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BRIEF COMMUNICATION

Phenotypic association of 15q11.2 CNVs of the region of breakpoints 1–2 (BP1–BP2) in a large cohort of samples referred for genetic diagnosis

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Abstract

In view of conflicting reports on the pathogenicity of 15q11.2 CNVs of the breakpoints 1–2 (BP1–BP2) region and lack of association with a specific phenotype, we collected phenotypic data on 51,462 patients referred for genetic testing at two centers (Magee-Womens Hospital of UPMC and Baylor Genetics Laboratories, Baylor College of Medicine). Using array CGH, 262 patients with deletions and 215 with duplications were identified and tested for their association with four phenotypes (developmental delay, dysmorphic features, autism group of disorders, and epilepsy/seizures). Only association of deletions with dysmorphic features was observed ($P = 0.013$) with low penetrance (3.8%). Our results, viewed in the context of other reports suggesting the lack of a clear phenotypic outcome, underscore the need for detailed phenotypic studies to better understand the pathogenicity of 15q11.2 (BP1-BP2) CNVs.

The proximal region of the long arm of the human chromosome 15 (15q11.2-13.3) contains five clusters of low-copy repeats, referred to as breakpoints 1–5 (BP1–BP5) that participate in non-allelic homologous recombination (NAHR [1, 2]). NAHR results in recurrent deletions and duplications that are together termed as copy-number variants (CNVs). The BP1–BP5 segment includes the Prader–Willi/Angelman syndrome imprinted region (BP2–BP3) wherein patients with the CNVs fall into two categories namely, class I (deletions/duplications from BP1–BP3) and class II (BP2–BP3). Many, but not all studies report that patients with class I deletions present more severe neurodevelopmental phenotypes than those with class II [3], implicating the genes in the BP1–BP2 (15q11.2) region (*TUBGCP5, CYFIP1, NIPA1*, and *NIPA2*). Case-control and phenotypic association studies till date gave conflicting reports on the outcome of 15q11.2 (BP1–BP2) CNVs ranging from association with different phenotypes (such as schizophrenia, epilepsy, autism, developmental delay, dysmorphic features, cognitive defects, cardiovascular defects, and others [4–7]) to being non-pathogenic [8, 9]. Further, in studies reporting positive association, low penetrance was observed (0.02–10.4 [10, 11]). Taken together, these reports demonstrate the need for replication studies to better understand the pathogenicity of the 15q11.2 (BP1–BP2) CNVs. Here, we collected phenotypic data on a cohort of 51,462 patients referred for genetic testing at two diagnostic centers in USA, identified individuals with 15q11.2 (BP1–BP2) CNVs, and compared the frequencies of four abnormal phenotypes (developmental delay/intellectual disability, dysmorphic features, epilepsy/seizures, and autism/autism spectrum/Asperger syndrome/pervasive developmental disorder) among these individuals with the frequencies of

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Table 1 Analysis of association between BP1–BP2 deletions and duplications with the four phenotypes under study

Phenotype	Total patients	15q11.2 deletions			15q11.2 duplications		
		Cases with deletion and with phenotype (frequency)	Cases without phenotype but with deletion (frequency)	*P*-value (χ^2 value)	Cases with duplication and with phenotype (frequency)	Cases without phenotype but with duplication (frequency)	*P*-value (χ^2 value)
Developmental delay/ intellectual disability	20,415	91 (0.0045)	171 (0.0055)	0.1154 (2.479)	86 (0.0042)	129 (0.0042)	0.9767 (0.001)
Dysmorphic features	6005	44 (0.0073)	218 (0.0048)	**0.0126 (6.220)**	25 (0.0042)	190 (0.0042)	0.9851 (0.000)
Autism group	7308	25 (0.0034)	237 (0.0054)	0.0378 (4.315)	30 (0.0041)	185 (0.0042)	0.9951 (0.000)
Epilepsy/seizures	4836	27 (0.0056)	235 (0.0050)	0.6900 (0.159)	18 (0.0037)	197 (0.0042)	0.6898 (0.159)
Total	38,564	187	–	–	159	–	–

Significant association of deletions with dysmorphic features was found (bold). In case of autism group of disorders, there is significantly higher frequency of deletions in cases without autism than with autism (underlined)

patients with the corresponding phenotypes but without the CNVs.

