Precision medicine: Advanced data analysis enhances prenatal genetic testing

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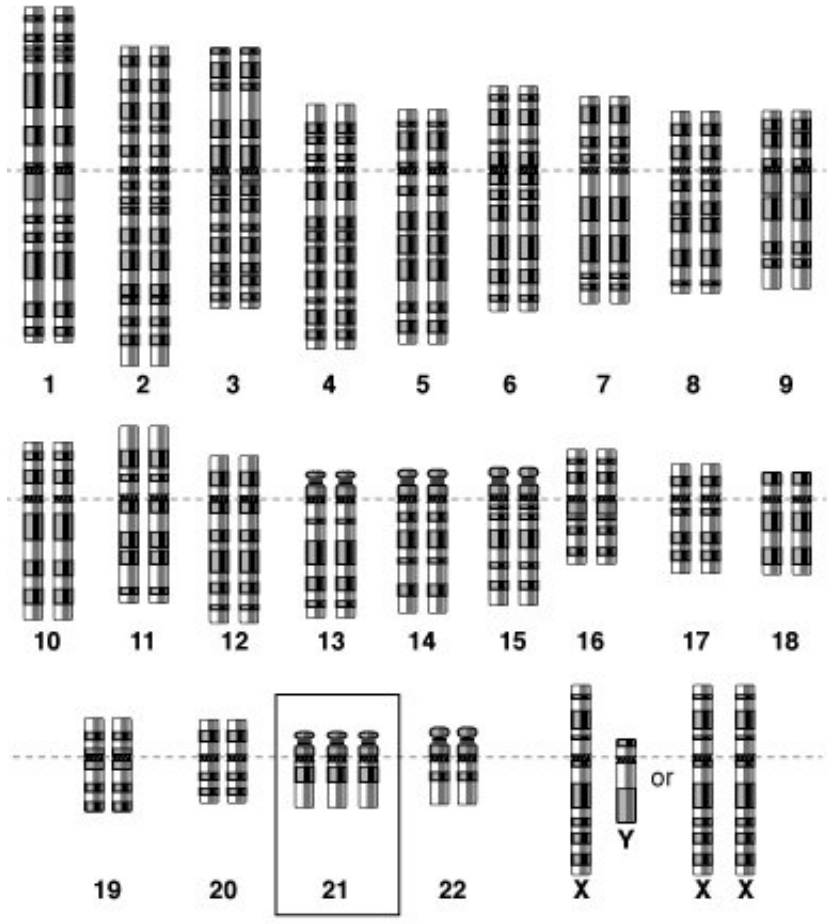

Scheme of a genetic mutation, in this case Trisomy 21 Courtesy: National Human Genome Research Institute. CC0: Public domain

Scientists have published a novel computational framework for highly

accurate and targeted Non-Invasive Prenatal genetic Testing (NIPT) assay, which enables the application of cost-effective TAC-seq laboratory method in clinical practice. The developed computational workflow allows for the detection of frequent fetal trisomies and the parental origin of trisomic chromosomes from the mother's blood cell-free DNA sample in the early stages of pregnancy.

This novel open-source computational framework, combined with targeted high-coverage sequencing data promotes the R&D of Non-Invasive Prenatal genetic Screening (NIPT) to make it completely affordable and routinely applicable in clinics. The developed data analysis method uses high-coverage sequencing data from targeted genomic regions to detect fetal trisomies and the parental origin of the trisomic chromosome from the mother's blood sample in the first trimester of pregnancy.

Researchers from the University of Helsinki, University of Tartu, and the Competence Centre on Health Technologies (CCHT) have recently published an article in *PLOS ONE*, demonstrating a novel computational framework for targeted high-coverage sequencing-based NIPT. This computational analysis framework allows for detection of fetal trisomy and the parental origin of the trisomic chromosome using targeted high-coverage sequencing data of a pregnant patient's blood sample.

The developed framework incorporates two analytical layers. First, sequentially located targeted genomic positions are classified by a hidden Markov model, which has been parameterized using the targets of the normal reference chromosome of the same sample. Next, results of a studied sample are grouped and classified for each studied chromosome (eg. Chr 21, causing Down syndrome) using supplemental machine learning methods, such as decision tree and support vector machine. The final outcome is an estimation of euploidy or trisomy for each studied chromosome.

According to the lead author of the study, senior researcher Dr. Priit Palta at the Institute for Molecular Medicine Finland (FIMM), the developed analytical pipeline was the missing part for implementing the novel advanced laboratory method called TAC-seq for NIPT applications.

"NIPT data analysis and fetus trisomy detection based on the mother's blood sample is always a challenging task. We now have both—laboratory and computational tools for developing and providing more feasible and cost-effective NIPT applications that have potential in clinical practice."

Multiple previously developed NIPT tests are based on whole-genome sequencing. Although the entire genome is covered at ultra-low sequencing depth, it is still a resource-demanding approach. The latter is reflected in the relatively high retail price of NIPT, which for example, is currently available for 250 and 550 euros in Estonia and Finland, respectively. However, targeted sequencing approaches like TAC-seq enable to focus only on the relevant chromosomes or regions of the genome, allowing processing more patients in parallel. In addition to reduced sequencing demand, robust cell-free DNA library preparation further decreases the overall NIPT cost per sample.

The head of CCHT NIPT service and R&D laboratory, Dr. Kaarel Krjutškov, noted that NIPT is a perfect example of much-praised precision medicine, which is already available and used daily in clinical practice.

"Blood origin cell-free DNA sequencing is the core technology for NIPT assays. Sequencing itself is an extremely powerful method for analyzing the content and quantity of DNA strands. Now, applying this novel computational method, we can develop cheaper targeted assays in order to read out more from the sequencing data of studied samples, increasing

the usefulness of cell-free DNA sequencing and improving the quality of pregnancy-related healthcare in the near future."

More information: Hindrek Teder et al. Computational framework for targeted high-coverage sequencing based NIPT, *PLOS ONE* (2019). DOI: 10.1371/journal.pone.0209139

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