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Has Anything Changed? Reclassification of Epilepsy Genetic Variants

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BACKGROUND

- Genetic testing has become a valuable tool in the evaluation of many neurologic diseases. Studies in the field of epilepsy genetics have demonstrated a high diagnostic yield and impact on treatment and counseling.
- Advances in genomic technology have made it feasible to analyze hundreds of genes in a single genetic test. However, the clinical significance and interpretation of genetic variants is evolving.
- Laboratory guidelines (College of American Pathologist and American College of Medical Genetics and Genomics [ACMG]) outline variant classification structure and recommend a periodic review of all reported genetic variants. ACMG is currently establishing guidelines for reanalysis of genetic testing results for variants. Despite these guidelines, no clear timeline has been established to guide in the frequency of variant reinterpretation.
- In this study, we examined the frequency and significance of reclassifications within our laboratory's epilepsy cohort.

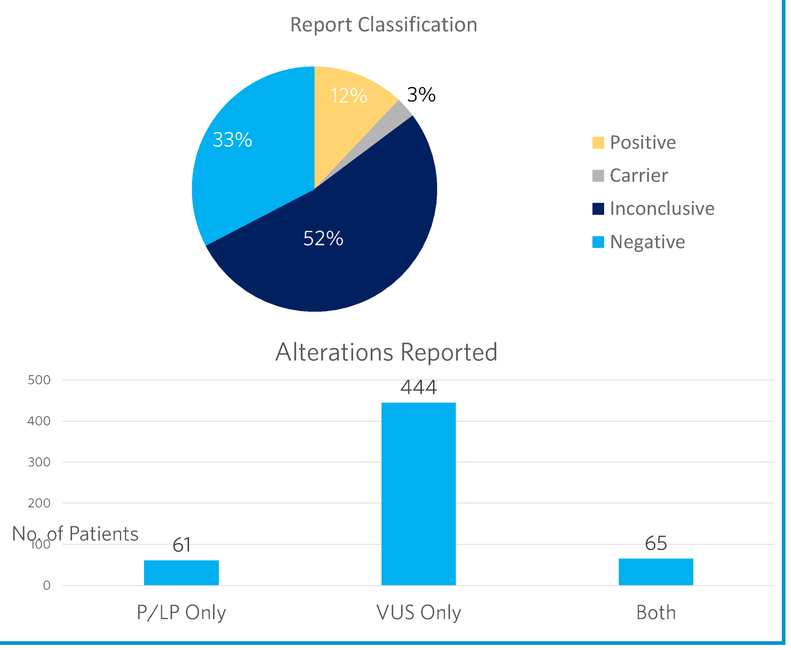
METHODS

- We retrospectively reviewed an unselected cohort of 846 patients referred for epilepsy genetic testing at one commercial laboratory.
- Patients underwent epilepsy multigene panel testing (MGPT) ranging from 16 to 96 genes. All patients received results prior to 12/31/17 to allow time for reclassification.
- The overall result categories and variant classifications were determined according to predefined diagnostic variant assessment criteria. A reclassification was defined by any change in variant classification.

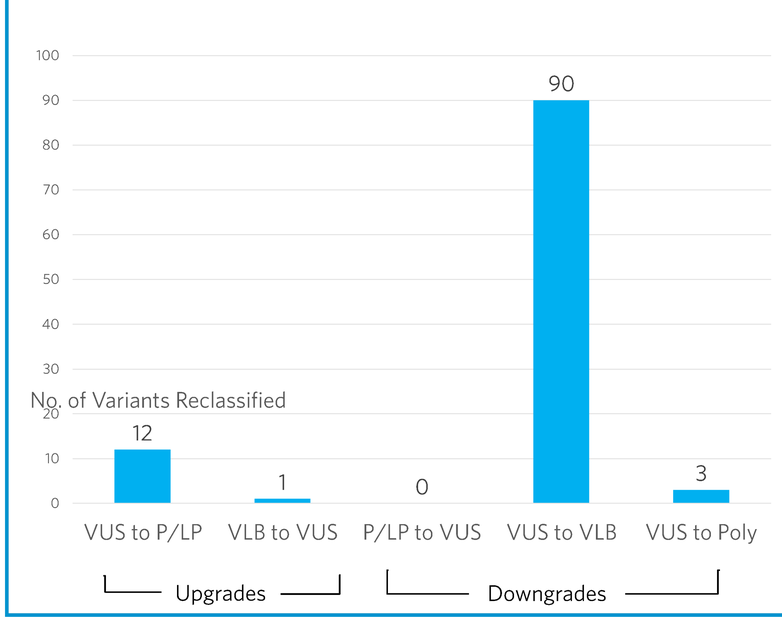
Abbreviations

P – Pathogenic variant
LP – Likely pathogenic variant
VUS – Variant of unknown significance
VLB – Variant likely benign
Poly – Polymorphism (benign)

