Copy number variation analysis in 189 Romanian patients with global developmental delay/intellectual disability

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Abstract

Developmental delay and intellectual disability represent a common pathology in general population, involving about 3% of the pediatric age population and more and more often the genetic etiology is proven. The aim of this study was to determine the clinically relevant copy number variants in patients diagnosed with global developmental delay/intellectual disability in our population, using the technology SNP array.

Material and methods. We analyzed 189 patients diagnosed with GDD//ID, presented in Clinical Emergency Hospital for Children Cluj-Napoca. The patients were completely clinically investigated, including dysmorphic evaluation, internal malformation evaluation, psychiatric and neuropsychological examinations, metabolic evaluation, standard karyotyping. Genomic analysis was done using SNP array technique.

Results. 50/189 patients (26.45%) presented pathogenic CNVs and uniparental disomy (32/189 patients, 16.93%) or VOUS (variants of unknown significance) (18/189 patients, 9.52%). Two patients presented uniparental disomy of chromosome 15, one with clinical phenotype of Prader-Willi syndrome and the other with clinical phenotype with Angelman syndrome. The recurrent pathogenic CNVs were seen in 18/32 patients (56%) with pathogenic findings (CNVs or uniparental disomy).

Conclusions. These data encouraged to continue using a microarray genetic testing as useful test for the diagnostic performance together with other new tools as exome or genome sequencing for a global genome view in diseases which have not a specific phenotype, such as intellectual disability.

Background

Developmental delay and intellectual disability represent a common pathology in general population, involving about 3% of the paediatric age population (1).

Global developmental delay (GDD) is a diagnosis reserved for a child under five years and is defined as a significant delay, at least 2SD, in two or more developmental domains (gross or fine motor abilities, speech/language, cognition, social/personal and activities of daily living) (2).

Intellectual disability (ID) is a diagnosis which can be established beginning with the age of five years and it is affirmed when the following three criteria are met simultaneously: deficits in intellectual function (usually measured by intellectual coefficient), deficits in adaptative function (conceptual, social or practical skills) and an onset of these deficits during the developmental period (3). The diagnosis of GDD is usually seen as a temporary diagnosis, sometimes but not always being transformed in intellectual disability. Intellectual disability can be correctly evaluated using standardised test only after the age of five years. The aetiology for both, GDD and ID, is similar and usually the investigations are the same.

The clinical diagnosis is particularly important for a correct classification within this diagnosis, for a clear indication of a genetic testing. An adequate clinical evaluation can also lead to an orientation to a more genetic or more environmental cause, some authors saying that in up to 40% of patients with GDD/ID an etiological orientation can be performed (3). The clinical diagnosis is very important for a good treatment and prognosis, with a properly initiation of the therapeutic intervention and genetic counselling.

The aetiology in GDD/ID is represented by genetic causes in up to 70% of cases, about 30% of these being represented by numerical chromosomal abnormalities and structural chromosomal abnormalities, including CNVs (copy number variants). The other genetic causes are smaller abnormalities, involving one or several nucleotides, in monogenic or oligogenic disorders. Other “more environmental” causes are given by exposition to different prenatal teratogens (including the quite common foetal alcohol exposure), perinatal factors (prematurity, asphyxia or other neonatal complications) or postnatal causes (as CNS infections, traumatisms, toxic, psychosocial environment). However, today, with larger and not too expensive possibilities of genetic testing, including exome or genome sequencing, there are cases without a specified diagnosis.

Now, a first tier test in genetic investigations in GDD/ID is represented a genomic analysis by chromosomal microarray analysis or exome sequencing, which can elucidate a diagnosis in almost 30–40% of these cases (4), thus increasing the diagnosis efficiency in patients with GDD/ID. In karyotype era, the diagnosis was established in about 5% of the cases with GDD/ID, mostly of them being with numerical chromosomal abnormalities (most of the cases 21 trisomy) or large structural imbalances, larger than 5–10 MB, the karyotype resolution. Thus, the weak resolution for the karyotype, even as a genomic technique it was not very encouraging in

establishing the etiologic diagnosis in GDD/ID. Than we passed in FISH (fluorescent in situ hybridisation) era, with a better resolution than the karyotype but the main disadvantage here was done by the need of a quite precise clinical diagnosis which targeted the genetic testing to one region. The possibility to perform a more resolutive genetic testing as chromosomal microarray, which can observe genomic changes until 1kb, indicate it as a first line test in GDD/ID.

