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SHORT COMMUNICATION

16p13.11 duplication is a risk factor for a wide spectrum of neuropsychiatric disorders

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The chromosome 16p13.11 heterozygous deletion is associated with a diverse array of neuropsychiatric disorders including intellectual disabilities, autism, schizophrenia, epilepsy and attention-deficit hyperactivity disorder. However the clinical significance of its reciprocal duplication is not clearly defined yet. We evaluated 1645 consecutive pediatric patients with various developmental disorders by high-resolution microarray-based comparative genomic hybridization and identified four deletions and eight duplications within the 16p13.11 region, representing ~0.73% (12/1645) of the patients analyzed. Recurrent clinical features in these patients include mental retardation/intellectual disability, autism, seizure, dysmorphic feature or multiple congenital anomalies. Our data expand the spectrum of the clinical findings in patients with these genomic abnormalities and provide further support for the pathogenic involvement of this duplication in patients who carry them.
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Approximately 5% of the human genome consists of low copy repeats (LCRs), which are defined as continuous portions of DNA that map to two or more genomic locations with >90% sequence identity and >1 kb in size.[1] LCR-mediated non-allelic homologous recombination is one of the major underlying mechanisms leading to the occurrence of recurrent microdeletion/duplication syndromes.[2] Chromosome 16 is especially rich in intrachromosomal LCRs. Over 10% of the euchromatic region of the short arm of chromosome 16 (16p) is composed of highly complex LCRs.[3] Several distinct genomic disorders on 16p caused by LCR-mediated non-allelic homologous recombination mechanism have been described.[4–9] One of them is the 16p13.11 microdeletion syndrome characterized by developmental delay/intellectual disabilities (DD/ID) with or without multiple congenital abnormalities.[6–8,10,11] Although 16p13.11 microduplication was initially considered to be a rare benign variant,[6] accumulated evidence indicates that this duplication is enriched in patients with autism,[8] unexplained ID,[10] schizophrenia,[12] epilepsy,[13] and attention-deficit hyperactivity disorder.[14]

Since 2008, we have evaluated 1645 consecutive pediatric patients by microarray-based comparative genomic hybridization (aCGH) technique using the Agilent Human Genome Microarray Kit 244K platform according to the described protocol.[15] Referral justification for the aCGH testing included one or more of the following conditions in these patients: DD, autism, seizure, dysmorphic features or multiple congenital anomalies. The study protocol was approved by the institutional review board of the Children's Mercy Hospitals and Clinics. Of the 1645 pediatric patients, we identified 12 patients carrying genomic imbalances including four deletions and eight duplications on 16p12.3–p13.11 between 14.69 and 18.21 Mb (Human Genome Build 36) (Table 1), representing ~0.73% of the patients analyzed. The imbalanced 16p13.11 region could be subdivided into three intervals (I, II, and III) and each interval is flanked by sequences rich in LCRs with 99% sequence homology[12] (Figure 1). Of the 12 deletions/duplications, three deletions and five duplications contain intervals I and II with distal breakpoints at 14.69–15.03 Mb and proximal breakpoints at 16.20–16.43 Mb. One deletion and one duplication contain interval II with distal breakpoint at 15.40 Mb and proximal breakpoint at 16.20 Mb. The remaining two duplications contain intervals I and II with distal breakpoint at 15.40 Mb and proximal breakpoints at 18.07–18.21 Mb. There were no other genomic abnormalities with clinical relevance in these patients. The genomic imbalances on 16p12.3–p13.11 in these patients were confirmed by quantitative real-time PCR technique targeting to the *MYH11* and *NDE1* genes within 16p13.11 region based on the procedures published before[16] (data not shown). The quantitative PCR method was also carried out for available parental follow-up studies.

The four patients with the 16p deletion in this study have similar clinical pattern as described before.[6–8,10,11] Recurrent features in the four patients include DD (4/4), epilepsy (3/4) and autism spectrum

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Table 1 Chromosome 16p13.11 deletion/duplication in patients in this study

