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Impact of Clinician Provided Clinical Information on Whole Exome Sequencing (WES) Analysis

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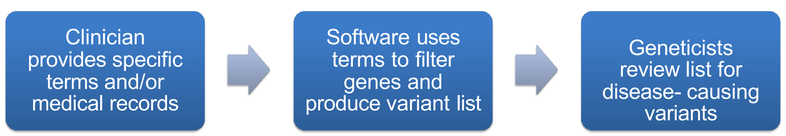
Background

- Whole exome sequencing (WES) analyzes almost all genes from the human genome and looks for genetic changes (variants) that may cause disease.
- WES as a first-tier genetic test has become a consideration for many healthcare providers[1] and is effective at identifying new genes associated with autism and intellectual disability[2].
- Clinical utility of WES varies between clinical indication[3] but was ~26% in a cohort of patients with a diagnosed of suspected autism spectrum disorder[4]
- WES utilizes patient symptoms to focus on the most relevant genes and ranks the most suspicious genetic variants in a list.
- Symptoms can be obtained from a clinician provided checklist, extracted from comprehensive medical records, or a combination of both. Checklist symptoms are the most relevant to the analysis and can be more easily reviewed than medical records.
- How symptoms are included in analysis:



Objectives

- Understand the relationship between variant ranking and symptoms from clinician-provided checklists and symptoms extracted from medical records.
- Determine if the addition of extraneous symptoms provide "noise" that may make it more difficult to find the disease-causing variant.

Methods

- Retrospective chart review was performed to identify 100 positive WES tests where analysis was performed using both a clinician provided checklist and medical records. Lists of patient symptoms were created based on source (e.g. checklist, medical records)
- Disease-causing variant rankings were compared using each list of symptoms. Main analyses compared:
  1. Combined list of symptoms from medical records and clinician provided checklist vs. clinician provided checklist only.
  2. Clinician provided symptoms vs. clinician provided symptoms with added "noise" symptoms.

Results

- Using only clinical checklist terms yielded a worse ranking when compared to the combination of both the clinical checklist terms and medical records (p=0.01). The disease-causing variant was on average 2.2 rankings lower from the top of the list of candidate variants during analysis 1 and was still identifiable in all cases.
- Introducing noise does not significantly change the ranking of the disease-causing variant (p=0.62). Mean ranking for the disease-causing variant was not significantly worse during analysis 2 when "noise" is added.

Comparison of Variant Ranking Differences Between Analyses

	Analysis 1: *CL minus Combined*	**Analysis 2:** *CL minus CLN*
Mean	2.2	-0.2
Minimum	-31.0	-26.0
Maximum	55.0	37.0
Range	86.0	63.0
Count	100.0	99.0

CL: Clinician provided symptoms from checklist
Combined: List of symptoms used in original analysis (combination of medical records and checklist)
CLN: Combination of CL symptoms and added "noise" symptoms

Discussion

- Performing analysis with a combined list of terms from the checklist and medical records more easily identifies the disease-causing variant compared to using checklist terms alone, though the disease-causing variant was still able to be identified using just clinician provided checklist terms.
- Using only a clinician provided checklist may help streamline analysis due to its ease of completion by clinicians and reduction of review time by the lab.
- The addition of unrelated terms to the analysis does not significantly make it more difficult to identify the disease-causing genetic variant.
- Furthering our understanding of WES and increasing its efficiency can assist in the uncovering of additional genes associated with autism and other developmental disabilities.

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Acknowledgements

Special thanks to my thesis committee, Dr. Gary Heiman, Connie Schultz, and Dr. Gregory Fischer, as well as the LEND faculty and fellows.