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Review Article

Gene Big Data - A Research for Monogenic Hypertension Diagnosis

Kuangyi Wei*

Shenzhen College of International Education, Gongyuan 1st road, Shenzhen, Guangdong

Abstract: This paper designed a detailed procedure for monogenic hypertension diagnosis by Whole Exome Sequencing (WES) and provided reliable precise medication guidance. Identification of mutated points provides the clinician valuable information for effective individualized therapeutic option. Therapeutic options that specifically restore the pathway disturbed by these point mutations can be selected to give a precise medicinal guidance.

Keywords: Acute coronary syndrome, Tirofiban hydrochloride, Receptor, Platelet glycoprotein IIb/IIIa

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Corresponding author: Kuangyi Wei, liaoquanneng@ivygate.cn

1 Background

While essential hypertension can be caused by a combination of well-known factors ranging from environmental factors, behavioral factors, and polygenic inheritance, specific gain- or loss-of-function mutations can also cause series of hypertension syndromes which are identified as monogenic hypertension. These mutations usually interfere with balancing of electrolyte absorption and volume homeostasis via alternation in mineralocorticoid, glucocorticoid, or sympathetic pathways, resulting in an early-onset hypertension that can be inherited in a Mendelian fashion. Liddle syndrome is one of such heritable monogenic hypertensions arising from excessive aldosterone-independent sodium retention via the overexpressed epithelial Na+ channel (ENaC) at distal nephron apical membrane. This is caused by the mutation in *SCNN1A*, *SCNN1B* or *SCNN1G* encoding for regulatory PY motif of ENaC. General antihypertensive drug options for essential hypertension cannot effectively and specifically restore the function disturbed by single gene mutation, and lack of effective care could ultimately lead to severe sequelae of chronic hypertension.

This project aims to approach diagnosis of monogenic hypertension by detecting causative gene variants in dominant and recessive disorders via exomic sequencing. This patent develops a next generation sequencing panel covering the protein-coding regions to capture the variants underlying the common monogenic hypertension. This non-invasive approach holds tremendous clinical diagnostic potential as it provides an evidence-based diagnosis for monogenic hypertension and is amenable to automation. Moreover, identifying the cause of the inherent hypertension enables clinicians to provide individualized drug therapy by selecting medicine targeting specifically to the uncontrolled pathway. The drug options for known subtype of monogenic hypertension were summarized in table as a medication guidance.

2 Description of preferred embodiments

Different conditions of monogenic hypertension can be traced from variations on different genes or different variant locations on genes. The recommendation for the most effective medicines for each patient should be determined case by case. The determinant factors should include variant locations and genes affecting on each patient, as well as the drug impacts on genetic variance. The reference on conditions, the genotype and mode of inheritance of monogenic hypertension had been used for this patent, and double checked with Online Medalian Inheritance in Men (OMIM) for any possible omitted monogenic hypertension conditions.

All conditions then were searched on NCBI and gene variations with pathogenic characteristic were marked. Based on the protein change information linked with variance change, each specific variant location as well as its SNP were identified.

One of the main goals of this research project is consulting patients with monogenic hypertension to come up with the most effective medicinal plan based on the patient's gene variant type. Research on common drugs used to treat different types of monogenic hypertension collected a few different types of medicine. PharmGKB was used to find out targeted genes, SNPs and confidence level of clinic annotations for each medicine.

3 Experimental verification

Before comparing genome, the research team obtained data from the Whole Exome Sequencing (WES) and recorded useful and credible information from literature and data source in OMIM, and NCBI. In practice, the panel data from the exon of people with monogenic hypertension, where single-nucleotide polymorphisms (SNPs), multi-nucleotide polymorphisms (MNPs), small insertions and deletions (Indels), and combination of SNPs and Indels at a single position (MIXED) were assembled in reads in a *.fastq* file.

Stage 1. Quality control

By using FastQC, a software based on Java, the research team can evaluate the quality of the sequencing data efficiently. A total of four files, including two *.html* files and two *.zip* files, were produced from the command using FastQC. From the *.html* file, quality information across all bases sequenced was available. The research team analysed information about per base sequence quality, quality scores, sequence content, GC content, and N content, to decide if the data was credible enough to be used for later stages. After that, the team removed the adapter, primer, and Poly-A tails to obtain clean data.

Stage 2. Mapping

Mapping was performed by Burrows-Wheeler Aligner (BWA). First, an index file with reference sequence records was created. Second, the different sequences were compared with the reference by the BWA-MEM algorithm, outputting a *.sam* file. This .sam file was comprised of vital information, such as the position of match, quality of match, CIGAR, and detailed sequence.

Stage 3. Preprocessing

After the sequence information was mapped with reference, a series of preprocessing before data analysis was necessary to ensure the information was suited and optimized.

Stage 4. Mutation site detection and analysis

After preprocessing, the data obtained was clean enough for the final analysis. This includes calling to detect SNVs and Indels, filtering, and annotation.

Stage 5. Report generation

The research team inputted the T pass.avinput file into the scripts written in PERL language which matched the mutated information in the file (specifically SNPs, genes, and other information needed) with the entries in the drug knowledge base we previously built. Normally, there are three possibilities for each gene location: homologous mutations, heterozygous, and non-variants. Depending on the inheritance mode at each specific gene, the script would output the right outcome on the report.

4 Conclusion

The paper uses a mature panel with 19 related genes, which are filtered from databases such as NCBI and OMIM, to diagnose monogenic hypertension by detecting gene variants via exomic sequencing and provide a recommendation of personalized drug usage. Also, the drugs which are used to rebalance the pathway were summarized in a table for clinic purpose. This invention is part of the individualized drug therapy and can be applied under a variety of situations such as hospitals, gene centers, labs, health centers, Gene Company and pharmaceutical factories to help patients and medical workers to reduce their risk in excessive side effects.