Case	*Result*	*Start (Mb)*	*Stop (Mb)*	*Interval*	*Size (Mb)*	*Inheritance*	*Dup/ Del*	*Development*	*Neurology*	*Behavior*	*Congenital anomalies and/or dysmorphism and comments*
1	16p13.11×3	14.88	16.43	I+II	1.56	Maternally inherited	Dup	—	—	ASD	Hypoplastic left heart syndrome, mother with cognitive delay and CHD
2	16p13.11×3	14.96	16.22	I+II	1.26	Maternally inherited	Dup	DD	Microcephaly	—	CHD, femoral hypoplasia and vertebral anomalies with scoliosis
3	16p13.11×3	15.02	16.43	I+II	1.41	Unavailable	Dup	—	Generalized epilepsy	—	—
4	16p13.11x3	15.03	16.20	I+II	1.17	*de novo*	Dup	—	—	ASD, ADHD, anxiety disorder	—
5	16p13.11×3	15.03	16.43	I+II	1.40	Maternally inherited	Dup	—	Abnormal MRI of brain	ASD, ADHD	—
6	16p13.11×3	15.40	16.20	II	0.79	Maternally inherited	Dup	Global DD, Failure to thrive	No septum pellucidum and delayed sulcation	—	Severe dysmorphism including upslanting eyes, flat nasal bridge, retrognathia and MCA involving heart, kidney, bone. A diabetic mother with mild dysmorphism
7	16p13.11p12.3×3	15.40	18.21	II+III	2.82	Unavailable	Dup	Learning disability	Generalized epilepsy	—	—
8	16p13.11p12.3×3	15.40	18.07	II+III	2.67	Unavailable	Dup	Global DD	Macrocephaly	ASD	—
9	16p13.12p13.11×1	14.69	16.20	I+II	1.51	Unavailable	Del	Global DD	Generalized epilepsy	—	Craniofacial dysmorphism including, frontal bossing and flat midface and MCA involving heart, kidney, bone, fingers and toes, and teeth.
10	16p13.11×1	14.82	16.20	I+II	1.38	Unavailable	Del	Global DD	Microcephaly, epilepsy and static encephalopathy	ASD, aggressive behavior	Small stature
11	16p13.11×1	14.96	16.20	I+II	1.24	Unavailable	Del	Severe cognitive disability	—	ASD	Strabismus
12	16p13.11×1	15.40	16.20	II	0.80	Paternally inherited	Del	Global DD, particularly in language and cognition, hypotonia	Epilepsy	—	Father has a history of seizure, cognitive and speech delay, macrocephaly, tall stature and mild dysmorphic features. Mother has epilepsy, sleep apnea and DD

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CHD, congenital heart defect; DD, developmental delay; del, deletion; dup, duplication; MCA, multiple congenital anomalies; MRI, magnetic resonance imaging.

disorder (2/4). Some isolated findings were also observed, such as, microcephaly, small stature and strabismus. Parental DNA samples were not available to determine the inheritance of the 16p13.11 deletion for patients 9, 10 and 11 whereas the deletion in patient 12 was paternally inherited. Interestingly both parents of the affected child have a history of seizure, DD, and other neurodevelopmental problems. In addition to global DD and epilepsy, one child (patient 9) has craniofacial dysmorphia and multiple congenital anomalies involving heart, kidney, bone, teeth, fingers and toes. We are not sure whether the ~1.51 Mb 16p13.11 deletion is the underlying cause of the complex anomalies in this child.

The clinical features in the eight patients with 16p13.11 duplication include DD (4/8), autism spectrum disorder (4/8), attention deficit hyperactivity disorder (2/8), epilepsy (2/8), abnormal MRI of brain (2/8), microcephaly (1/8), macrocephaly (1/8) and congenital heart defect (2/8). Although parental DNA samples for patients 3, 7 and 8 were not available for testing, the duplication in patients 1, 2, 5, and 6 were confirmed to be maternally inherited and the duplication in patient 4 occurred *de novo*. The mother for patient 1 has cognitive delay and congenital heart defect, but the other three mothers who carried the duplication were reported to be healthy although their complete health information was not available. It is worth mentioning that patient 6 has severe dysmorphism and multiple congenital anomalies involving heart, kidney and bone whereas her mother did not show visible clinical concerns.

Based on other reports and our data it is reasonable to believe that the 16p13.11 duplication with variable breakpoints is a risk factor for a wide spectrum of neurodevelopmental disorders and possibly other clinical features. There are several facts that support the conclusion. (1) This duplication was independently reported to be associated with a variety of neuropsychiatric problems, such as intellectual disability, autism, schizophrenia, epilepsy and attention-deficit hyperactivity disorder.[8,10,12–14]. Apparently the major clinical features in the eight patients with 16p13.11 duplication in this study are consistent with the clinical findings described in the literatures. (2) The 16p13.11 duplication in patient 4 occurred *de novo*, providing additional

