Characterization of CNVs identified by genetic testing of epilepsy

Lotta Koskinen, Julie Hathaway, Kirsi Alakurtti, Mònica Segura Castell, Åsa Hagström, Heli Kuisma, Kimberly Gall, Inka Saarinen, Mikko Muona, Tuuli Pietilä, Janica Djupsjöbacka, Massimiliano Gentile, Pertteli Salmenperä, Sari Tuupanen, Tiia Kangas-Kontio, Kati Kämpjärvi, **Eija H Seppälä**, Jussi Paananen, Samuel Myllykangas, Juha Koskenvuo

Blueprint Genetics, a Quest Diagnostics company, Keilaranta 16 A-B, 02150 Espoo, Finland

Introduction

Epilepsy is a neurological disorder that affects up to 3% of the population. Chromosome abnormalities, copy number variants (CNVs), and sequence variants are the underlying causes of an important proportion of epilepsy cases. Identifying the precise genetic etiology is paramount to guiding medical management, as epilepsy is increasingly amenable to precision medicine therapies. Although multiple studies have reported on the genetic findings in cohorts of patients with epilepsy using microarray, multigene panels, exome sequencing and genome sequencing, the sensitivity at which small (intragenic) CNVs are detected is quite variable across these assays, as CNVs remain a challenging variant type to detect with many NGS assays. This study describes intragenic CNVs identified in patients with epilepsy undergoing NGS multigene panel testing to further define their prevalence and clinical implications.

Methods

We conducted a retrospective review of consecutive, deidentified results of patients who underwent genetic testing with a comprehensive epilepsy panel at Blueprint Genetics. The panels included sequencing and CNV analysis by NGS from a validated whole exome or clinical exome assay. The target regions of the panels included between 194 to 474 genes associated with epilepsy (panel content evolved over time) and included both nuclear and the 37 mitochondrial DNA genes. An informative case was defined as the identification of pathogenic (P) or likely pathogenic (LP) variant(s) (classified applying ACMG/AMP variant classification scheme) consistent with the patient's reported phenotype.

Results

A total of 1,626 index patients underwent testing with a comprehensive epilepsy panel; 53.3% (n=867) were male, and average age at the time of testing was 8.9 years. The largest number of patients (48.8%, n=793) underwent testing with a 379-gene panel; 24.8% (n=403) underwent testing with a 283-gene panel, 18.5 % (n=300) with a 474-gene panel and 1.9% (n=30) with a 194 or 195 gene panel.

In this cohort, 21.1% of patients (n=343) received an informative genetic test result. Table 1 illustrates the distribution of informative results by patient age group. Four patients (1.2%; 0.25% of all patients in this cohort) had a P/LP in >1 gene, suggesting >1 genetic explanation for their clinical presentation (*IQSEC2* + *MT-TL1*, SCN1A + 2q deletion, *SCN1A* + 16p deletion, *SCN1A* + *TSC1*; one patient each).

P/LP CNVs were identified in 3.1% of all patients in the overall cohort and in 14.6% of patients who received an informative genetic test result (n=50). Of these P/LP CNVs, 26% (n=13) were intragenic and 54% of intragenic P/LP CNVs (n=7) were <1000 bp in size (Figure). Intragenic CNVs, implicated genes, and size of the CNVs are listed in Table 2. Among patients with intragenic P/LP CNVs, 4 had CNVs in genes associated with a gene-specific treatment (*SCN1A,* n=3; *SCN2A,* n=1), and 4 had CNVs in genes associated with a gene-specific interventional trial as listed in clinicaltrials.gov (*SCN1A* n=2, *CLN3* n=1, *CDKL5* n=1). These are outlined in Table 3.

Greater than one in 5 patients undergoing next-generation sequencing (NGS) panel testing for an epilepsy indication received an informative test result.

4% of informative results were explained by small, intragenic CNVs;
60% (8/13) of these were associated with gene-specific therapy or interventional clinical trial[1]

Patient age at the time of testing	# of patients	% of cohort	% with informative result (n)
Adult ≥ 18 years	213	13.1%	10.3% (n=22)
Pediatric (3-17 years)	873	53.7%	45.5% (n=156)
Pediatric (0-2 years)	540	33.2%	48.1% (n=165)

Table 1. Distribution of informative results by patient age group

Gene	Type of CNV	Size of CNV (bp)
GLDC	Loss	241
DEPDC5	Loss	241
KMT2E	Loss	241
NPRL3	Loss	259
CACNA1A	Loss	315
MEF2C	Loss	325
CLN3	Loss	455
SCN1A	Loss	5503
SCN2A	Gain	5557
DEPDC5	Loss	5998
SCN1A	Gain	29812
WWOX	Loss	46029
CDKL5	Loss	57807

Table 2. Genes implicated and size of intragenic CNV

Gene	# of patients	Clinical Implications
SCN1A	2	Gene-specific treatment, Interventional Clinical Trial (NCT05419492)
SCN2A	1	Gene-specific treatment
CLN3	1	Interventional Clinical Trial (NCT03770572, NCT04637282)
CDKL5	1	Interventional Clinical Trial (NCT05064878)

Table 3. Clinical Implications of intragenic CNVs

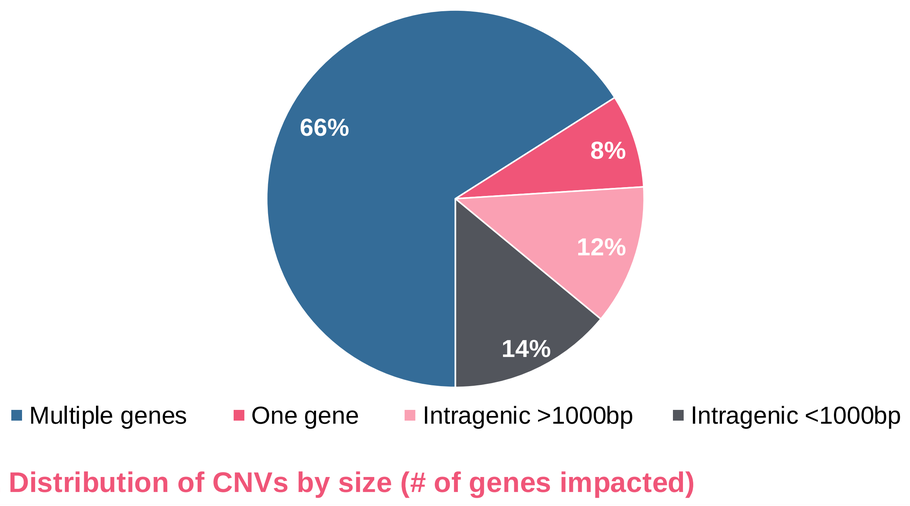

Figure. Distribution of CNVs by size (# of genes impacted)

Conclusions

- Four percent of patients receiving an informative genetic test result (n=13) had an intragenic P/LP CNV
- Of these 13 patients, 60% had a P/LP CNV in a gene associated with a gene specific treatment or clinical trial.
- In this cohort, 0.25% of patients received a molecular result consistent with multiple etiologies explaining their clinical presentation.
- in patients with epilepsy, high-resolution CNV analysis with simultaneous detection of sequence variants and should be considered, as broad genetic testing approaches are being considered as a first-line step.

Blueprint Genetics

Conflict of interest statement: All authors are employed by Blueprint Genetics.

Reference:

1. Clinical Trials. U.S. National Library of Medicine. Accessed May 21, 2023. ClinicalTrials.gov