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Duplications at 19q13.33 in patients with neurodevelopmental disorders

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Abstract

Objective

After the recent publication of the first patients with disease-associated missense variants in the *GRIN2D* gene, we evaluate the effect of copy number variants (CNVs) overlapping this gene toward the presentation of neurodevelopmental disorders (NDDs).

Methods

We explored ClinVar (number of CNVs = 50,794) and DECIPHER (number of CNVs = 28,085) clinical databases of genomic variations for patients with copy number changes overlapping the *GRIN2D* gene at the 19q13.33 locus and evaluated their respective phenotype alongside their frequency, gene content, and expression, with publicly available reference databases.

Results

We identified 11 patients with microduplications at the 19q13.33 locus. The majority of CNVs arose de novo, and comparable CNVs are not present in control databases. All patients were reported to have NDDs and dysmorphic features as the most common clinical phenotype (N = 8/11), followed by seizures (N = 6/11) and intellectual disability (N = 5/11). All duplications shared a consensus region of 405 kb overlapping 13 genes. After screening for duplication tolerance in control populations, positive gene brain expression, and gene dosage sensitivity analysis, we highlight 4 genes for future evaluation: *CARD8*, *C19orf68*, *KDELR1*, and *GRIN2D*, which are promising candidates for disease causality. Furthermore, investigation of the literature especially supports *GRIN2D* as the best candidate gene.

Conclusions

Our study presents dup19q13.33 as a novel duplication syndrome locus associated with NDDs. *CARD8*, *C19orf68*, *KDELR1*, and *GRIN2D* are promising candidates for functional follow-up.

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Glossary

DD = developmental delay; **ID** = intellectual disability; **LoF** = loss of function; **NDD** = neurodevelopmental disorder.

NMDA receptors are involved in neurodevelopmental processes such as synaptogenesis, learning, and memory. Structurally, NMDA receptors are composed of 2 subunits of GluN1 and GluN2, which are specifically encoded by the *GRIN1* and *GRIN2A* to *GRIN2D* genes, respectively.[1] While single nucleotide and copy number variants (CNVs) in the NMDA receptor subunits *GRIN1*, *GRIN2A*, and *GRIN2B* have been associated with a range of neurodevelopmental disorders (NDDs), little is known about the association of *GRIN2D* variants and NDDs. Recently, de novo missense mutations in *GRIN2D* (p.Val667Ile) have been identified as the cause of severe epileptic encephalopathy[2] in 2 independent patients. However, whether CNVs covering the *GRIN2D* locus are also associated with disease has not been studied. *GRIN2D* is encoded at the end of the long arm of chromosome 19 at the 19q13.33 locus. We hypothesize that dosage changes in *GRIN2D* are highly likely to be disease associated based on the high sequence homology, expression during neurodevelopment, and a functional relationship with the established disease-associated paralogous genes.

Methods

Standard protocol approvals, registrations, and patient consents

We obtained approval from an ethical standards committee on human experimentation (institutional or regional) for any experiments using human subjects. Written informed consent was obtained from all patients (or guardians of patients) participating in the study (consent for research), following the guidelines provided by ClinVar and DECHIPER databases. We obtained authorization for disclosure (consent to disclose) of the photograph that may be published in the journal, in derivative works by the AAN, or on the journal's website.

Data analysis

Using the gene-oriented query "*GRIN2D*," we accessed 2 publicly available repositories of clinical genetic variation: (1) The Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources, DECIPHER[3] (URL: https://decipher.sanger.ac.uk, accessed on July 2016) and (2) The public archive of interpretations of clinically relevant variants, ClinVar[4] (URL: http://www.ncbi.nlm.nih.gov/clinvar, accessed on July 2016). For DECIPHER patients, the individual scientists were contacted to acquire further phenotype information including the presence of intellectual disability (ID), developmental delay (DD), seizures, hypotonia, dysmorphism (Dysm), learning difficulties, behavioral problems as well as social communication, and behavioral disorders of the autism spectrum disorder.[5] We considered only DECIPHER entries with positive submitter contact. All phenotypes evaluated were considered as binary denominators (i.e., Yes/No). Gene annotations of the extracted CNVs refer to the genome build GRCh37/hg19. A consensus region was determined with an in-house Python script (available on request). Genes inside the consensus region were further evaluated as disease candidate genes with additional publicly available resources for (1) brain expression, strongly brain-expressed genes (n = 4,756), specified by a log (RPKM) >4.5 of the BrainSpan RNA.Seq transcriptome data set[6]; (2) overlapping CNVs reported in the curated control inclusive map of the Database of Genomic Variants[7]; (3) loss-of-function (LoF) intolerance reported in the Exome Aggregation Consortium,[8] given by a probability of being LoF intolerant (pLI score) equal to or greater than 0.9 based on the observed genetic variation of 60,706 healthy individuals; and (4) overlapping CNVs reported in 20,227 controls.[9] Genome-wide brain-specific noncoding functional elements were extracted from the GenoSkyline; project (http://genocanyon.med.yale.edu/GenoSkyline), which implements a statistical framework based on high-throughput genetic and epigenetic data to predict tissue-specific functional noncoding elements.[10]

