
Article:
Siddique, A., Willoughby, J. and McNeill, A. (2017) A 7q21.11 microdeletion presenting with apparent intellectual disability without epilepsy. American Journal of Medical Genetics Part A, 173 (4). pp. 1128-1130. ISSN 1552-4825

https://doi.org/10.1002/ajmg.a.38136

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

Azeem Siddique(1), Josh Willoughby(2), DDD Study, Alisdair McNeill (1,2).

1. Sheffield Institute for Translational Neuroscience, 385a Glossop Road, Sheffield. S10 2HQ.
2. Sheffield Diagnostic Genetics Service, Sheffield Childrens Hospital NHS Foundation Trust, Western Bank, Sheffield.

Corresponding Author:

Dr Alisdair McNeill MRCP (UK) PhD DCH

Senior Research Fellow & Honorary Consultant in Clinical Genetics.

Sheffield Institute for Translational Neuroscience, 385a Glossop Road, Sheffield. South Yorkshire. United Kingdom. S10 2HQ.

a.mcneill@sheffield.ac.uk

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*

[2011[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.

ACKNOWLEDGEMENTS

The DDD study presents independent research commissioned by the Health Innovation Challenge Fund [grant number HICF-1009-003] see Nature 2015;519:223-8 or www.ddduk.org/access.html for full acknowledgement.

INTERNET RESOURCES

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

REFERENCES

Ahmed MY, Chioza BA, Rajab A, Schmitz-Abe K. *I*, Al-Khayat A, Al-Turki S, Baple EL, Patton MA, Al-Memar AY, Hurles ME, Partlow JN, Hills RS, Evrony GD, Servattalab S, Markianos K, Walsh CA, Crosby AH, Mochida GH. 2015. Loss of PCLO function underlies pontocerebellar hypoplasia type 3. Neurology 84: 1745-1750.

Geisler S, Schopf CL, Obermair GJ. 2015. Emerging evidence for specific neuronal functions of auxiliary calcium channel alpha2delta subunits. Gen Physiol Biophys 34: 105-118.

Hempel A, Pagnamenta AT, Blyth M, Mansour S, McConnell V, Kou I, Ikegawa S, Tsurusaki Y, Matsumoto N, Lo-Castro A, Plessis G, Albrecht B, Battaglia A, Taylor JC, Howard MF, Keays D, Sohal AS, DDD Collaboration, Kuhl SJ, Kini U, McNeill A. 2016. Deletions and de novo mutations of SOX11 are associated with neurodevelopmental disorders with features of Coffin-Siris syndrome. J Med Genet 53: 152-162.

Maas C, Torres VI, Leal-Oritz S, Wagh D, Terry-Lorenzo RT, Fejtova A, Gundelfinger ED, Ziv NE, Garner CC. 2012. Formation of Golgi-derived active zone precursor vesicles. J Neurosci 32: 11095-11108.

Mazzaschi RL, Ashton F, Aftimos S, George AM, Love DR. 2013. Implications of a Chr7q21.11 microdeletion and the role of the PCLO gene in developmental delay. Sultan Qaboos Univ Med J 13: 306-310.

Mefford HC, Yendle SC, Hsu C, Cook J, Geraghty E, McMahon JM, Eeg-Olofsson O, Sadleir LG, Gill D, Ben-Zeev B, Lerman-Sagie T, Mackay M, Freeman JL,

Andermann E, Pelakanos JT, Andrews I, Wallace G, Eichler EE, Berkovic SF, Scheffer IE. 2011. Rare copy number variants are an important cause of epileptic encephalopathies. Ann Neurol 70: 974-985.

Vergult S, Dheedene A, Meurs A, Faes F, Isidor B, Janssens S, Gautier A, Le Caignec C, Menten B. 2015. Genomic aberrations of the CACNA2D1 gene in three patients with epilepsy and intellectual disability. Eur J Hum Genet 23: 628 – 632.

Wight CF, Fitzgerald TW, Jones WD, Clayton S, McRae JF, van Kogelenberg M, King DA, Ambridge K, Barrett DM, Bayzetinova T, Bevan AP, Bragin E, Chatzimichali EA, Gribble S, Jones P, Krishnappa N, Mason LE, Miller R, Morley KI, Parthiban V, Prigmore E, Rajan D, Sifrim A, Swaminathan GJ, Tivey AR, Middleton A, Parker M, Carter NP, Barrett JC, Hurles ME, FitzPatrick DR, Firth HV; DDD stud *l*. 2015. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. Lancet 385: 1305 – 1314.

Zarrei M, MacDonald JR, Merico D, Scherer SW. 2015. A copy number variation map of the human genome. Nat Rev Genet 16:172–83.

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.