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A 7q21.11 microdeletion presenting with apparent intellectual disability without epilepsy

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To the Editor,

Chromosome deletions at 7q21.11 are rare, with few patients reported in the literature [Vergult et al 2015; Mazzaschi et al, 2013; Mefford et al, 2011]. Vergult et al [2015] reported three children with heterogenous 7q21 deletions who presented with epilepsy and apparent intellectual disability. One of these patients had a translocation, the break points of which were said to disrupt the CACNA2D1 gene. This suggested that CACNA2D1 is the likely candidate gene for the observed clinical features. Mazzaschi et al [2013] described a boy with apparent intellectual disability without epilepsy with a 7q21.11 deletion. Mefford et al [2011] reported a 3.9 Mb and 8.2 Mb deletion associated with epilepsy and intellectual disability. Here we report a further patient with the 7q21.11 deletion. We also examined exome sequencing data from the Deciphering Developmental Disorders (DDD) project [Wight et al, 2015] in an attempt to identify pathogenic single nucleotide variants (SNVs) in genes from the 7q21.11 deletion region in 4,293 children with developmental disorders. This is based on the hypothesis that deletion regions can be used to identify candidate genes for developmental disorders [Hempel et al, 2016].

The proband was a six year old male who presented with autistic behavior and learning difficulties. He was the second child of healthy, non-consanguineous parents. He was born at 37 weeks of gestation after an uncomplicated pregnancy. There were no neonatal complications. He had a history of global developmental delay. He first walked at 24 months of age. At the age of six years he could run but not use a tricycle. He first started to scribble at five years of age and could only use a spoon with difficulty by the age of six years. At the age of six years he did not have recognizable words. He
attended a special educational needs school. He had no neurological symptoms of note and there was no history of seizures. On examination his OFC was 52 cm (60th centile), height 107.5 cm (9th centile), and weight 16.35 kg (2nd centile). He was non-dysmorphic. His hands and feet were normal. Cardiovascular, respiratory and neurological examination were normal. Magnetic resonance imaging of the brain was normal. The following tests were normal or negative: Fragile X, full blood count, liver function test, and urine and blood metabolic screens (glycosaminoglycans and organic and amino acids). Written consent was obtained from the parents to give permission for publication of this report. This data in this report were considered to be part of routine clinical care and research approval was not required.

Comparative genomic hybridization (OGT 60K v2.0 ISCA oligo array) demonstrated a 3.3 Mb deletion at 7q21.11 which included seven protein-coding genes. The breakpoints were reported as 7q21.1(79,622,282-82,919,619). Figure 1 illustrates the deletion in comparison to the previously reported patients. Neither parent had the deletion. No similar deletions were found in the recently published copy number variant (CNV) map of the human genome [Zarrei et al, 2015], which integrates CNV data from healthy individuals from multiple data sets such as the database of genomic variants.

Trio exome sequencing data from 4,293 children in the DDD study was examined for plausible pathogenic SNVs in the seven protein coding genes found within the 7q21.11 deletion region. The methods of the DDD study have been described [Wight et al, 2015]. We could not identify any plausible pathogenic SNVs in any of these seven protein coding genes in children without a genomic diagnosis. We defined plausible pathogenic SNVs as being de novo, having a minor allele frequency of <0.5% in the
Exome Aggregation Consortium database, and being predicted to be damaging by Polyphen or SIFT for missense variants or being predicted to be truncating (frameshift, nonsense).

Here we report a further patient with a 7q21.11 deletion, demonstrating that this deletion can present with apparent intellectual disability without epilepsy. We cannot exclude that the individual described here will develop epilepsy in the future, but the previously reported patients presented with epilepsy before the age of five years. The individual we describe was non-dysmorphic. However, two of the patients described by Vergult et al [2015] had facial dysmorphism, thus there may not be a consistent facial phenotype. Given the limited number of patients it is not possible to provide a definitive phenotypic description of the spectrum of clinical features associated with 7q21.11 deletion. However, apparent intellectual disability was consistent across all reported patients. This deletion should be considered in the differential diagnosis of individuals presenting with both syndromic and non-syndromic intellectual disability.

The mechanism by which 7q21.11 deletions cause epilepsy and apparent intellectual disability is unclear. The smallest region of overlap between the published cases and the case described here contains three genes (HGF, CACNA2D1 and PCLO), implicating them in the pathogenesis. Haploinsufficiency for one of these genes could underlie the patients’ phenotype. In an attempt to identify a single candidate gene for the 7q21.11 deletion syndrome we examined trio exome sequencing data from 4,293 children with undiagnosed developmental disorders in the DDD study. We could not identify any plausible pathogenic SNVs in the seven protein coding genes contained within the 7q21.11 deletion region in our case. This is consistent with Mefford et al...
who did not identify any CACNA2D1 pathogenic SNVs in a series of 94 patients with epilepsy. This suggests that haploinsufficiency for a single protein coding gene from the 7q21.11 region may not be responsible for the phenotype.

As an alternative, it is possible that haploinsufficiency for a combination of protein coding genes results in the 7q21.11 deletion phenotype and it may be a true contiguous gene syndrome. From the genes found within the smallest region of overlap, only CACNA2D1 and PCLO are expressed within the brain (data from gtex). The PCLO gene encodes a pre-synaptic protein which plays a role in regulating neurotransmitter release. Homozygous mutations in PCLO are associated with pontocerebellar hypoplasia type three [Maas et al, 2012]. Evidence from animal models suggests that PCLO plays a role in the formation and transport of pre-synaptic vesicles to the pre-synaptic membrane [Geisler et al, 2015]. The CACNA2D1 gene encodes the alpha2delta1 subunit of the neuronal voltage gated calcium channel [Geisler et al, 2015]. Neuronal calcium channels are found in both pre- and post-synaptic neuronal membranes and play a key role in synaptic signaling [Geisler et al, 2015]. It is possible that haploinsufficiency for both PCLO and CACNA2D1 might disrupt synaptic signaling and thus result in intellectual disability with or without epilepsy.

In conclusion, we report an additional patient with the 7q21.11 deletion syndrome and provide evidence that haploinsufficiency for a single gene may not be the disease mechanism. In vitro studies of the interaction between PCLO and CACNA2D1 will be required to examine the hypothesis that combined haploinsufficiency for these two synaptic proteins results in neuronal dysfunction.

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INTERNET RESOURCES

GTEX: http://www.gtexportal.org/home/
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FIGURE LEGENDS

Figure 1. Reported deletions at 7q21.11. Black horizontal bars represent deletions at 7q21.11. The vertical dashed lines indicate the smallest region of overlap. This contains the HGF, CACNA2D1, and PCLO genes. Only CACNA2D1 and PCLO are expressed in the brain. The deletion labelled Vergult P2 extends into 7q21.12 to include the GRM3 gene. The deletion labeled Mefford P2 extends to 7q11.23 to include the TRIM74 and MAGI2 genes.