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14q32.11 microdeletion including CALM1, TTC7B, PSMC1, and RPS6KA5: a new potential cause of developmental and language delay in three unrelated patients

Running Title: 14q32.11 microdeletion

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We present three unrelated patients with similar microdeletions of chromosome 14q32.11 with shared phenotypes including language and developmental delay, and four overlapping genes -CALM1, TTC7B, PSMC1, and RPS6KA5. All four genes are expressed in the brain and have haploinsufficiency scores, which reflect low tolerance to loss of function variation. We provide insight on the genes in the overlapping region, which may influence the resulting phenotype. Given the three patients’ similar phenotypes and lack of normal variation in this region, we suggest this microdeletion may be associated with developmental and language delay.

KEYWORDS
Microdeletion 14q32.11; developmental delay; speech delay; CALM1, TTC7B, PSMC1, RPS6KA5

1. INTRODUCTION

Rare chromosomal copy number variants (CNVs) are the cause of many congenital syndromes to date (Sagoo et al., 2009); however, without previous reports or known dosage-sensitive genes in the region, it may be difficult to determine the pathogenicity (C. Lee, Iafrate, & Brothman, 2007). We report three patients with a rare microdeletion on 14q32.11 found by chromosomal microarray and discuss the genes in the smallest region of overlap that may lead to the shared phenotypes, including developmental delay and speech and language delay. Two of the three patients exhibit sleep irregularities.

2. CLINICAL REPORTS

2.1 Patient 1

A 4-year-old Caucasian male presented to the genetics clinic with concern for expressive language delay. He was born at 38 weeks gestation to a G10P5 37-year-old mother and 22-year-
old father. Pregnancy history included heroin and tobacco use throughout pregnancy and at
delivery, mother tested positive for heroin. He was approximately 6 pounds at birth and passed
the newborn hearing screen. He was placed in the care of his maternal aunt. His developmental
motor history is relatively unknown except for walking at 12 months. His first words were at 2.5
years after starting therapies (physical, occupational and speech). He had oral motor delay with
difficulty eating and profusely drooling. He exhibited overall left-sided weakness and appeared
to skip rather than run. Neurologist ordered brain MRI without contrast, which was reported to
be within normal limits. There was no etiology identified for the left-sided weakness. His
behavioral issues included repetitive hitting of animals. His guardian noted his irregular sleep
patterns and sweating profusely during sleep. No sleep studies were reported in the limited
notes available. His appearance is not overtly dysmorphic with the only abnormalities being
retrognathia, narrow, small nose, doughy hands with tapered fingers, posteriorly rotated ears,
and wide-spaced nipples. He exhibits a leg length discrepancy; however, X-rays were normal.
Currently at 6 years of age, his speech significantly improved, and he is now doing well
academically with noted improvements in speech, language, and motor. He does not take any
medications. Following the report of the microdeletion (see Discussion), a cardiologist ordered
several EKGs, and Holter monitoring. All cardiac results were normal.

The proband is the only child to his parental union. His mother has a history of mental
illness and has four other children with two other partners. The proband’s maternal half-
sibling(s) are reported to have depression and drug abuse. Multiple maternal aunts have
depression. The proband’s father had a history of substance addiction and was reported to have
died from sepsis at age 25. The proband has one paternal half-sibling who is in the care of his
paternal grandmother. Paternal family history is unknown. The maternal aunt reported no other
pertinent family history including developmental and/or language delay or sleep disturbances.
2.2 Patient 2

A 3-year-old male Caucasian presented to the genetics clinic with autism, severe sleep disturbance, mild intellectual disability, social developmental delay, emotional developmental delay, hypersensitivity and delayed speech and language development. Gross motor development was within normal range. He was born at full term to a 28-year-old mom and a 34-year-old father, both healthy. There were no complications during pregnancy. No dysmorphic features were noticed. His mother had a postpartum depression that was treated. The home is bilingual and in the first years both languages were spoken at home. At age 5, his speech was as of a 3-year-old boy.

Currently he is 9-years-old and in a special school for children with autism. His language has improved, and he is good at math. He still has sleep disturbances and wakes up every night for several hours. The family is struggling to change his sleeping behavior and reports that no definitive reasons for his sleep disturbances has been found. The family has tried melatonin and Circadian treatment with no effect. There is no family history of developmental delay or sleep disturbances.

He is listed on the DECIPHER database (Firth et al., 2009), as patient ID# 270294.