Results

We detected 11 patients with CNVs overlapping the 19q13.33 locus (table 1). Of interest, all of them were duplications. Three were annotated in ClinVar (patients 1 through 3) and 8 in DECIPHER (patients 4 through 11). Although a ninth individual did fulfill the inclusion criteria (DECIPHER entry 275388), given the actual size of the reported variant in comparison with the entire chromosome 19 (CNV = 58.83 Mb vs Chr19 = 59.12 Mb), it was considered a chromosome trisomy and therefore was excluded. Detailed clinical phenotypes are provided in table 1. Notably, all patients were reported to have mild to severe forms of NDDs. Of all the phenotypes evaluated, mild but distinct dysmorphic features were the most frequent (n = 8), followed by seizures (n = 6, including generalized tonic and febrile seizures), ID (n = 5), and DD (n = 4). In particular, dysmorphisms were present in patients carrying CNVs larger than 3 Mb (pathogenic size according to the American College of Human Genetics). The image of 1 of such patients is shown in figure, A, showing a child with signs of macrostomia, midface hypoplasia, and progenia.

For DECIPHER entries with available parental information, 85.7% (n = 6) of observed microduplications were de novo, and only 1 was inherited from an affected family member. The majority of (87.5%, n = 7) patients did not carry additional CNVs, and none of the additional CNVs found in 3 patients covered a known disease locus or known disease

Table 1 Clinical phenotypes of the 11 retrieved patients with GRIN2D variants at the 19q13.33 locus

