GeNeXpreSS

Marching Towards Perfection

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Mystery of LCC (leukoencephalopathy, intracranial calcifications and cysts)– SNORDed out… (Jenkinson et al., 2016)

Monogenic causes of ribosomal dysfunction can confer a remarkable degree of specificity in terms of human disease phenotype. Box C/D small nucleolar RNAs (snoRNAs) are evolutionarily conserved non-protein-coding RNAs involved in ribosome biogenesis. Biallelic mutations in the gene *SNORD118*, encoding the box C/D snoRNA U8, cause the cerebral microangiopathic leukoencephalopathy with calcifications and cysts (LCC), presenting at any age from early childhood to late adulthood. These mutations affect U8 expression, processing and protein-binding and thus implicate U8 as essential in cerebral vascular homeostasis.

Want "Mr Perfect genome" – Barcode it (Peters et al., 2014)

Next generation sequencing (NGS) technologies, primarily based on massively parallel sequencing, have touched and radically changed almost all aspects of research worldwide. Despite all of this progress, the current state-of-the-art in sequence technology is far from generating a "perfect genome" sequence and much remains to be understood in the biology of human and other organisms' genomes. In this paper, the authors outline why the "perfect genome" in humans is important, what is lacking from current human whole genome sequences, and a potential strategy for achieving the "perfect genome" in a cost effective manner. The "Perfect genome" solution employs advanced massively parallel DNA sequencing of "co-barcoded" reads from long genomic DNA molecules, and efficient *de novo* assembly empowered by these barcoded reads.

Whole genome sequencing in pediatric practice– Now, next or later (Stavopoulous et al., 2016)

The recommended first-tier clinical investigation for identifying the etiology of congenital malformations and neurodevelopmental disorders is chromosome microarray analysis (CMA) for copy-number variations (CNVs), often followed by gene(s)-specific sequencing to search for smaller insertion–deletions (indels) and single-nucleotide variant (SNV) mutations. In this prospective study the authors utilized whole genome sequencing (WGS) and comprehensive medical annotation to assess 100 patients referred to a Pediatric Genetics service and compared the diagnostic yield versus standard genetic testing. WGS identified genetic variants meeting clinical diagnostic criteria in 34% of cases, representing a fourfold increase in the diagnostic rate over CMA alone and more than twofold increase in CMA plus targeted gene sequencing. WGS identified all rare clinically significant CNVs that were detected by CMA. Clinical implementation of WGS as a primary test will provide a higher diagnostic yield than conventional genetic testing and potentially reduce the time required to reach a genetic diagnosis.

Holoprosencephaly– Not so simple (Mouden et al., 2016)

Holoprosencephaly (HPE) is the most common congenital cerebral malformation, characterized by impaired forebrain cleavage and midline facial anomalies. Heterozygous mutations in 14 genes have been associated with HPE and are often inherited from an unaffected parent, underlying complex genetic bases. HPE may result from a combination of multiple genetic events. In this study the authors

have used whole exome sequencing and targeted high-throughput sequencing approaches to identify mutations in HPE subjects. They reported two HPE families in which two mutations are implicated in the disease. In the first family with two fetuses with alobar and semi-lobar HPE, mutations were found in two genes involved in HPE, *SHH* and *DISP1*, inherited respectively from the father and the mother. The second reported case was a family with a 9-year-old girl presenting with lobar HPE, who was found to harbour two compound heterozygous mutations in *DISP1*. Together, these cases of digenic inheritance and autosomal recessive HPE suggest that in some families, several genetic events are necessary to cause HPE. This study highlights the complexity of HPE inheritance and has to be taken into account by clinicians to improve genetic counseling for HPE.

References

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