Fast Forward – is Multiomics a resurgence of old?

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BACKGROUND

- High-throughput next generation sequencing (NGS) including exome and genome sequencing has become the first-tier diagnostic testing to ascertain clinical diagnosis.
- One of the challenges is to understand the disease mechanism of the variants of uncertain significance detected by NGS in known Mendelian genes, newly discovered genes and identify new deep intronic variants.
- Single site omics approaches such as biochemical confirmation have been used in genetics for a long time. Multiomics is an approach to collectively assess and analyze data sets from different omic technologies including genome, proteome, transcriptome, and epigenome.
- Incorporating mRNA and protein expression data generated by RNAseq, biochemical data such as enzyme activity and biomarker profile, we have reclassified variants from uncertain significance to disease causing

RESULTS

Correlation of molecular variants with biochemical results

GAA Variants	# of cases	Average enzyme activity (normal range: >=2.10)
biallelic LP/P	26	0.42 (0.21 -0.75)
1 LP/P (+VOUS/Pseudo/neg)	19	1.63 (0.35-2.63)
2 VOUS / 1 VOUS+1 pseudo / 2 pseudo	25	1.53 (0.72-5.53)
1 VOUS / 1 pseudo + neg & neg	11	1.61 (0.82 -2.87)
Total	81	-

GBA Variants	# of cases	Average enzyme activity (normal range: >=1.60)	Average biomarker (normal range: <=17.41)
Biallelic LP/P	27	0.47 (<0.26-0.78)	49.22 (12.64->200)
1 LP/P + 1 VOUS	4	0.58 (<0.26-1.07)	13.91 (14.55->200)
1 LP/P + neg	5	1.48 (1.30-1.75)	6.90 (<5-6.9)
Total	36	-	-

Gender	*GLA* Variant	# of cases	Average enzyme activity (normal range: >=1.10)	Average biomarker (normal range: <=1.11)
Male	LP/P*	20	0.53 (<0.23 – 0.89)	22.6 (0.69 – 130.56)
	c.427G>A (p.Ala143Thr) LP	9	2.05 (0.92 – 4.22)	0.79 (<0.45 – 1.21)
	VOUS or Neg	4	1.34 (0.69 – 2.72)	1.03 (0.63 -1.47)
Female	LP/P	7	NA	2.62 (0.46 – 5.01)
	VOUS	3	NA	4.40 (0.58 -11.15)

* Exclude c.427G>A (p.Ala143Thr) variant

Variant reclassification examples

***DMD* c.531-10T>A**

- 11 yo male with toe-walking, delayed motor development, clinical suspicion of Becker muscular dystrophy.
- *DMD* c.531-10T>A VOUS was identified
- Follow up RNAseq on muscle biopsy showed a frameshift of amino acid sequence, reduced *DMD* mRNA expression and unstable dystrophin in the presence of this variant.
- *DMD* c.531-10T>A was reclassified as LP

***ABCD1* c.598G>A (p.Asp200Asn)**

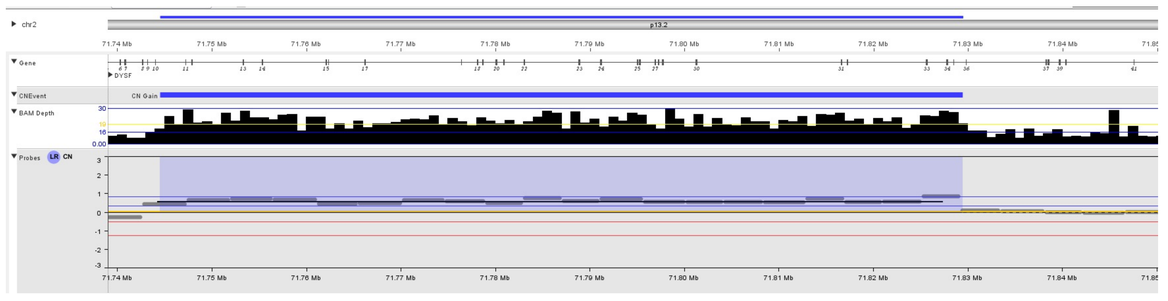
- This variant was identified in a male infant with abnormal NBS
- Follow up parental testing showed maternal inheritance
- Maternal grandfather with clinical suspicion of XALD and abrnomal biochemical profile
  - C26:0 2.78 (ref 0.31-0.81)
  - C24:c22 1.42 (ref 0.726-0.988)
  - C26:C22 0.05 (ref 0.049-0.0118)
- Reclassified *ABCD1* c.598G>A (p.Asp200Asn) to LP

***GAA* c.1796C>A (p.Ser599Tyr)**

- This variant was identified in and adult with muscle weakness and clinical suspicion of late onset Pompe disease
- *GAA* c.1796C>A (p.Ser599Tyr) was originally reported as VOUS
- Enzyme performed: GAA = 0.41 µmol/L/hr (Normal > or = 2.10 µmol/L/hr)
- *GAA* c.1796C>A (p.Ser599Tyr) reclassified as LP
- This variant was also identified in another adult patient with hypotonia, muscle weakness, abnormal EMG, diaphragmatic weakness, reduced pulmonary function, low enzyme activity (performed in an external lab) and clinical suspicion of Pompe disease.

***DYSF* exon 10-35 dup**

This duplication has not been reported to be disease casing.
RNAseq confirmed this duplication.



CONCLUSION

- Our data shed lights on the correlation between biochemical results and molecular findings, as well as genotype-phenotype relationship in Pompe, Gaucher and Fabry diseases.
- The technological advances in multiomics approaches are very promising for improving diagnostic performances and personalized treatment, but it's required datasets from multiple measurements, large reference databases for different genes and diseases, integrated analysis methods and strong computational infrastructure.