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Autism spectrum disorder in patients with rare diseases

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Introduction

Autism Spectrum Disorder (ASD) is a heterogeneous group of neurodevelopmental disorders defined by impaired social-communication and the presence of restricted, repetitive patterns of behavior or interests. According to the Autism and Developmental Disabilities Monitoring Network the overall prevalence of ASD in USA for 2010 was 1 in 68 children with male to female ratio of 5:1, while in UK, according to European Comission, estimated prevalence for 2005 was between 10-30 per 10 000. The ASD has a strong genetic basis. This is indicated by higher reccurence risk within affected families and in monozygotic vs. dizygotic twins, as well as by co-occurence with chromosomal disorders and rare genetic syndromes.

- Objective: clinical and molecular analysis of ASD patients to identify patients with rare disorders associated with copy number variants (CNVs).

Materials and methods

Our study included 110 children referred to Department of Medical Genetics at Children's University Hospital Zagreb with psychiatric diagnosis of ASD. Patient's samples were screened for clinically relevant CNVs using chromosomal microarray (CMA) in period from Jan-2016 until Jan-2018. To determine the origin of detected CNVs in children we also analyzed available parental samples using CMA, multiplex-ligation-dependent probe amplification and high resolution karyotyping. CMA analysis was performed using SurePrint G3 Unrestricted CGH ISCAv2, 8x60K kit, Agilent SureScan Dx Microarray scanner and Agilent Cytogenomics software.

Table 1. CNVs and additional symptoms in 21 patients with ASD diagnosis.

	Pt	Sex	Gene/region	Size (Mb)	CNV	Origin	Associated syndrome	Symptoms
Pathogenic CNVs (Group A)	1	F	1p36	2.8	loss	dn	1p36 del	dysmorphic features, hypotonia, BP, SD, DD
	2	F	*NRXN1*	0.06	loss	unk	-	dysmorphic features, SD, BP, ID
	3	M	2q21.1	0.41	loss	mat	-	brahidactyly type E, IVH gr II, adiposity, speech regression, BP, ID
	4	M	2q32q35	22.2	loss	dn	Glass	dysmorphic features, DAB, CP, conductive hearing impairment, SD, FP
	5	M	*CNTNAP2*	0.14	loss	mat	-	myoclonic epilepsy, SD, ID
	6	F	4p16.3p16.1 8p23.3p23.1	8.68 6.69	loss gain	dn	4p16.3 dup 8p23 del	dysmorphic features, MND II, SD, ID
	7	M	15q11.2	0.54	loss	mat	Burnside-Butler	dysmorphic features, adiposity, hypothyreosis, Arnold Chiary type I in obs., BP, GERD
	8	M	15q11.2	0.45	loss	unk	Burnside-Butler	absence seizures, SD, ID
	9	M	15q13.2q13.3	1.6	loss	mat	15q13.3 del	-
	10	F	15q11.2q13.3	10.1	gain	dn	15q11-q13 dup	epilepsy, neuromotor delay
	11	M	17p11.2	3.65	loss	dn	Smith-Magenis	dysmorphic features, syndactyly, BP, SD, ID
	12	M	22q11.21	0.28	gain	mat	-	dysmorphic features
	13	M	22q13.31	5.16	loss	dn	Phelan-McDermid	dysmorphic features, hypotonia, convulsions, ID, SD
Variants of unknown significance (Group B)	14	M	1p13.3	0.41	gain	mat	-	SD, ID
	15*	F	*FGF12*	0.52	gain	pat	-	dysmorphic features, SD, BP
	16*	F	*FGF12*	0.52	gain	pat	-	IUGR, dysmorphic features, SD, BP
	17	M	7q32.3q33	1.36	gain	mat	-	-
	18	M	*CNTNAP2*	0.13	gain	unk	-	SD, FP
	19	F	16p13.11	1.68	gain	pat	-	SD
	20	M	*BRWD3*	0.16	gain	unk	-	-
	21	M	Xq26.2	0.28	gain	mat	-	dysmorphic features, DD

* Monozygotic twins

Note: Pt, patient; CNV, copy number variant; F, female; M, male; dn, *de novo*; unk, unknown; mat, maternal; pat, paternal; del, deletion; dup, duplication; BP, behavioral problems; SD, speach delay; DD, developmental delay; ID, intellectual disability; DAB, ductus arteriosus Botalli; CP, cleft palate; FP, feeding problems; MND, motor neuron disease; obs, observation; GERD, gastroesophageal reflux disease; IUGR, intrauterine growth retardation.