2.3 Patient 3 and mother.

The 6-year-old boy is the only child of a non-consanguineous couple. He was born at term with normal measurements. He had feeding difficulties during the first years of life with good evolution. He had normal global motor development, walking at 13 months but had moderate speech delay, speaking his first words at 2 years of age, with good evolution. He was
described as a bit anxious, with attention disorder, few stereotypic features, but no sleep disorder. He has coarse facies with epicanthus. At 6 ½ years, he is healthy with normal measurements. He needs help at school because of hyperactivity with attention disorder, but he has adequate conversational abilities. He has adequate reading abilities but has difficulties writing. Cardiac evaluation was normal.

The mother is an only child. She carries the same deletion as her son, which was identified during inheritance follow-up studies using fluorescent in situ hybridization (FISH). She had mild learning difficulties, had no sleep disorder, and no behavioral issues. A cardiac evaluation of the mother was normal. She has normal cognitive function, and she is now able to find a steady employment. There is no other history of learning difficulties in the family.

He is listed on the DECIPHER database (Firth et al., 2009), as patient ID# 379359.

3. METHODS

3.1 Ethical considerations

Written informed consent was obtained from the patients’ families.

3.2 Chromosome Microarray Analysis (CMA)

Whole-genome CMA was performed to assess for genomic gains or losses using the Affymetrix Cytoscan HD platform (patient 1), the Illumina CytoSNP-12 v.2.1 platform (patient 2), and the Cytogenomics 3.0.6.6 platform using an Agilent 60K array (patient 3). Genomic coordinates were based upon genome build 37/hg19 (UCSC Genome Browser, http://genome.ucsc.edu/cgi-bin/hgGateway, hg19, February 2009).

4. RESULTS

4.1 Patient 1
Chromosomal microarray analysis shows a male with a copy number loss of the chromosome 14q32.11q32.12 region of approximately 1.989 Mb (megabases) in size (arr[GRCh37] 14q32.11q32.12(90327503_92316026)x1). The deleted genes in this region include EFCAB11, TDP1, KCNK13, PSMC1, NRDE2, CALM1, TTC7B, RPS6KA5, SNORA11B, C14orf159, GPR68, CCDC88C, SMEK1, CATSPERB, and TC2N. The microdeletion was confirmed to not have been inherited maternally, and the father’s sample was not available for testing. No further genetic testing was ordered.

4.2 Patient 2

Chromosomal microarray analysis shows a male with a de novo 1.05 Mb copy number loss involving chromosomal region 14q32.11 (arr[GRCh37] 14q32.11(90381587_91432118)x1 dn). The genes in this region include EFCAB11, TDP1, KCNK13, PSMC1, NRDE2, CALM1, TTC7B, and RPS6KA5. No further genetic testing was ordered.

4.3 Patient 3

Chromosomal microarray analysis shows a male with maternally-inherited 2.17 Mb copy number loss involving chromosomal region 14q32.11q32.12 (arr[GRCh37] 14q32.11(90544390_92709536)x1 mat). The genes in this region include KCNK13, PSMC1, NRDE2, CALM1, TTC7B, RPS6KA5, SNORA11B, C14orf159, GPR68, CCDC88C, SMEK1, CATSPERB, TC2N, FBLN5, TRIP11, ATXN3, NDUFB1, and CPSF2. Fragile-X syndrome was ruled out. No further genetic testing was ordered. Mother of patient 3 was tested by FISH using the probe RP11-552G22. No further genetic testing was ordered.

5. DISCUSSION
We report three unrelated patients and one mother with developmental and speech/language delays. Of note, the mother of patient 3 was tested using FISH, therefore the inheritance of the deletion is suggested; however, the exact deletion is not confirmed. Two of the four patients have sleep disturbances, and three have behavioral issues. Loss of this 14q32.11 region has not been associated with a syndrome to date, and there is no overlap with rare/benign copy number loss in the databases of genomic variants (Lappalainen et al., 2013), or in gnomAD structural variation (Collins et al., 2020). In addition, multiple US clinical laboratories were contacted, and no other patients with similar deletions were reported in their databases (as of 10/24/20). The smallest region of overlap (chr14: 90544390-91432118) contains six RefSeq genes: KCNK13, PSMC1, NRDE2, CALM1, TTC7B, and RPS6KA5 (Figure 1). CALM1, PSMC1, RPS6KA5 and TTC7B have low observed/expected (o/e) ratios (ranging from 0 to 0.11) suggestive of a gene that is intolerant to loss of function variants (Karczewski et al., 2020; Samocha et al., 2014) and low haploinsufficiency (HI) scores (ranging from 0.15 to 37.33) (0-10% indicates haploinsufficiency is likely, while 90-100% indicates that haploinsufficiency is unlikely) (Huang, Lee, Marcotte, & Hurles, 2010) suggesting deletions of these genes may have consequences on the phenotype. These scores allow for modelling the consequences of gene disruption by utilizing the normal variation in the population and known haploinsufficient genes. O/e ratio takes into account the size of the gene and determines the number of expected (e) loss of function variants in a gene, the observed (o) is the actual number of truncating variants, thus a very low o/e ratio suggests intolerance to loss of function. However, o/e ratio does not address deletions spanning the gene, only single nucleotide variants (SNVs) in the canonical transcript. The HI score accounts for genic deletions or deletions in the start codon, splicing sites, or resulting in a frameshift.