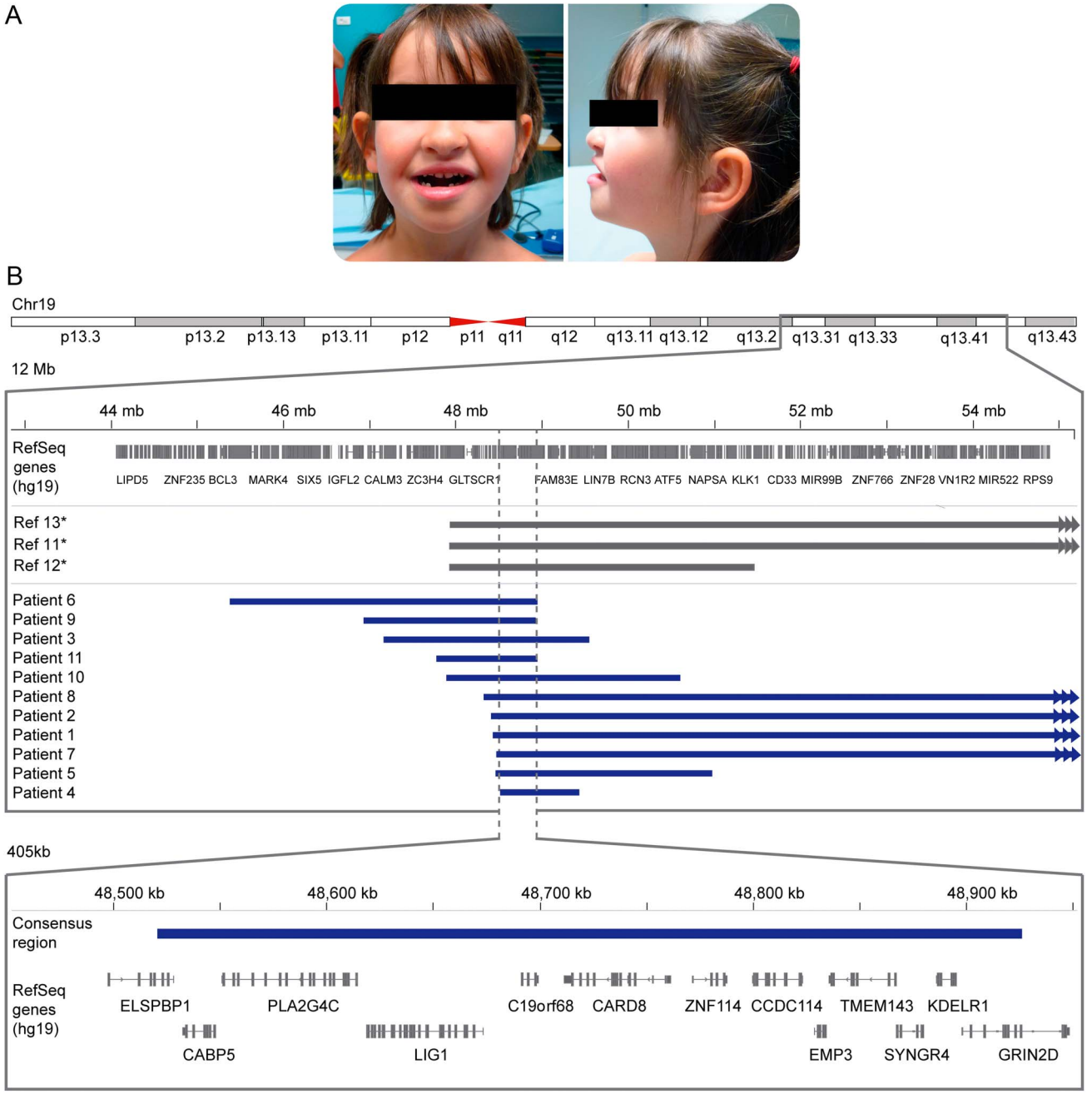
Patient	Resource	Database entry ID	Size (Mb)	Sex	Type of variant	De novo	No CNVs	ID	DD	Seizures	Hypotonia	ASD	Dysm	Learning difficulties	Behavioral problems
1	ClinVar	59117	10.65	—	Gain	—	—	—	Yes	Yes	—	—	Yes	—	—
2	ClinVar	59116	10.64	—	Gain	—	—	—	Yes*	—	—	—	?	—	—
3	ClinVar	59115	2.39	—	Gain	—	—	—	—	Yes	—	—	—	—	—
4	DECIPHER	257554	0.91	M	Gain	No**	1	—	—	Yes	—	—	—	Yes	—
5	DECIPHER	262506	2.51	F	Gain	Yes	1	Yes	Yes	Yes	Yes	—	Yes	Yes	—
6	DECIPHER	269407	3.57	M	Gain	Yes	1	Yes	—	—	—	—	Yes	—	—
7	DECIPHER	274058	10.64	F	Gain	Yes	1	Yes	—	Yes	—	—	Yes	—	Yes
8	DECIPHER	275426	7.78	F	Gain	Yes	1	—	Yes	Yes	Yes	—	Yes	—	—
9	DECIPHER	282304	2	F	Gain	—	2	—	Yes	—	—	—	Yes	—	—
10	DECIPHER	282364	2.72	F	Gain	Yes	1	Yes	—	—	—	—	Yes	Yes	—
11	DECIPHER	328426	1.16	F	Gain	Yes	1	Yes	—	—	—	—	Yes	—	—

	Literature	Patient	Size (Mb)	Sex	Type of variant	De novo	No CNVs	ID	DD	Seizures	Hypotonia	ASD	Dysm	Learning difficulties	Behavioral problems
12	Dorn et al.[13]	[1]	15.7	M	Gain	—	1	Yes	Yes	Yes	—	—	Yes	—	—
13	Dorn et al.[13]	[2]	15.7	F	Gain	—	1	Yes	—	Yes	—	—	Yes	—	—
14	Carvalheira et al.[11]	[1]	10.6	F	Gain	Yes	1	Yes	Yes	Yes	—	—	Yes	Yes	—
15	Wang et al.[12]	[1]	1.22	—	Gain	—	1	—	—	Yes	—	—	—	—	—
16	Wang et al.[12]	[5]	1.22	—	Gain	—	1	—	—	Yes	—	—	—	—	—
17	Wang et al.[12]	[7]	1.22	—	Gain	—	1	—	—	Yes	—	—	—	—	—

	GRIN2D pathogenic SNV	Patient	Mutation	Sex	Effect	De novo	No CNVs	ID	DD	Seizures	Hypotonia	ASD	Dysm	Learning difficulties	Behavioral problems
18	Li et al.[2]	[1]	p. Val667Ile		Gain of function	Yes	—	—	Yes	Yes	Yes	—	Yes	Yes	—
19	Li et al.[2]	[2]	p. Val667Ile		Gain of function	Yes	—	—	Yes	Yes	Yes	—	—	Yes	—

Abbreviations: ? = not clear; * = developmental delay and/or other significant developmental or morphological phenotypes; ** = from affected parent; ASD = autism spectrum disorder; DD = developmental delay; Dysm = dysmorphism; ID = intellectual disability; No CNVs = number of copy number variants annotated in patient; P = patient; SNV = single nucleotide variant.

