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Title: Genome analysis and clinical translation for patients with intellectual disability

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Abstract (50-75 words): Treatable intellectual disability endeavor in B.C. (TIDE BC) is a collaborative initiative in BC, Canada with a focus on prevention and treatment of intellectual disability (ID). We conduct exome and full-genome sequencing on patients with ID to identify and treat genetic defects that are not detectable by traditional technologies. We further research effective ways to report the predicted causal variations to clinicians to help them make informed clinical decisions.

Description: The project is a branch of a collaborative initiative in BC, Canada, called TIDE BC with a focus on prevention and treatment of intellectual disability (ID). Certain cases of ID are due to genetic conditions known as inborn errors of metabolism, where treatment is available through diet or drugs. However, majority of such treatable ID are undetected due to low resolution with current diagnosis techniques. Furthermore, there are cases where the symptoms suggest a metabolic disorder (hence possibly treatable), but traditional array-based detections fail to identify the underlying genetic causes. Symptoms of ID tend to worsen with time, so families with history of ID would also like to know in advance if their newborns have genetic defects associated with ID to start early preventive measures.

Emerging high-throughput DNA sequencing technologies (exome or full-genome) are revolutionizing identification of de novo variations that are causal for phenotypes (ex. ID). The project has two main goals: 1) to establish a bioinformatics pipeline for exome/full-genome analysis, and 2) subsequent translation of the computational results into clinical practice. First, when selecting for patients, we focus on ID subjects whose phenotype suggests a metabolic defect undetected by current diagnostic protocols. Once sequencing is done, our bioinformatics pipeline maps the patient DNA reads from the sequencing machine to the human genome reference and search for variation relative to it. We use a combination of different aligner software (Bowtie, BWA, Novocraft) and integrative analysis package (Samtools, Picard, GATK) to enhance the detection of indels while maintaining decent computational time. The project considers not only the missense variations as usually done, but also regulatory variations within cis-regulatory sequences governing gene transcription and RNA processing. Current work includes devising an algorithm to prioritize variants based on their predicted relevance to ID by comparing against online database resources like OMIM and similarity to previous research findings via a quantitative annotation profiles named MeSHOPs. To integrate genomic output into clinical work flow, we are designing an interface to facilitate clinical doctors to

understand and make informed clinical decisions based on the list of prioritized variations we provide for each ID subject. Initial design phase involves conducting exclusive interviews with clinical doctors to determine what information needs to be presented and how to present it. Later development stages will consist of an iterative development cycle where at each stage, a prototype is tested to groups of clinicians, and modified based on the feedback received. Final research product will provide valuable insights to the interactions between genetic researchers and clinicians, along with an integrative pipeline to efficiently detect treatable and non-treatable causes of ID and provide appropriate treatments where possible.