Epilepsia dos 0 aos 18 anos Novas realidades

15º Congresso Sociedade Portuguesa Neuropediatria EVENTO VIRTUAL

Characterization of copy number variants in 199 patients with neurodevelopmental disorders

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Background

- CNVs have been established as relevant contributors for several neurodevelopmental disorders (NDD).

Table I – A multitude of technologies/assays currently used to detect a range of CNVs in a diagnostic setting.

Method	Resolution	Target region
Karyotype	5 - 10 Mb	Genome
FISH	~100 kb	Probes used
MLPA	Single exon (up to)	Probes used
Array-CGH (aCGH)	15 kb (up to)	Genome
Whole-exome sequencing (WES)	100 bp - ~150 kb	Exome
Whole-genome sequencing (WGS)	10 bp - >500 kb	Genome

- In routine molecular genetic diagnosis, gene-specific or genome-wide detection of copy number variants (CNVs) enabled the characterization of patients within cohorts with a broad phenotypic spectrum.

Aim

Evaluate the diagnostic yield attributable to clinically relevant CNVs in a large patient cohort with NDD.

Methods

Cohort of 3,057 patients (from 2016-2020)

CNVs detection methods:
- MLPA (MRC Holland)
- aCGH
- WES (Illumina)

Divided in two groups:
- Without epilepsy (n=143)
- Epilepsy (n=56)

Patients with CNVs: 199
Yield = 6.5%

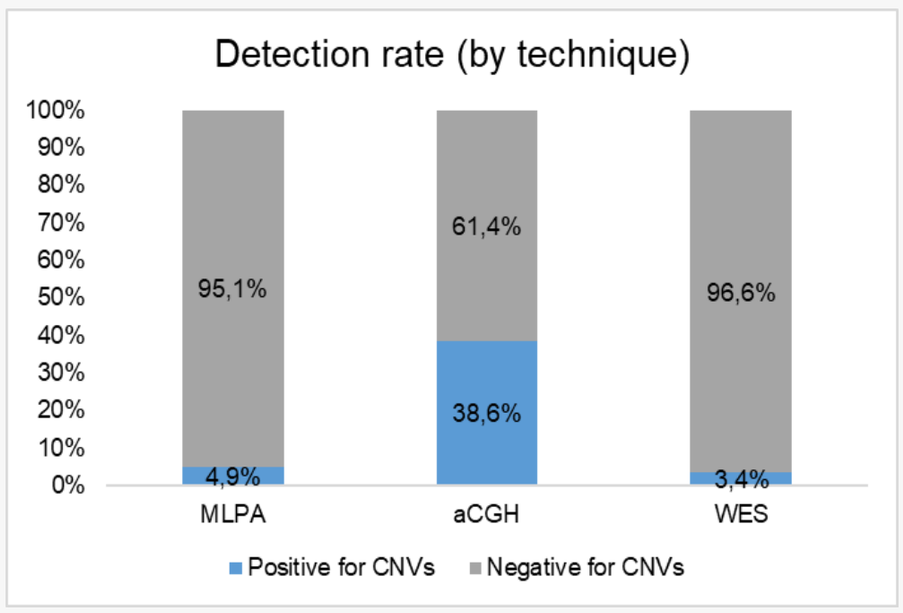

Figure 1 – Detection rate distribution by technique for the 3,057 patients considered in this study. MLPA and WES have similar CNV detection rates (4.9% and 3.4 %, respectively) while aCGH presents a significantly higher value. This occurs because aCGH is a genome-wide technique (unlike MLPA which is target) solely focused in the detection of CNVs (unlike WES which is used for both SNVs and CNVs detection).

Results

6.5% of the patients with CNVs:

Table II – Distribution of the CNVs detected in each group (patients with vs without epilepsy).

Total of 230 CNVs detected*			
	Without epilepsy (143 patients)	Epilepsy (56 patients)	**Total**
CNV type			
Loss	108	41	149
Gain	60	21	81
	Yield = **5.0%**	Yield = **2.3%**	

*Some patients harbor more than 1 CNV.

Table III – Distribution of patients with CNVs by the technique used.

	Without epilepsy	**Epilepsy**
Technique		
MLPA	30 (4.6%)	11 (6.0%)
aCGH	66 (33.5%)	10 (5.1%)
WES	47 (2.3%)	35 (1.7%)
Total	**143**	**56**

In both groups, the majority of the CNVs found were at the single-gene level (for both deletions and duplications).

Genotype-phenotype correlations were established based on the clinical information available for each patient.

Example:
- Clinical presentation: F, 1 yr, global developmental delay with seizures, West syndrome.
- Requested test: WES-based multigene panel for epileptic encephalopathies (with CNV detection).
- Molecular findings: ~290 Kb duplication at Xq28 affecting 7 gene including the *MECP2* and *FLNA* genes.

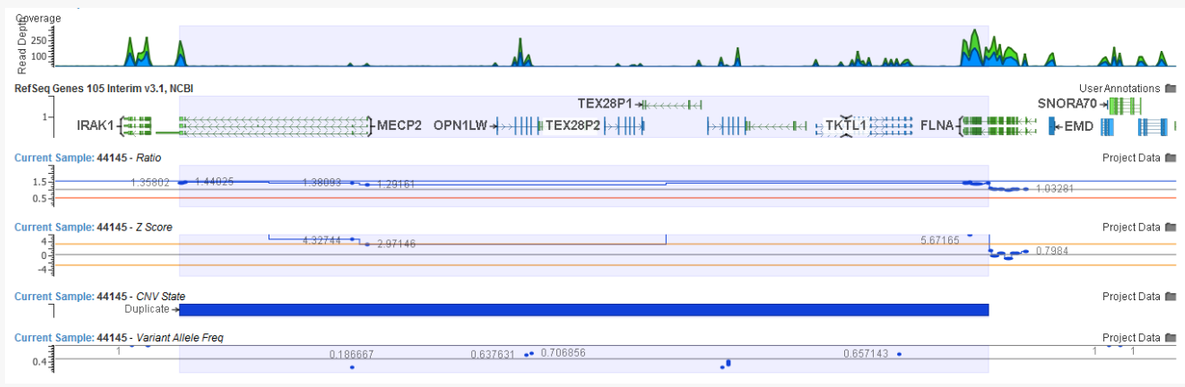

Figure 2 – Duplication at Xq28 affecting the *MECP2* gene.
The blue bar highlights the duplicated region.

Conclusions

- CNVs screening is a mandatory aspect to consider for the molecular diagnosis of NDD patients (with or without epilepsy).
- Genome wide CNV detection approaches (namelly aCGH and read depth-based using NGS data) can significantly increase the diagnostic yield.

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