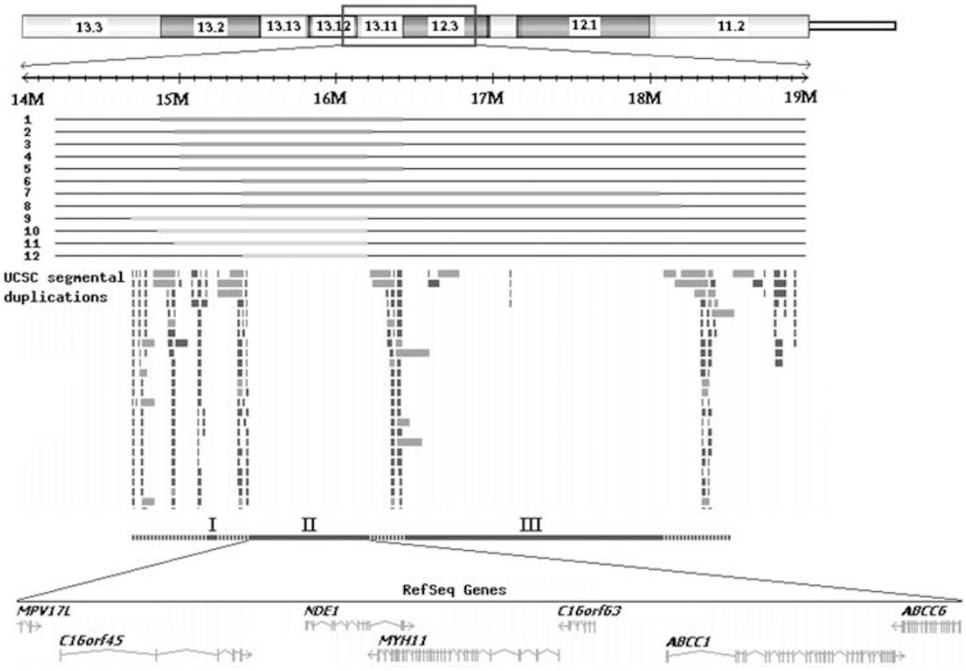

Figure 1 Genomic overview of the recurrent deletions (patients 9–12)/duplications (patients 1–8) within 16p13.11 region. The ~3.5 Mb region between 14.69 and 18.21 Mb contains three intervals (I, II and III), and each interval is flanked by low copy repeats, or called segmental duplication shown at the bottom. The seven annotated genes and transcripts (*MPV17L, C16orf45, NDE1, MYH11, C16orf63, ABCC1* and *ABCC6)* with the interval II were depicted at the bottom. A full color version of this figure is available at the *Journal of Human Genetics* journal online.

support about its pathological relevance to autism, attention deficit hyperactivity disorder and anxiety disorder in the patient. (3) The 0.49% (8/1645) detection rate of 16p13.11 duplication in this cohort is significantly higher than that in several recently reported control groups ($P>0.0001$), such as, the 0.09% (31/35 079) in Ingason's report,[12] the 0.08% (1/1156) in Williams' report[14] and 0.00% (0/2493) in Itsara's report.[17] This 0.49% (8/1645) detection rate in our study is also higher than other control groups, although in a less significance statistically, such as the 0.25% (5/2000) in Hannes's report,[6] the 0.21% (6/2792) in Kirov's report,[18] and the 0.22% (7/3181) in a report by the International Schizophrenia Consortium.[19]

Non-allelic homologous recombination mediated by LCRs flanking the three intervals within 16p13.11 is likely to be the underlying mechanism leading to the formation of the reciprocal microdeletions/microduplications as identified in our study and others.[3–9] The ~0.8 Mb of interval II with distal breakpoint at 15.40 Mb and proximal breakpoint at 16.20 was shared by all affected individuals carrying 16p13.11 duplication. There are seven annotated genes and transcripts within this region including *MPV17L, C16orf45, NDE1, MYH11, C16orf63, ABCC1* and *ABCC6.* Of them, *NDE1* is likely to be the candidate gene responsible for the neurological and behavioral phenotypes observed in patients with the deletion and duplication of this region. This gene encodes a member of the nuclear distribution E (NudE) family of proteins having an essential role in microtubule organization, mitosis and neuronal migration.[20] The *Nde1*-null mice showed small-brain phenotype with the cerebral cortex being affected the most.[21] The interaction of Nde1 with Lis1 seems to be essential for the development of mouse central nervous system.[22] No mutation in *NDE1* was identified in the retained homologous allele in patients carrying 16p13.11 heterozygous deletions, suggesting that haploinsufficiency of this gene could be the underlying genetic mechanism leading to the abnormal clinical features in these patients who carry the deletion.[6] However, the clinical significance of the three copies of *NDE1* gene remains unknown at this point.

In summary, we identified 12 patients carrying genomic imbalances within 16p12.3p13.11 region, representing ~0.73% of the patients analyzed. Our data expanded the spectrum of the clinical findings in patients with these genomic abnormalities. The 0.49% (8/1645) detection rate of 16p13.11 duplication in this cohort is significantly higher than that in several control groups, providing further support for the pathogenic involvement of this duplication.

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