Results

CMA analysis detected CNVs in 21 of total 110 patients studied (Figure 1.). Pathogenic CNVs were found in 13 patients (Group A). CNVs known to cause rare genetic syndromes with ASD were found in patients: 1, 4, 6-11,13 (Table 1.). We also found small deletions (patients: 2, 3, 5,) associated with autism that affected gene/region:

- *NRXN1* (1) - synapse formation and signal transduction
- 2q21.1 (1), *AMER3*, *ARHGEF4*, *FAM168B*, *PLEKHB2* - neurogenesis and neuronal interactions
- *CNTNAP2* (1) - neuron and glia interactions

In 8 additional patients (Group B) we detected duplications that ranged in size from 131Kb to 1.6Mb (Table 1.). These CNVs were categorized as variants of unknown significance (VOUS). In two patients (14, 21) we found CNVs in regions 1p13.3 and Xq26.2 that have been previously detected in patients with intellectual disability but their clinical significance remains uncertain. One patient (19) had 16p13.11 microduplication known to be associated with ASD and other variable phenotypic features but it's pathogenicity is unclear since it has also been found in healthy individuals. Among patients in Group B (15-18,20) other candidate genes are also affected:

- *FGF12* (2) - neuronal development and function
- *PLXNA4* (1) - axon guidance
- *CNTNAP2* (1) - neuron and glia interactions
- *BRWD3(1)* - mutations cause cognitive disabilities

Duplications of these genes have no evidence of pathogenicity but due to their function in CNS they might have a role in ASD phenotype.

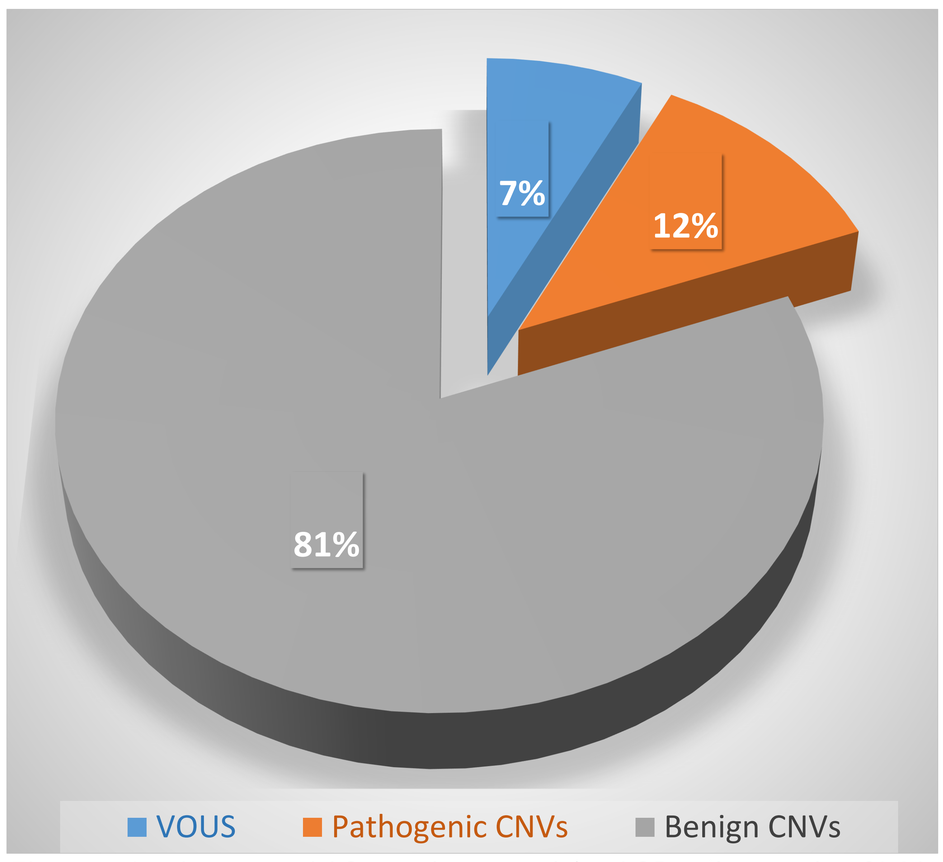

Figure 1. Among 110 patients with ASD diagnosis CMA analysis detected pathogenic CNVs in 13 patients (12%) and variants of unknown significance in 8 (7%) of them.

Conclusion

Detailed clinical and diagnostic assessment should be performed in all patients presenting with autistic features. CMA analysis proved to be useful diagnostic tool in diagnosing rare genetic conditions in individuals with autistic spectrum disorder.

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