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1q21.1 Duplication syndrome and epilepsy

Case report and review

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Copy number variants (CNVs) of 1q21.1 are increasingly being recognized due to the widespread use of genetic screening tests for the investigation of developmental disorders and epilepsy. These include microdeletion and microduplication syndromes, associated with a wide variety of pathology including autism spectrum disorders, attention-deficit disorder, learning disabilities, hypotonia, facial dysmorphisms, and schizophrenia. The 1q21.1 region is considered to be genetically unstable because it contains one of the largest areas of identical duplication sequences in the human genome. Epilepsy has been reported in the literature, particularly in microdeletion syndromes, but rarely in association with microduplication syndromes. We report a patient with epilepsy and autism spectrum disorder due to a distal 1q21.1 microduplication and review the available literature and genetic information.

Case report

We present a 10-year-old girl with a low-functioning autism spectrum disorder and focal motor epilepsy. On examination, she has hypertelorism, minimal communicative language skills, and severe macrocephaly (HC = 57 cm, 3.6 SD > 99%). Seizures started at 7 years of age and consisted of head deviation to the left, generalized stiffening, clonic activity of the mouth, and fluttering of the eyelids, lasting for 1–2 minutes. Multiple video EEG recordings showed a right temporal focus with a less active, independent left temporal focus. 3T MRI scan of the brain was normal. Her seizure control was poor despite high doses of oxcarbazepine. She had multiple clusters of seizures after ingestion of large amounts of caffeine in the form of red velvet cookies. She was switched to lamotrigine and was placed on a caffeine-free diet. She has been seizure-free for nearly 1 year on this regimen. Chromosomal single nucleotide polymorphism Affymetrix CytoScan-HD microarray showed a distal 1q21.1-1q21.2 duplication (arr[hg19] 1q21.1q21.2[146,503,349–147,819,438] × 3), 1.3 Mb in size. None of the genes in this region are definitively known to cause neurologic disease, although this duplication is one of the more common CNVs associated with autism spectrum disorders and intellectual disability.[1]

Discussion

Our patient has many clinical features previously reported with 1q21.1 duplication syndrome, including autism with intellectual disability, hyperactivity and impulsivity, macrocephaly, hypertelorism, and hypotonia. Microduplications have also been reported in "normal" individuals, subsequently often found to have subtle features of the disorder.[2] Multiple authors have postulated that clinical expression of the disorder varies widely and that penetrance is incomplete. Duplications of this region have also been associated with a host of non-neurological congenital anomalies with no clear pattern of abnormalities.

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Table Review of published cases of 1q21.1 microduplication syndrome and epilepsy: Clinical, EEG, and genetic information

Author/patient no. (total no. of patients)	Type of epilepsy	Other neurologic features	Non-neurological clinical features	Inheritance	EEG results	MRI results	Locus on chr 1
Mefford/1 (11)	Not specified	ASD; LD	Hemivertebra; univentricular heart	Paternal, unaffected father	Not specified	Choroid plexus carcinoma	142,000,000–146,500,000 (locus for individual patients not specified)
Mefford/2[a] (11)	GEUE	MR	None	Paternal, unaffected father	Not specified	Not specified	
Mefford/3[a] (11)	GEUE	MR	None	Unknown	Not specified	Hypoplasia of corpus callosum and cerebellar vermis	
Rosenfeld/1 (16)	Not specified	Global DD; hemiplegia	Hypermobility	Paternal	Not specified	Right brain atrophy	144,100,000–144,500,000 (locus for individual patients not specified)
Rosenfeld/2 (16)	Not specified	Hypotonia; hearing loss; severe DD; microcephaly	Short stature; FTT; dysmorphic features; strabismus; idiopathic liver failure	Paternal	Not specified	Prominent extra-axial space, abnormal globus pallidus	
Brunetti/1 (23)	Not specified	Speech delay	None	Maternal	Not specified	Not specified	144,750,000–145,950,000
Brunetti/2 (23)	Not specified	Hypotonia	Cryptorchidism; dysmorphic features	Unknown, parents unaffected	Not specified	Not specified	
Du/1 (1)	1- IS	ID; mild DD	Not specified	De novo	Hypsarrhythmia	Delayed myelination, enlarged ventricles	145,764,453–147,824,207
Gourari/1 (1)	Focal epilepsy	ASD; macrocephaly	None	Unknown, Parents unaffected	Right temporal interictal epileptiform activity	Normal (3T MRI)	146,403,349–147,819,438
Bernier/1 (19)	0[b]	Not specified	Not specified	Not specified	Focal sharp waves	Not specified	146,577,487–147,394,506

Abbreviations: ASD = autism spectrum disorder; FTT = failure to thrive; DD = developmental delay; GEUE = generalized epilepsy of undetermined etiology; ID = intellectual disability; IS = infantile spasms; LD = learning disability; MR = magnetic resonance.
HYDIN2 gene locus: 146,547,489–146,822,034.
PRKAB2 gene locus: 147,155,106–147,172,544.
CHD1L gene locus: 147,242,684–147,295,762.
[a] Patients from Dutch studies in supplemental appendix of the Mefford article.
[b] No patients with clinical seizures, only epileptiform EEG.

Seizures have rarely been reported in published review articles of 1q21.1 microduplication syndromes (see table for details of reported cases). Numbers of affected patients were small in each study, and very little information was published about types of seizures, EEG findings, etc.

The UCSC Genome Browser lists 2 genes in this region of distal microduplication, which might contribute to epilepsy, *CHD1L* and *PRKAB2*. *CHD1L* encodes a helicase responsible for DNA repair, so far associated only with various cancers. However, it comes from the same family as *CHD2*, a gene associated with epileptic encephalopathies and a variety of generalized epilepsy syndromes. *PRKAB2* encodes a protein responsible for lipid metabolism. It is a regulatory subunit for AMPK (AMP-activated protein kinase). The laforin-malin complex, a set of proteins implicated in Lafora progressive myoclonus epilepsy, promotes ubiquitination of AMPK.[3] Further research is needed to determine whether and how this interaction could explain the development of epilepsy. This region also contains the *HYDIN2* gene, which was long thought to be a pseudogene, but which was recently shown to be highly transcribed, particularly in neuronal tissue, including the fetal brain. The function of *HYDIN2* is currently unknown. It was thought to be related to the head size, but this has been shown to be erroneous. *HYDIN2* is involved in 87% of individuals with developmental disabilities and 1q21.1 duplications and 93% of deletions, but CNVs of this gene are extremely rare in normal controls.[1] It is possible that abnormalities of this gene contribute to the development of epilepsy.

We reviewed available genetic information of patients with 1q21.1 microduplication syndrome and epilepsy.[2,4–7] Review of loci showed 10 patients with proximal microduplications[2,4,5] and only 3 patients with pure distal microduplications and epilepsy. There was no section of the duplicated locus ubiquitous to all patients, indicating that most likely there is more than 1 gene causing epilepsy in this population. Further research into the function of genes in the 1q21.1 region is likely to contribute substantially to our understanding of the genetic basis of epilepsy in individuals with autism spectrum disorders.

Author contributions

Ioulia Gourari: study concept and design and acquisition of data. Romaine Schubert: study supervision and acquisition of data. Aparna Prasad: critical revision of the manuscript for important intellectual content.

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Disclosure

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