The aim of this study was to determine the clinically relevant CNVs in patients diagnosed with global developmental delay/intellectual disability in our population, using the technology SNP array.

Method

We analysed 189 patients diagnosed with GDD/ID, presented in Clinical Emergency Hospital for Children Cluj-Napoca, in period 1 january 2015-1 july 2017. The age of the patients was between 1 and 18 years. The inclusion criterion was represented by the presence of diagnosis of GDD or ID. An exclusion criterion was the presence of Down syndrome confirmed by karyotype. The diagnosis of GDD/ID was based on the intelligent coeficient evaluated by WISC-IV test (Wechsler Intelligence Scale for Children) and DQ (for children younger than 6 years), evaluated by Portage test and NEPSY test (A Developmental NEuroPSYchological Assessment). The patients were completely clinically investigated, including dysmorphic evaluation, internal malformation evaluation, psychiatric and neuropsychological examinations, metabolic evaluation, standard karyotyping. Brain imaging and EEG were effectuated in case of neurologist indications. Other analysis was done depending on clinical evaluation of each case.

The research was approved by Ethic Committee of Clinical Emergency Hospital for Children, Cluj-Napoca. Written informed consent was obtained from the parents of all the participants in the study.

High density SNP array analysis

The DNA was purified using Wizard® Genomic DNA Purification Kit (Promega, Madison, WI, USA) from 3 ml peripheral blood from each patient. Then, a SNP array analysis was done using Infinium OmniExpress-24 BeadChip array kit (Illumina, San Diego, CA, USA) and the platform iScan System (Illumina, San Diego, CA, USA). The SNP array kit permitted us to analyse about 700,000 markers. For bioinformatic analysis it was use the Genome Studio software version 2.0 (Illumina, San Diego, CA, USA). The interpretation of each CNV was done using the recommendations of American College of Medical Genetics (5, 6).

Results

The study group included 189 patients, 91 girls and 98 boys, with an age between 3 and 18 years. 50/189 patients (26.45%) presented pathogenic CNVs and uniparental disomy (32/189 patients, 16.93%) or VOUS (variants of unknown significance) (18/189 patients, 9.52%). The average age at genetic evaluation was 11.17 years (min 3 years; max 18 years). 28/189 patients (14.81%) were under five years of age and 161/189 (85.19%) were older than five years of age. The pathogenic CNVs seen in our patients are described in Table 1. Two patients presented uniparental disomy of chromosome 15, one with clinical phenotype of Prader-Willi syndrome and the other with clinical phenotype with Angelman syndrome (patients 76 and 78). Among pathogenic CNVs, 19 patients presented deletions and 11 patients duplications.

Table 1
Pathogenic CNVs observed in our GDD/ID patients

Patient	CNV (del/dup)	Chr	Start (hg19)	Stop (hg19)	Size (Kb)	Known Genetic Syndrome	Morbid OMIM genes	Patient phenotype
1	Del	17q12	34,856,055	36,248,918	1,392	17q12 deletion syndrome	HNF1B, PIGW	GDD/ID, dysmorphic features, ataxia
3	Dup	Xq27.1-q27.3	139,283,418	146,699,586	7,416		SOX3	GDD/ID
		22q11.1-q11.21	17,397,498	18,984,519	1,587	Cat Eye syndrome	PEX26, PRODH, TUBA8 ADA2	
5	Dup	1q41-q44	219,786,897	249,212,668	29,425	1q41-44 duplication	ZBTB18 and 42 OMIM morbid genes	GDD/ID, Dysmorphic signs
6	Dup	16p13.13-p13.2	8226775	12071213	3,844	16p13.2 deletion syndrome	GRIN2A, ABAT, LITAF	GDD/ID, ASD, Obesity
45	Del	14q32.2	99448000	100,800,103	1,352	14q32 deletion syndrome	BCL11B, CCNK, EML1, YY1	GDD/ID, short stature, dysmorphic syndrome
55	Del	5q35.2-5q35.3	175346223	177484097	2,137	Sotos syndrome	NSD1, SNCB, FGFR4, SLC34A1, HAF, DDX41, B4GALT7, PROP1	Sotos syndrome
59	Del	1q21.2-21.2	146501348	147911246	1,409	1q21.1 deletion syndrome	GJA5 GJA8	GDD/ID, Dysmorphic features
61	Dup	16p11.2	28615243	29028905	413	16p11.2 duplication syndrome	ATP2A1, TUFM, CD19, LAT	GDD/ID, Dysmorphic features
62	Dup	18p11.32-11.21	112535	14791236	18,678	18p Deletion syndrome	11 morbid OMIM genes	GDD/ID, Dysmorphic features
66	Dup	17p11.2	16777177	20239827	3,462	Potocki-Lupski syndrome	RAI1, ALDH3A2, AKAP10, TOP3A MYO15A	GDD/ID, Dysmorphic features
67	Del	22q11.2	18886915	21462353	2,575	DiGeorge syndrome	14 morbid OMIM genes	GDD/ID, Obesity, Dysmorphic features
71	Del	6q15q21	91,305,608	111,699,368	20,393	6q syndrome deletion	20 morbid OMIM genes	GDD/ID, Dysmorphic features
90	Del	4p16.1-p16.3	71,566	8,357,645	8,286	4p deletion syndrome	20 morbid OMIM genes	Wolf-Hirschhorn syndrome
91	Del	16p11.2	29595483	30187676	592	16p11.2 deletion syndrome	PRRT2, KNSL4, TBX6	GDD/ID, Language delay, dysmorphic syndrome
106	Del	9p24.3-p13.1	46587	39179289	39,132	9p deletion syndrome	41 morbid OMIM genes	GDD/ID, Dysmorphic syndrome

