GeNeXpreSS

Beyond Exome: Fishing for Answers in the Expansive Ocean of "Omics"!

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Balanced but not benign– WGS unravels pathogenic events in balanced chromosomal rearrangements

(Schluth-Bolard et al., 2019)

Schluth-Bolard et al. report a study of 55 patients with developmental disorders and balanced chromosomal rearrangements where Whole genome paired end sequencing was done to look for pathogenic events that could explain the abnormal phenotypes. Gene expression analysis of disrupted & surrounding genes, and disruption of topology associated domains was also taken into account for analysis. Forty-nine out of 55 of the rearrangements could be detected using WGS. Molecular signatures at breakpoints indicated that most events arose randomly with non-homologous end joining being the main mechanism. Twenty-two patients achieved a diagnosis, of which 15 had a gene disruption and 7 showed a position effect. Authors were also able to discover 16 novel candidate genes using this approach. The authors conclude by saying that paired end WGS can be used for structural variant characterisation in clinical settings

RNA–seq and WGS– Two heads are better than one (Bronstein et al., 2020)

Bronstein et al. report a family with retinal dystrophy where a combined WGS and RNA-seq approach was used for identification of the causative variant in a non-coding region as well as functional validation of the variant in retinal organoids was done. A five-member family of a non-consanguineous couple with two children affected with retinal dystrophy underwent whole exome sequencing, which identified a single known pathogenic frameshift variant in *CNGB3* in the affected siblings. WGS revealed two additional variants in *CNGB3*, both being in the intronic region. The authors subsequently used patient derived induced pluripotent stem cells (iPSCs) and used this to generate retinal organoids. These organoids were used for transcriptome analysis using RNA-seq. Analysis of the alternative transcripts revealed one of the intronic variants as disrupting splicing. Immunocytochemical analysis of retinal organoids demonstrated mis-localisation of the truncated *CNGB3* proteins. The authors conclude that this combined approach can be useful in identifying and functionally validating variants in non-coding region for cases with unresolved genetic diagnosis.

WGS as first tier test for intellectual disability (Lindstrand et al., 2019)

Lindstrand et al used WGS in a mixed cohort of patients with intellectual disability (n=324) to identify the underlying genetic mechanisms. The authors obtained an overall diagnostic yield of 27%. This approach enabled detection of structural variants, single nucleotide variants, uniparental disomy as well as short tandem repeat (STR) expansion. In at least 7% cases, WGS enabled detection of complex structural rearrangements.

Metabolomics– the new kid on the block

(Yazdani et al., 2019)

Yazdani et al. report a systems biology approach in an attempt to unravel the gene-disease mechanisms in complex disorders. They used exome sequencing datasets from the Atherosclerosis Risk in Communities study, and studied effects of annotated loss-of-function variants on 122 metabolites.

The authors found effect of *KIAA1755* variants on levels of eicosapentaenoate, which is known to be associated with essential hypertension. Similarly, they found effect of *CLDN17* loss-of-function mutations on metabolites from amino acid and lipid pathways. The authors suggest that this approach integrates several biological processes, and leads to findings that may functionally connect genetic variants with complex diseases

References

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