This work was approved by the institutional review board(s) or the institutional human ethics committee(s) of the participating institutions. A total of 51,462 patients were referred for genetic testing by array CGH [12, 13] at the genetics laboratories in Baylor College of Medicine (39,215 patients), and Magee-Womens Hospital of UPMC (12,247 patients) during the period 2009–2017. It may be noted that obtaining comprehensive phenotypic information was not possible as the analysis is limited to the information that is provided and contains one to four main phenotypes because of which a referral was made (Supplementary Table 1).

A majority of the patients were found to be with one or more of the four phenotypes namely, developmental delay, dysmorphic features, autism group of disorders (autism/ASD/Asperger syndrome/pervasive developmental disorder), and epilepsy/seizures (Table 1). Following array CGH analysis, 348 were found to have 15q11.2 (BP1–BP2) deletions and 290 had 15q11.2 (BP1–BP2) duplications, giving a CNV frequency of 0.0124. The CNV frequencies obtained here were similar to those from other published reports involving patients referred for genetic testing [5, 14]. Also, there is no significant difference in these frequencies between the two diagnostic centers. Among the deletions and duplications, there were 86 and 75 cases, respectively, with other CNVs and therefore excluded from further analysis. Among the remaining 262 deletion cases, the four phenotypes were present in 187 patients (71%), whereas these phenotypes were found in 159 patients out of 215 duplication cases (74%).

We then used the individual number of patients with each phenotype to test for an association of either deletion or duplication. It may be noted that in these samples, there are patients with more than just one phenotype, and in these cases, a patient with multiple phenotypes is considered for analysis of more than one phenotype. As an example, we describe here the test for association of 15q11.2 (BP1–BP2) deletions with developmental delay/intellectual disability (Table 1). Out of 20,415 patients with this phenotype 91 had deletions, leaving 20,324 patients without deletions. Consequently, there were 31,047 patients without developmental delay/intellectual disability (51,462– 20,415) of which 171 patients had deletions and the remaining 30,876 were without deletions. A chi-square test with Yate's correction was performed using the two combinations of deletions (with and without developmental delay/intellectual disability) and the remaining two combinations of patients without deletions (with and without developmental delay/intellectual disability). A χ^2 value of 2.479 with a corresponding *P*-value of 0.1154 was obtained, suggesting no significant association of the deletions with this phenotype. Similar analyses for the remaining phenotypes showed association between deletions and dysmorphic features ($\chi^2 = 6.22$; $P = 0.0126$). No other associations were observed. We next tested whether the CNVs have association with combinations of two or more phenotypes and observed no significant association with any of the combined phenotype (Supplementary Table 2).

To estimate the likelihood of the deletion causing dysmorphic features, we calculated penetrance [10] (Supplementary Table 3). Using frequencies of the deletions among controls reported by Rosenfeld et al. [11], we obtained a value of 3.8%, suggesting low penetrance. Given that the general incidence of dysmorphic features is ~ 2.0% [15], our penetrance estimates suggest that 15q11.2 (BP1–BP2) deletion increases the risk further by ~1.8 %.

Family studies reported by other groups showed that 15q11.2 (BP1–BP2) deletions can be transmitted from parents to both probands and normal siblings indicating lack

of penetrance [6, 10, 11]. In some cases, the parent carrying deletion was even observed to be normal. In this study, the parents of the patients with deletions were phenotypically normal, but because of non-availability of DNA samples we were unable to ascertain whether the deletions were inherited or *de novo*. However, given the phenotypic variability (normal to pathogenic) [5–9] and low penetrance observed by us and others, the presence of a 15q11.2 (BP1–BP2) CNV may not warrant any clinical action. For example, being male without a deletion seems to be a greater risk factor for autism (1 in 42 boys; www.autismspeaks.org/what-autism/prevalence) than with the CNV. Similarly, being a twin is likely a greater risk factor for developmental delay (e.g., speech delay) than being a singleton with a deletion [16, 17]. Thus, it is difficult to argue that an otherwise normal infant with the CNV should be treated differently by the parents or the pediatrician.

Perhaps the most challenging question is whether to report deletions or duplications in prenatal samples. Parents could be given an option in a prenatal consent whether they wish to be informed about such findings or not. Unless such a consent is in place, it seems preferable to report the finding with a statement that these CNVs rarely cause a defect that requires a clinical action or reproductive decision [18]. However, given the fact that the current phenotypic information is limited, future studies with more detailed phenotypic information are needed to obtain a greater understanding of the impact of 15q11.2 (BP1–BP2) CNVs to aid clinical decision making.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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