Patient	CNV (del/dup)	Chr	Start (hg19)	Stop (hg19)	Size (Kb)	Known Genetic Syndrome	Morbid OMIM genes	Patient phenotype
109	Dup	16p24.3	89542695	89656251	113	16q24.3 deletion syndrome	ANKRD11, PGN	GDD/ID, Dysmorphic features
117	Del	18p11.32-11.31	13034	4390081	4,377	18p Deletion syndrome	SMCHD1, LAPIN2,TGIF1	GDD/ID, Dysmorphic features
118	Del	15q11.2-q31.1	23656946	28535266	4,878	Prader-Willi syndrome	SNPRN, UBE3A, HERC2	GDD, hypotonia
130	Del	15q11.2-q31.1	23656946	28535266	4,878	Prader-Willi Syndrome	SNPRN, UBE3A, HERC2	GDD/ID, obesity
136	Del	1p36.33-1p36.32	82154	3821782	3,739	1p36 deletion syndrome	14 morbid OMIM genes	GDD/ID, Dysmorphic syndrome
149	Dup	16p11.2	29,595,483	30,215,621	620	16p11.2 duplication syndrome	PRRT2, TBX6, KIF22, ALDOA	GDD/ID, short stature, deafness
150	Del	7q11.23	73110603	73,702,525	592Kb	Williams syndrome	ELN	GDD/ID, dysmorphic syndrome
153	Del	7p15.3p21.1	18,814,931	23,539,546	4,726	Partial monosomy 7p	DNAH11, IL6, GPNMB	GDD/ID, dysmorphic syndrome
156	Dup	16p12.2-p11.2	21,610,804	30,198,151	8,587	16p11.2–p12.2 duplication syndrome	20 morbid OMIM genes	GDD/ID, Dysmorphic features
157	Dup	18p11.21-11.32	13034	15375878	15,362	18p Deletion syndrome	12 morbid OMIM genes	GDD/ID, Epilepsy
160	Del	16p11.2	28593316	28995057	401	16p11.2 deletion syndrome	ATP2A1, TUFM, CD19	GDD/ID, Dysmorphic fetaures
161	Del	22q11.21	18889490	21797812	2,908	DiGeorge syndrome	14 morbid OMIM genes	GDD/ID, Dysmorphic features, Cardiac and renal malformation
166	Del	4q22.2-4q24	94,543,233	107,486,817	12,943	4q deletion syndrome	20 morbid OMIM genes	GDD/ID, Dysmorphic syndrome, language delay
184	Del	4p16.2-16.3	48283	5405805	5,357	4p deletion syndrome	6 morbid OMIM genes	GDD/ID, Epilepsy, Cardiac malformation, Dysmorphic features
189	Dup	18q21.2-23	48866388	77888708	29,022	18q21q24 duplication	22 morbid OMIM genes	GDD/ID, microcrania, dysmorphic features