Calmodulin 1 (CALM1 MIM# 114180) functions in growth and the cell cycle, signal transduction, and synthesis and release of neurotransmitters. CALM1 is highly expressed in brain tissue (GTEx).
One intronic deletion (172 bp) has been reported in a single allele gnomAD structural variant database (DEL_14_144786), and no deletions have been reported in the gold standard DGV. Heterozygous missense variants in the calmodulin family (CALM1-3) have been associated with Long QT syndrome 14 (MIM# 616247), catecholaminergic polymorphic ventricular tachycardia (CPVT), or idiopathic ventricular fibrillation (IVF). Most pathogenic variants in CALM1 reside in the EF-hand Ca2+ binding loop III and IV, affecting the residues involved in Ca2+ binding affinity (Crotti et al., 2019). Patients 1 and 3 have been and/or is presently monitored for a cardiac phenotype, which all results have been normal to date. While a deletion of this gene may not result in the same phenotype as reported for pathogenic variants, CALM1 deletion may result in sleep irregularities. Melatonin inhibits calcium binding to calmodulin, which may allow the hormone to modulate rhythmically cellular functions (Benítez-King & Antón-Tay, 1993; de Almeida-Paula et al., 2005) possibly resulting in a sleep phenotype as that seen in patients with variation in two melatonin pathway genes, acetylserotonin O-methyltransferase (ASMT) and cytochrome P450 1A2 (CYP1A2) (Veatch et al., 2015).

Patient 3 and his mother have not reported any sleep disturbances suggesting that if this microdeletion leads to sleep irregularities, the causative region may either exhibit variable penetrance or may lie in the smallest region of overlap of patients 1 and 2 and not in the deleted region of patient 3 and mother. Interestingly, the only gene fitting the latter situation is Tyrosyl-DNA phosphodiesterase 1 (TDP1). TDP1 is involved in repair of chromosomal single-stranded repair breaks independent of DNA replication or oxidative stress and homozygous variants in this gene are associated with spinocerebellar ataxia with axonal neuropathy (El-Khamisy et al., 2005; Takashima et al., 2002). TDP1 has been reported with a higher gene expression pattern in cases of chronic fatigue syndrome/myalgic encephalomyelitis compared to controls; however, the study has notable weaknesses which the author acknowledges (Kerr, 2008; Kerr et al., 2008). The pLI is 0, o/e is 0.91
and the Haploinsufficiency Index is 48.95%, suggesting this gene is tolerant to loss of function. One partial deletion of this gene has been reported in gnomAD-SV (DEL_14_144764) and no deletions in DGV gold standard variants. Given this information, a heterozygous loss of this gene alone would be considered a variant of uncertain significance, possibly benign.

Tetratricopeptide repeat protein 7B (TTC7B) localizes phosphatidylinositol 4-kinase (PI4K) to the plasma membrane (Baskin et al., 2016; Nakatsu et al., 2012). *TTC7B* is highly expressed in the cerebellum/cerebral hemisphere (GTEx). No deletions have been reported in gnomAD structural variant database, and a single intronic deletion has been reported in the gold standard DGV. No variants in this gene have been associated to any human disorders to date; however, a homozygous knockout mouse (MGI:6189597) is described as lethal pre-weaning stage with complete penetrance (Dickinson et al., 2016).

Proteasome 26S subunit, ATPase 1 (PSMC1; MIM# 602706) is involved in the degradation of ubiquitinated proteins and has the highest expression in skeletal muscle tissue (GTEx). One intronic deletion (545 bp) has been reported in a single allele gnomAD structural variant database (DEL_14_144777), and no deletions have been reported in the gold standard DGV. Homozygous knockout mice are prenatal lethal (MGI:106054). Conditional mouse model displays 26S proteasome depletion and impairment of ubiquitin-mediated protein degradation resulting in neurodegeneration in the nigrostriatal pathway and forebrain regions (Bedford et al., 2008). While heterozygous knockout mouse brain had no observable differences from that of wild type, an age-related neuronal ubiquitin immunoreactivity, decreased PSMC1 protein expression, altered assembly of the 26S proteasome and an effect on cell cycle progression was observed (Rezvani et al., 2012).
Ribosomal protein S6 kinase 5 (RPS6KA5 MIM# 603607) belongs to the extracellular signal-regulated kinase family. RPS6KA5 is highly expressed in the cerebellum/cerebral hemisphere (GTEx). Multiple intronic deletions have been reported in the gnomAD structural variant database, and no deletions have been reported in the gold standard DGV. Studies utilizing cell lines (Deak, Clifton, Lucocq, & Alessi, 1998) and murine fibroblasts (Wiggin et al., 2002) demonstrated the ability of the MAPK cascade and the SAPK2/p38 pathways to activate RPS6KA5 (MSK1) and RPS6KA4 (MSK2). Subsequently, RPS6KA5 and RPS6KA4 phosphorylates CREB and ATF1 in response to mitogens and cellular stress. While no variants have been associated with human disorders to date, kinase-dead mouse models implicate this gene as a key regulator of both activity and experience-dependent synaptic adaptation (Corrêa et al., 2012). Knock-out mice have spontaneous age-dependent striatal atrophy (Martin et al., 2011).

