Genotype-first analysis is an effective strategy for identifying diagnostic variants in known disease genes and candidate variants in novel genes.

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Introduction

Multiple approaches exist for the identification of variants that may explain a patient's phenotype once sequencing is completed. Most strategies primarily use a phenotype-driven approach to variant analysis. However, this approach can be problematic for cases with atypical presentations, patients with multiple diagnoses, or situations where detailed clinical information is limited or not available. On the other hand, a genotype-first analysis initially considers the properties of the variants, such as frequency, predicted effect on encoded protein, and inheritance. Following this first level of analysis, the variants are then are compared to the patient's reported phenotype.

Methods

To evaluate genotype-first analysis, we reviewed 731 exome sequencing cases.

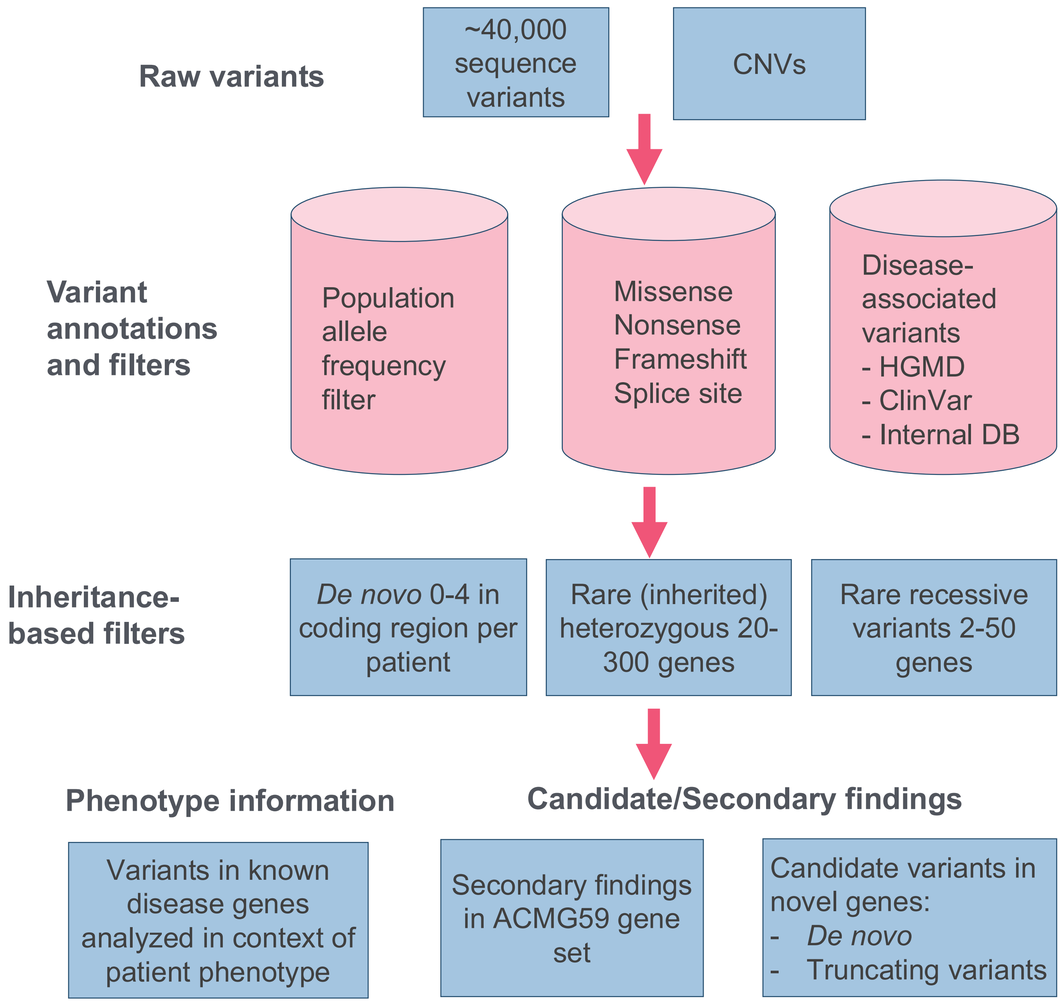
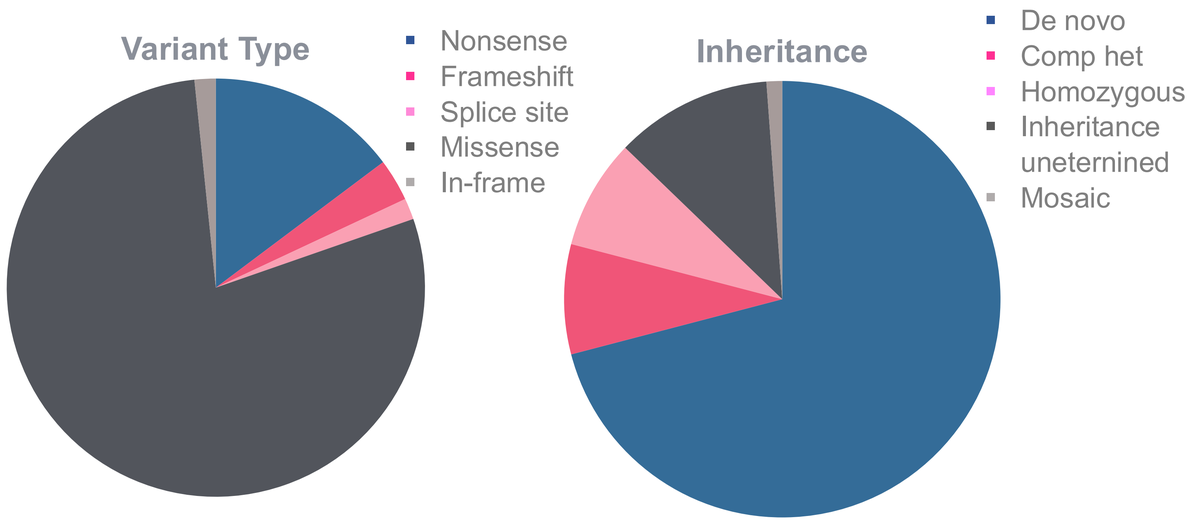


