cell CLL/lymphoma 11A isoform 3 (*BCL11*), poly(A) polymerase gamma (*PAPOLG*), v-rel reticuloendotheliosis viral oncogene (REL), pseudouridylate synthase 10 (*PUS10*), peroxisome biogenesis factor 13 (*PEX13*), Homo sapiens small nucleolar RNA (*SNORA70B*), activator of heat shock 90Da protein (*AHSA2*), ubiquitin specific protease 34 (*USP34*), exportin 1 (*XPO1*) and 6 other genes with unknown function. The deletion of the present report also includes additional genes: COOMM domain containing protein1 (*COMMD1*), chaperonin containing TCP1 subunit 4 (*CCT4*), transmembrane protein 17 (*TMEM17*) and UDP Glc NAc: beta gal member of beta gal member of beta 1–3-acetylglucosamyltransferase family (*B3GNT2*) (Fig 2).

Chaubchoub et al.[2008] suggested the gene vaccinia related kinase 2 isoform 1 (*VRK2*), located on 2p16 as responsible for the cortical dysplasia reported in the two original patients reported by Rajcan-Separovic et al. [2007]. The suggestion was based on a report of 3 children from three related families and one additional unrelated child presenting microcephaly, seizures and brain malformation with simplified gyration associated with non-thickened cortex and severe hypoplasia of corpus callosum. Homozygosity mapping using a dense SNP chip array was able to identify a homozygous region located on 2p16 [Chandler et al, 2006]. The fact that patient reported here and the one reported by Chaubchoub et al. [2008] and Liang et al. [2009] do not have brain malformations on MRI and their deletions do not include the *VRK2* gene, are consistent with this hypothesis; however the association of the *VRK2* gene with cortical dysplasia remains to be verified, as MRI imaging of the brain and gene content of the 2p15-p16 deletion becomes established in more patients.

Four out of six patients reported with 2p15-p16 microdeletion syndrome, including the present report presented with congenital contractures including camptodactyly and metatarsus abductus. Congenital contractures as in the distal arthrogryposis are caused by genes in fast-twitch myofibers such as the one that code for proteins in the tropomyosin-actin complex [Sung et al., 2003]. Congenital contractures may be secondary to brain anomalies due to decreased fetal movements; however the patient reported here did not have the brain anomalies of cortical dysplasia reported by Rajcan-Separovic et al. [2007]. The microdeletion region in our case included the *CCT4* gene, which functions to assist the folding of a small set of proteins. This gene is known *in vitro* and *in vivo* to play a role in the folding of actin and tubulin and other cytoskeletal proteins such as heavy meromyosin subunit. The role of *CCT4* gene in the contractures of 2p15-p16.1 syndrome and arthrogryposis syndromes remains to be determined.

Based on the few cases reported so far, the 2p15-p16.1 microdeletion is a clinically definable syndrome presenting with intellectual disability associated with pre and postnatal growth deficiency, microcephaly, ptosis, broad and high nasal root and camptodactyly. Our case and the Liang et al. [2009] were the only reported cases in which the origin of the deletion was investigated, and both occurred on the paternal chromosome. Based on those few cases reported so far, we can not exclude a difference in clinical findings according to the parental origin of the deletion. Description of additional cases and studies of parental origin will allow a better understanding of genotype/phenotype correlation and also to refine the critical region for this newly recognized syndrome.

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Figure 1.
Patient at age 4 years; (a) Frontal view; (b) camptodactyly; (c) frontal face view showing ptosis of eyelids, long eyelashes, smooth philtrum; (d) lateral view: short forehead.

Figure 2.

On the top, result of the array GCH showing chromosome 2 with 2p15-p16.1 deletion. The region of the critical region of chromosome 2p15-p16.1 was expanded (56,000,000–64,000,000 position based on UCSC Genome Browser February 2009-<http://genome.ucsc.edu/>). The genes in the region are reported. On the bottom, the deleted area of the 5 cases reported previously in the literature and the present report. The critical region of the present report and the cases reported previously are indicated.

Table 1

Comparison of clinical features of microdeletion syndrome 2p15-p16.1.

Clinical features	Rajcan-Separovic et al., [2007]		De Leeuw et al., [2008]	Chabchoub et al., [2008]	Liang et al., [2009]	Present report
	Subject 1	Subject 2				
Deletion size	4.5Mb	5.7Mb	3.9Mb	570kb	3.2Mb	3.35Mb
Gender	Female	Male	Male	Male	Female	Female
Age at the time of assessment (years)	8	6	32	16	4.5	4
IUGR	+	—	—	NM	+	+
Postnatal growth retardation	—	+	+	—	+	+
Feeding problems	+	+	+	NM	—	+
Microcephaly	+	+	+	—	+	+
Short Forehead	+	+	+	—	—	+
Prosis	+	+	+	—	+	+
Telecanthus	+	+	+	+	+	+
Short palpebral fissures	+	+	+	NM	+	+
Long eyelashes	+	+	+	NM	—	+
Vision abnormalities	Strabismus, optic nerve hypoplasia	Hyperopia, optic nerve hypoplasia	Optic nerve atrophy	NM	Optic nerve atrophy	Mild hypermetropia
High palate	+	+	+	+	—	+
Large ears	+	+	—	+	—	+
Deafness	—	+	—	—	—	—
Broad and high nasal root	+	+	+	+	+/-	+
Thoracic abnormalities	↑ inter nipple distance	↑ inter nipple distance	↑ inter nipple distance	Pectus excavatum	—	↑ inter nipple distance
Hand Camptodactyly	3–5 th bilaterally	5 th bilaterally	—	—	—	2–5 th bilaterally
Metatarsus abductus	+	+	—	—	*	+
Moderate intellectual disability	+	+	+	+	+	+
Delayed language skills	Severe	Severe	+	Mild	+	Severe
Autistic behavior	+	+	—	—	+	—
Urogenital abnormalities	Left multicystic kidney, hydronephrosis	Left hydronephrosis micropenis	Dystrophic kidney	Small testis, bilateral inguinal hernia	—	—
Cardiac anomalies	NM	NM	NM	+	—	—

Clinical features	Rajcan-Separovic et al., [2007]		De Leeuw et al., [2008]	Chabchoub et al., [2008]	Liang et al., [2009]	Present report
	Subject 1	Subject 2				
Respiratory anomalies	Frequent upper respiratory infection	Laryngomalacia, obstructive sleep apnea	–	NM	–	–
Abnormal EEG	–	+	NM	NM	–	+
Cortical dysplasia	+	+	NM	–	–	–

+ present, – absent, NM not mentioned,
* metatarsus adductovarus