Figure Genomic and facial overview of the microduplications overlapping the GRIN2D gene found in the retrieved patients



(A) Clinical anteroposterior facial photograph of patient 10 depicting characteristic facial features. (B) Thirteen patients were identified with GRIN2D duplications at the 19q13.33 locus. Blue horizontal bars represent the respective microduplication size and breakpoints according to GRCh37/hg19 human genome reference in a 12-Mb genomic window. Gray horizontal bars represent the respective microduplication reported in the study by Dorn et al.[13] Carvalheira et al.[11] and Wang et al.[12] in which no exact copy number variant boundaries are specified (*). Microduplications larger than the depicted genomic interval are shown with arrows at boundaries (patients 1, 2, 7, and 8). Bottom panel: The consensus duplicated region of the 12 patients is depicted in the blue horizontal bar in a 405-kb window. Thirteen RefSeq genes are located in this region.

genes. All 11 CNVs were highly heterogeneous in their size (average = 4.99 Mb; SD = 4.05 Mb) and breakpoint distribution (encompassing from Chr19: 45.38 Mb–59.09 Mb, Hg19) (table 1).

To identify additional CNVs absent in ClinVar and/or DECIPHER databases, we screened the literature and retrieved 3 additional studies, including 6 patients with duplications at the 19q13.33 locus.[11–13] All of these patients had seizures. Three patients carried CNVs of 1.22 Mb size, whereas the remaining 3 duplications were >10 Mb. Patients affected by the large CNVs were, in addition to seizures, also affected by other NDDs including ID and dysmorphism.

Of interest, the 2 independent patients with the p.Val667Ile mutation on *GRIN2D* featured similar NDDs including DD, dysmorphism, seizures, and muscular hypotonia (table 1).

Overall, the consensus duplicated region was determined to be located within the coordinates 48,520,809 bp–48,926,006 bp, with a final size of 405 kb. This is consistent with previous reports.[11–13] The consensus region overlapped 13 RefSeq genes (figure, B) that were further examined for brain expression, the presence of CNVs overlapping these genes in control cohorts, and variation intolerance (table 2). Four genes persisted above all available filters, namely, the caspase recruitment domain family member 8 (*CARD8*), the chromosome 19 open reading frame 68 (*C19orf68*), the KDEL endoplasmic reticulum protein retention receptor 1 (*KDELR1*), and the glutamate ionotropic receptor NMDA type subunit 2D (*GRIN2D*). In our view, these 4 genes represent the most promising candidates.

We also searched for noncoding brain-specific functional elements within the consensus region. A total of 291 were found overlapping 9.87% of the consensus region (40,019 bp). Within the consensus regions of the duplications, the density of noncoding elements was not significantly higher than that outside of chromosome 19.

Discussion

Here, we report on 11 patients with duplications at a potential novel disease locus within 19q13.33. Several lines of evidence support the hypothesis that duplications at this locus are associated with NDDs: (1) duplications at this locus are virtually absent in healthy individuals from the general population[8]; (2) all of the identified duplications with parental information arose de novo with the exception of patient 4, which according to DECIPHER was inherited from an affected parent with a similar phenotype (DECIPHER entry 257554); (3) none of the patients carried additional likely pathogenic CNVs; and (4) all duplications covered multiple plausible disease candidate genes.

The NDDs observed in the 11 patients were characterized by dysmorphism as the most prominent feature, followed by ID and seizures (table 1). Our observations are in agreement with previous reports.[11–13] Although, 1 example[12] focused exclusively on seizures, we cannot rule out that other NDDs were actually present in those patients. Similarly, we acknowledge that DD, behavioral problems, and learning difficulties may be subject to interobserver variability to some extent. In this regard, future clinical studies of 19q13.33 duplication carriers need to be conducted to draw detailed and robust genotype-phenotype conclusions. Since previous reports from the