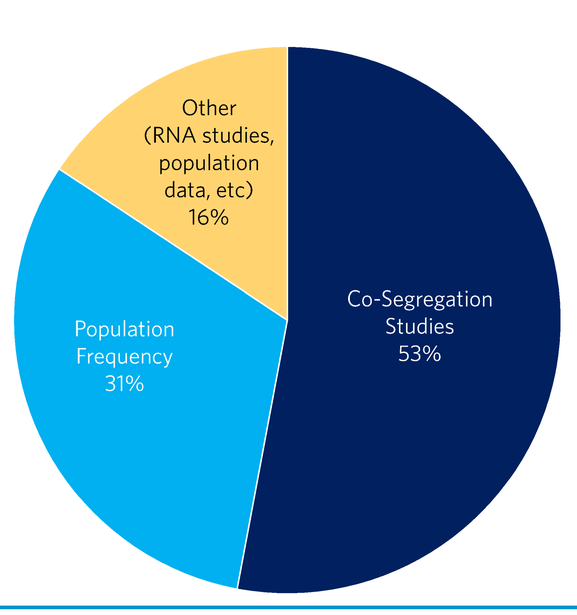
A. Original Report Characteristics



B. Gene Variant Reclassification



C. Lines of Evidence Leading to Reclassification



Results

- A total of 846 patients underwent MGPT testing for epilepsy (mean age 9 years, 54.7% male, 35.7% Caucasian), and 570 (67.4%) patients had at least one reportable alteration. Overall this resulted in 102 positive and 445 inconclusive test reports. The majority of patients were found to have only VLP/P or VUS reported. (Fig A.)
- A total of 106 unique variants underwent reclassification, with 116 (20.4%) patients having at least one variant reclassified and 12 patients having more than one variant reclassified. Thirteen (12.3%) variant classifications were upgraded impacting 13 patients. Additionally, 93 (87.7%) variant classifications were downgraded impacting 113 patients. Three variants reclassified from VUS to VLB were later reclassified to polymorphisms. (Fig. B)
- The changes in variant classification led to clinically actionable results in 12 patients (VUS to VLP). No clinically actionable variants were downgraded (Fig B). While all patients received an amended report, 56 (48.3%) patients had a change in their overall result category.
- Variants were reclassified due to a variety of reasons (Fig C). The majority of variants (53%) were reclassified due to data from co-segregation studies such as parental variant testing, family studies testing and exome segregation data. Changes in population frequency due to incorporation of large populations studies such as gnomAD accounted for the second most common line of evidence (31%). Other lines of evidence leading to reclassification include RNA studies and internal structural analysis.
- The average amount of time to reclassification was 242.3 days.

TAKE-HOME POINTS

- The relatively high rate of reclassification illustrates the importance of continued variant assessment following the initial identification of the variant.
- In contrast to our data, a recent study by SoRelle, et al. found that 10% of VLP/P variants were downgraded to VUS or VLB/polymorphism. The absence of similar reclassifications in our population underscores the importance of including multiple lines of evidence in variant classification.
- In addition to improved population frequency databases, family testing programs are a highly effective strategy for large genomic laboratories in the epilepsy genetic population.
- With the inclusion of familial testing programs, and upfront familial testing, variant reinterpretation is recommended within a year of initial identification.

REFERENCES

1. SoRelle, J. A., MD, Thodeson, D. M., MD, Arnold, S., MD, Gotway, G., MD, PhD, & Park, J. Y., MD, PhD. (2018). Clinical Utility of Reinterpreting Previously Reported Genomic Epilepsy Test Results for Pediatric Patients. JAMA Pediatrics, E1-E5. doi:10.1001/jamapediatrics.2018.2302