Here we report three unrelated patients with developmental and speech/language delays and two with sleep disturbances suggestive of a genetic disorder possibly resulting from a heterozygous deletion of chromosome 14q32.11. However, none of the patients had undergone clinical exome sequencing, therefore, while the microdeletion 14q32.11 is rare, this CNV alone may in fact not be pathogenic. For patient 1, the use of heroin in the prenatal period may have influenced his early neurodevelopment delays (S. J. Lee, Bora, Austin, Westerman, & Henderson, 2020), which have seemingly resolved as he has aged. A fourth patient with a similar deletion is listed in the Decipher database (patient 366514); however, the clinical team did not respond to our request, therefore neither the state of pathogenicity nor the phenotypes can be confirmed. We provide background on the genes in the smallest region of overlap, which may influence the resulting phenotype. Interestingly, no loss of function variants (deletions or SNVs) have been reported in literature in the genes of interest and many are highly expressed in brain tissue, making this copy number variant difficult to analyze. Given the three patients’ phenotypes and lack of normal CNVs in this region, we
suggest this microdeletion may be associated with developmental and language delays, and identification of additional individuals harboring such deletion, whether affected or unaffected, might help delineate the pathogenicity, as well as, further elucidate its clinical spectrum.

Acknowledgements

We thank the families for participating. This study makes use of data generated by the DECIPHER community. A full list of centres who contributed to the generation of the data is available from https://decipher.sanger.ac.uk/about/stats and via email from decipher@sanger.ac.uk. Funding for the DECIPHER project was provided by Wellcome.

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WEB RESOURCES

HUGO Gene Nomenclature Committee (HGNC): http://www.genenames.org/

Online Mendelian Inheritance in Man (OMIM): http://www.omim.org/

UCSC Genome Browser: http://genome.ucsc.edu/

Genotype-Tissue Expression (GTEx) project (06/05/2020): https://gtexportal.org/home/

gnomAD: https://gnomad.broadinstitute.org/

Mouse Genome Informatics: http://www.informatics.jax.org/

International Mouse Phenotyping Consortium: https://www.mousephenotype.org

CONFLICTS OF INTEREST
All the authors have approved the manuscript and have no conflicts of interest to declare regarding this work.

AUTHOR CONTRIBUTIONS

CE coordinated recruitment of patients, wrote, and edited manuscript. FQR performed diagnostic interpretation of patient 1, edited manuscript, and supervised project. JG, DS, MN, JK, RS, and JAM provided clinical information on patients and edited manuscript.

REFERENCES


FIGURES

Figure 1: **Patient Results.** UCSC Genome browser view of Patients 1-3 with the smallest region of overlap (SRO) marked by red dotted box. The black genes have a corresponding entry in the Protein Data Bank (PDB) and dark blue genes have been reviewed or validated. The gene expression track highlights the relative expression detected in brain tissues (GTEX). Only the gold-standard variants from the database of genomic variation is shown (normal variation in the population).
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☑ accepte la publication anonyme des données cliniques et génétiques me concernant dans une revue scientifique.

☐ accepte la publication anonyme de photographies dans une revue scientifique, ce qui peut aider au diagnostic de cette maladie pour d'autres patients.

Je comprends que ces informations peuvent être accessibles par la population générale et par les chercheurs scientifiques qui utilisent ces publications dans le cadre de leur formation professionnelle. Je comprends qu'il est possible que l'on puisse indirectement me reconnaître même si aucune information d'identification n'est associée à mes données cliniques et génétiques anonymisées.

En signant ce document, je déclare avoir lu les informations ci-dessus et être pleinement informé(e) de la nature scientifique de cette publication.

Fait à St André Cade d'Aix le : 8/10/2023

Signature du médecin recueillant consentement

Signature de la personne