Among the recurrent CNVs, it was observed: 15q11.2-q31.1 deletion (2 patients), 4p16 deletion (2 patients), 22q11.21 deletion (2 patients), 22q11.2 duplication (1 patient), 16p11.2 deletion (2 patients), 16p11.2 duplication (1 patient), 18p11 duplications (2

patients), 18p11 deletion (1 patient), 7p11.23 deletion (1 patient), 5q35 deletion (1 patient),1q21 deletion (1 patient), 1p36 deletion (1 patient), 17p11.2 duplication (1 patient) (Table1). 24/30 patients with pathogenic CNVs (80%) presented dysmorphic features as clinical signs associated to GDD/ID. The aetiology was suggested by the clinical phenotype in only 4 patients/189 (2.11%), confirmed later by SNP array analysis, these clinical diagnosis being: Wolf-Hirschhorn syndrome, Williams syndrome, Sotos syndrome and Prader-Willi syndrome. For most patients, the clinical phenotype was not specific for a particular aetiology.

The patients observed with VOUS in our study group are described in Table 2.

Table 2
VOUS observed in our GDD/ID patients

Patient	CNV/UPD	Chromosome	Start	Stop	Size(Kb)	Major genes involved
3	Dup	3q26.1	161,577,780	166,471,417	4,893	BCHE, SI
5	Del	11q25	133,531,291	134,868,407	1,337	JAM3, ACAD8, NCAPD3
8	Dup	17q21.33	48,263,589	48,607,252	344	COL1A1,XYLT2
62	Dup	21p11.1	34097891	34853011	755	IFNAR2 PARK20
65	Dup	15q12	26874395	26888344	14	GABR3
68	Del	10q21	68107483	68150124	42	CTNNA3
84	Del	12p12.1	23836212	23840513	4.3	SOX5
85	Del	1q34	237584925	237597163	12	RYR2
	Del	16q22.1	70513384	70519783	6	COG4
110	Dup	11q13.4	70969719	71419408	449	DHCR7
123	Del	19p13.11	33882222	33893008	10	PEPD
	Del homozygous	7p22.1	4823971	4839265	15	AP5Z1
163	Dup	3q27.1	184010230	184038969	28	PARK18
164	Del	6p25.1	5,256,116	5,391,419	135	FARS2, LYRM4
173	Dup	22q11.21	18877787	19008108	130	DGCR5, DGCR6, DGCR9, PRODH
178	Dup	22q11.21	18895227	19008108	112	DGCR5, DGCR6, DGCR9, PRODH
183	Del	10q22.3	79313729	79331919	18	KCNMA1
185	Del	18q21.1	43655010	43743081	88	ATP5A1
186	Del	Xp11.4	38230704	38246882	16	OTC
188	Del	Xp11.4	38235792	38256737	20	OTC

Discussions

In this study group of Romanian patients with GDD/ID we observed pathogenic CNVs or VOUS in 26% of patients. Pathogenic CNVs and uniparental disomy were seen in 17% of patients. The recurrent pathogenic CNVs were seen in 18/32 patients (56%) with pathogenic findings (CNVs or uniparental disomy).

A similar percentage of pathogenic CNVs was also seen in other studies (7, 8, 9). This high number of diagnosed cases using microarray analysis, sustain the great diagnosis performance given by this investigation, indicated as first tier test in GDD/ID (4). Also, a genomic approach for the patients with an unspecific phenotype such as GDD/ID associated or not with other signs is very useful, in our case, only in 2% of cases being suggested an etiologic diagnosis at physical evaluation.

The high percentage of recurrent CNVs, of 56% between pathogenic findings was also seen by other authors (10), these CNVs also having a potential recognisable phenotype, often partial, compared to the classical described in literature, and this could be an

argument to continue giving an importance to phenotype evaluation, which could bring in some situation a diagnosis, more easily and cheaply confirmed by a targeted genetic testing, such as MLPA, qPCR or FISH technique. These recurrent CNVs seen in our study were: 15q11.2-q31.1 deletion (Prader-Willi syndrome), 4p16 deletion (Wolf-Hirschhorn syndrome), 22q11.21 deletion/duplication (Velo-cardio-facial syndrome), 7p11.23 deletion (Williams syndrome), 5q35 deletion (Sotos syndrome), 16p11.2 deletion/16p11.2 duplication, 18p11 duplication, 18p11 deletion, 1q21 deletion, 1p36 deletion, 17p11.2 duplication, these findings were also remarqued by other studies (10, 11). Chromosome 8 was often involved in pathogenic CNVs, 4 patients presenting large deletion/duplication: 18q21.2-23 duplication, two 18p11.32-11.21 duplication and the same 18p11.32-11.21 deletion.

