An automated real-time solution for genetic disorders detection and classification

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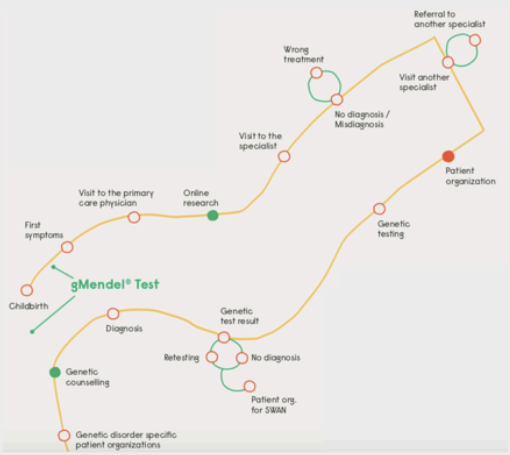
Background



- Diagnosis of genetic disorders (GDs) presents a great challenge, impacting the health, survival, and well-being of >350M people worldwide [1], [2]
- Currently, families with children affected with GDs often receive multiple misdiagnoses. The patients are faced with a lengthy and burdensome path to diagnosis, creating a heavy human, economic and societal burden, with lifetime costs surpassing €2.5M [3],[4]
- On average it takes six to eight years before a person with a GD receives the correct diagnosis and more than 40% of GDs patients are misdiagnosed at initial presentation
- Currently, diagnosis of GDs rely on a set of conventional techniques (e.g., Sanger sequencing, MLPA- and PCR-based techniques)
- Advanced genomic technologies have been changing the landscape in GDs. However, the translational gap between these and their clinical implementation has not been bridged, mainly due to:
  i) lack of clear demonstration & real-world evidence
  ii) demanding, time-consuming & complex analysis
  iii) technological limitation linked to the read length iv) lack of scalability due to costs, making it only available to few [5]

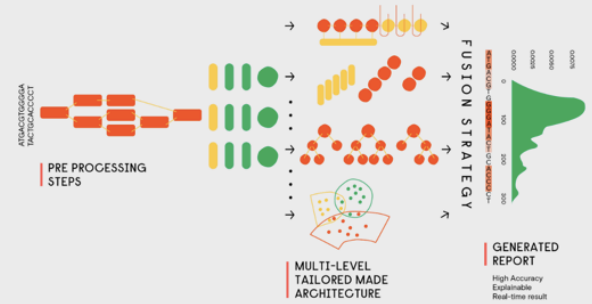
Tests and validation [7], [8]

- Several synthetically prepared samples from healthy persons and aberration positive persons
- The sequences that met the quality criteria are 81% of the total number of sequences generated by the Oxford Nanopore Technologies device.
- Demultiplexing of the barcodes in the sequence data is performed with macro-average precision of 98.2% and unclassified reads of 21%.
- In terms of computational efficiency, the proposed algorithm for demultiplexing is an order of magnitude faster than the guppy barcoder
- The ground truth chromosome classification is defined using the Smith–Waterman algorithm. In comparison to this algorithm, the proposed algorithm showed significant improvement in terms of computational efficiency.
- The chromosome classification is performed with macro-average precision of 99.1% and unclassified reads of 4%.
- The proposed algorithm manages to align a sequence in 1.1 milliseconds which is more than 50 times faster than the Smith–Waterman algorithm.
- The initial classification on the selected genetic disorders (Klinefelter, Turner, Down, Edwards, Patau and Prader-Willi/Angelman syndromes) obtained on a small subset (20%) of the synthetically prepared samples showed very promising results too (macro-average precision of 98% and computational efficiency of 0.4 milliseconds per sequence).
- All the experiments are performed on one referent hardware architecture (Intel i7 10th generation, 8 cores, 32 GB RAM, no CUDA) using thread parallelism of 10.

Process - step by step

1. Preparation of the library (multiplexing) [6], [7]
2. Oxford Nanopore Technologies device GridION x5 that provides max output of 420 bases / second is used for the DNA sequencing (2,560 channels across the device are sequenced at once)
3. The base-called .fastq files are stored and a custom tailor-made analysis pipeline for chromosomal aberration detection is triggered
4. Only the sequences that meet the quality criteria
   - Phred quality score above 10 and sequence length between 900 and 1200
   - Experimenting with sequence length between 500 and 600 (exploring the effects on the demultiplexing speed and the efficiency of chromosomal aberrations detection)
5. Demultiplexing of barcodes (person classification) [8]
6. Chromosome classification and chromosomal aberration detection [8]
7. Multiple base and conceptual models are built utilizing data driven sequence modeling for the specific chromosomal aberration (experimental phase)
   - CNN (Convolutional Neural Networks), RNN (Recurrent Neural Networks) and transformers
8. Following a multi model fusion strategy, the outcomes of the individual models are combined into a single and accurate decision.

The Phivea™ Platform



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