Figure 1. Genotype-first approach workflow

Results

In our cohort, 36.8% of exome trio and single cases are diagnostic.

a) Candidate variants – exome family



b) Candidate variants – exome (only index patient tested)

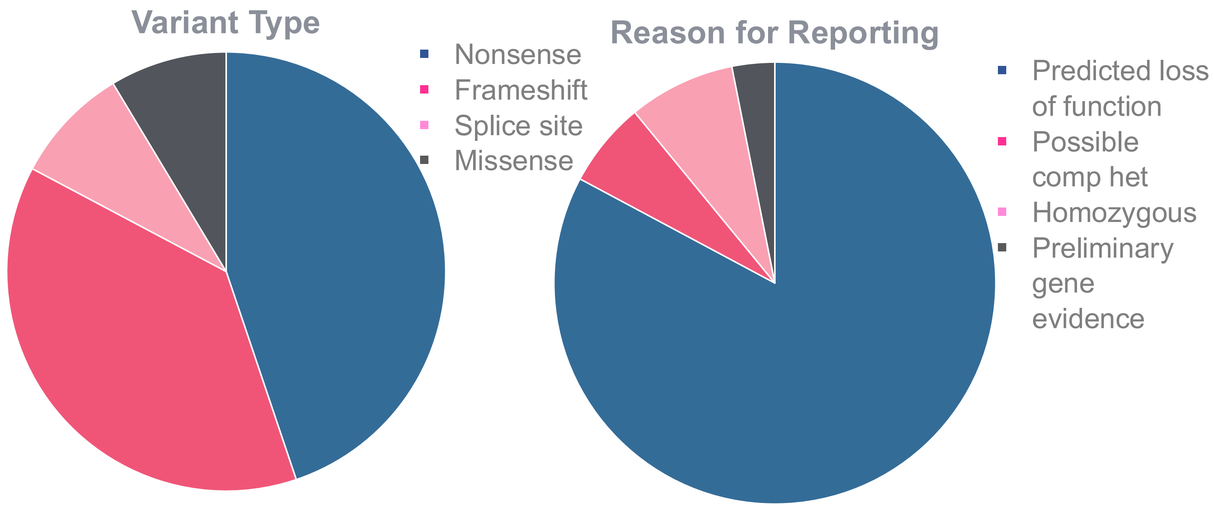


Figure 2. Candidate variants identified in both a) exome family and b) exome (only oatient tested)

Results

Table 1. Examples of reported candidate genes later reported in the medical literature

Gene	*U2AF2*	*H3F3B*	*SLC10A7*	*GNAI1*
Variant Type Identified	Missense (de novo)	Missense (de novo)	Homozygous nonsense (patient only exome)	Heterozygous missense (de novo)
Patient Phenotype	Seizures, developmental delay and dysmorphic features	Dev delay, seizures, dysmorphic features	Skeletal Dysplasia	Severe global developmental delay, cerebral palsy, mostly hypotonic, epilepsy and encephalopathy
Date of Report	January 2019	October 2020	June 2018	June 2020
Published Phenotype	Global developmental delay, systemic dysmorphism and epilepsy	Neurodevelopmental delay and/or congenital anomalies.	Skeletal Dysplasia	Developmental delay, seizures, and hypotonia
Reference	34112922 (ref 1)	33268356 (ref 2)	29878199 (ref 3) 30082715 (ref 4)	33473207 (ref 5)
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Genotype-first analysis is ideal for:

- Atypical presentations of known syndromes or genetically heterogeneous disorders
- Patients with rare disorders, not commonly identified clinically
- Cases with multiple diagnoses
- Even with genotype-first analysis, accurate and detailed clinical information is important for test interpretation

Conclusions

- Performing sequencing of additional family members allows for candidate missense variants to be identified (Figure 2 and table 1)
- Genotype-first analysis is an effective method for identifying strong candidate variants
- In multiple cases, reported candidate genes have later been reported in the medical literature (Table 1)

Blueprint Genetics

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

References:

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