Among the analysed cases, the patient 3, a 12 years old boy with isolated GDD/ID, presents a 7.4 Mb duplication of X chromosome, including more OMIM genes, *SOX3* being a known morbid gene, coding for a transcription factor implicated in neurogenesis, which is associated with mental retardation, X-linked, with isolated growth hormone deficiency. The patient presented a GDD/ID, same as other cases described in literature, but not short stature and GH deficiency (12, 13, 14, 15). CNV was interpreted as pathogenic CNVs. The particularity for patient 3 is the presence of 22q11.2 duplication, associated to X chromosome duplication.

The patient 5, a girl with GDD/ID and dysmorphic signs, presented 29.4Mb duplication of 1q41-1q44 region, which included 43 morbid OMIM genes (including *ZBTB18*) and this phenotype was already described in association with this CNVs (16, 17, 18, 19). This CNVs is known as 1q41-q42 microdeletion syndrome.

In patient 6, a boy with GDD/ID, ASD and obesity was observed a 16p13.2-16p13.13 duplication (3.8Mb), including *GRIN2A* gene, known to be associated with epilepsy and GDD/ID, which partially superpose with our patient picture. This duplication also included the region 16p13.2, known to be associated with 16p13.2 deletion syndrome (*USP7* gene), which is involves an autistic spectrum disorder and GDD/ID, also seen in our patient, as in other group of patients with same characteristics (11).

Another particular CNVs is 14q32.2 deletion, seen in patient 45, which included some genes involved in intellectual disability, as *YY1* gene, responsible of Gabriela de Vries syndrome(20). Overlapping CNVs were described in Decipher patients (260834, 291402), with similar phenotypes as our patient, however the cases with this CNV are very rares.

6q15-q21 deletion of 20.3 Mb seen in patient 71 is another rare CNV also recorded by some authors in association with intellectual delay (21, 22, 23), including an important number of OMIM genes involved in neurogenesis.

In patient 153, the 7p15.3-p21.1 deletion was also described in association with intellectual disability (24), including *TWIST1* gene, associated with Robinow-Sorauf syndrome and Sweeney-Cox syndrome.

The deletion in 4q22.2-q24 region in patient 166 is also a very rare CNVs, it was described in patients with intellectual disability, dysmorphic features and internal malformations (25, 26).

Conclusion

In conclusion, we aimed to identify an etiologic diagnosis in children with GDD/ID in our patients, study which is the first characterising the etiology in Romanian population and these data encouraged to continue using a microarray genetic testing as useful test for the diagnostic performance together with other tools as exome or genome sequencing for a global genome view in diseases which have not a specific phenotype, such as intellectual disability.

Abbreviations

SNP array – single nucleotide polymorphism array

GDD – global developmental delay

ID - intellectual disability

CNV – copy number variants

VOUS – variant of unknown significance

CNS – central nervous system

FISH – fluorescent in situ hybridization

WISC-IV - Wechsler Intelligence Scale for Children

DQ – development quotient

NEPSY - Developmental NEuroPSYchological Assessment

EEG - electroencephalogram

qPCR – quantitative polymerase chain reaction

MLPA – multiplex ligation-dependent probe amplification

Mb - megabase

Declarations

Ethics approval and consent to participate

The research was approved by Ethic Committee of Clinical Emergency Hospital for Children, Cluj-Napoca. Written informed consent was obtained from the parents of all the participants in the study.

Consent for publication

The consent for publication was obtained from the authors. The manuscript does not contain data from individual person.

Availability of data and material

Relevant data generated or analyzed during this study are included in this published article. The other datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

not applicable

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Authors' contributions

DM (conceptualization, methodology, validation, investigation, manuscript writing, manuscript supervising), SO (methodology, validation, investigation, manuscript writing), SB (methodology, investigation), DS (methodology, investigation), RP (methodology, investigation), MM (methodology, investigation), MP (methodology, investigation), CZ (methodology, investigation), ACE (methodology, investigation), CA (methodology, validation, investigation, manuscript supervising).

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