Table 2 Consensus region gene annotation and candidate gene filtering

Transcipt ID	chrom	cdsStart	cdsEnd	Gene	Size (pb)	Brain expressed?[a]	DGV [clean] CNVs not present in controls?[b]	ExAC LoF Intolerance?[c]	PCG Browser CNV not present in controls?[d]	Total
NM_022142	chr19	48,511,924	48,525,584	ELSPBP1	13,660	No	Yes	No	Yes	2/4
NM_019855	chr19	48,533,813	48,547,179	CABP5	13,366	No	Yes	No	Yes	2/4
NM_001159322	chr19	48,551,599	48,613,772	PLA2G4C	62,173	Yes	No	Yes	Yes	3/4
NM_001320971	chr19	48,618,905	48,668,823	LIG1	49,918	Yes	Yes	Yes	No	3/4
NM_199341	chr19	48,675,059	48,700,084	**C19orf68**	25,025	Yes	Yes	NA	Yes	**3/3**
NM_014959	chr19	48,714,966	48,744,277	**CARD8**	29,311	Yes	Yes	Yes	Yes	**4/4**
NM_153608	chr19	48,783,056	48,790,135	ZNF114	7,079	No	Yes	No	Yes	2/4
NM_144577	chr19	48,800,232	48,822,028	CCDC114	21,796	Yes	Yes	No	Yes	3/4
NM_001313905	chr19	48,830,101	48,833,727	EMP3	3,626	Yes	Yes	No	Yes	3/4
NM_018273	chr19	48,836,475	48,867,177	TMEM143	30,702	Yes	No	Yes	Yes	3/4
NM_012451	chr19	48,869,099	48,879,575	SYNGR4	10,476	No	Yes	Yes	Yes	3/4
NM_006801	chr19	48,886,549	48,894,615	**KDELR1**	8,066	Yes	Yes	Yes	Yes	**4/4**
NM_000836	chr19	48,901,649	48,947,194	**GRIN2D**	45,545	Yes	Yes	Yes	Yes	**4/4**

[a]Brain-expressed genes from Uddin et al.[6]
[b]DGV curated CNV control map from Zarrei et al.[7]
[c]ExAC LoF Intolerant genes from Lek et al.[8]
[d]PCG Control CNVs from Marshall et al.[9]
Bold genes are positive in all applicable filters and are highlighted as "candidates genes" for future evaluation.

literature were based on low-resolution cytogenetic methods,[13] identification of the underlying disease gene was not possible. Here, we show that by integration of multiple CNVs data sets from public repositories, we are able to narrow down the disease-associated genomic sequence to a few candidate genes at the 19q13.33 locus (figure).

Our included data sets do not allow estimation of 19q13.33 duplication frequency. However, the absence of 19q13.33 duplications in CNVs databases of the general population and the presence of only a few variant carrying patients in diagnostic CNVs databases with heterogeneous breakpoints indicate that 19q13.33 duplications are extremely rare (table 2).

All 11 of the identified patient CNVs shared a genomic interval of 405 kb, which includes 4 genes with genetic, population and biological support of disease association. These included *CARD8*, *C19orf68*, *KDELR1*, and *GRIN2D*. For *CARD8*, *C19orf68*, and *KDELR1*, no association with NDDs has been reported in the literature to date. Although we cannot rule out that brain-specific noncoding elements at 19q13.33 could be involved in the development of NDDs, *GRIN2D* represents a plausible candidate gene for association with NDDs. *GRIN2D*, encoding the NMDA receptor subunit GluN2D, is highly expressed prenatally and after birth before progressively declining through adulthood.[14] It is possible that *GRIN2D* microduplications may predispose to disease susceptibility in a dose-dependent manner by enhancing GluN2D expression during development, thereby influencing the NMDA receptor composition, which might provoke changes in neuronal networks, thus contributing to hyperexcitability and neurologic diseases.[15] Besides CNVs, the *GRIN2D* gene is also depleted due to negative selection of missense and truncating variants in the general population, supporting the *GRIN2D* association with disease.[8] In agreement, 2 recently identified *GRIN2D* single nucleotide variants also lead functionally to a gain-of-function mutation in 2 patients with similar outcomes[2] (table 1). Beyond the potential diagnostic relevance, our identification of *GRIN2D* as a possible new NDD gene has a potential clinical application, since memantine, a low-affinity therapeutic NMDA channel blocker, selectively blocks extrasynaptic NMDA receptors that are likely to contain GluN2C/2D subunits.[16] This might especially be relevant for patients with gain-of-function mutations or microduplications.[2]

Author contributions

Eduardo Pérez-Palma: analysis and interpretation of data and wrote the manuscript. Elmo Saarentaus: analysis and interpretation of clinical data. Giancarlo V. De Ferrari: critical revision of the manuscript for intellectual content. Marie Ravoet, Giancarlo V. De Ferrari, Peter Nürnberg, and Bertrand Isidor: clinical and critical revision of the manuscript for intellectual content. Bernd A. Neubauer: drafting of the manuscript and critical revision of the manuscript for intellectual content. Dennis Lal: study concept and design, analysis and interpretation of data, and wrote the manuscript.

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