Fast Forward – is Multiomics a resurgence How Does Multiomics Help Variant Reclassification?

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BACKGROUND

- One of the biggest challenges of whole exome and genome sequencing is to report variants of uncertain significance (VOUS) in genes related to the phenotype that potentially help understand the disease mechanism.
- Multiomics approaches have been implemented separately or collectively in assessing data to provide additional information regarding the alterations of the protein structure and function to further interpret the pathogenicity of a variant.
- We have reclassified variants from uncertain significance to disease-causing (*DMD* c.4806T>A; *DYSF* duplication of exons 10-35; *GAA* c.1796C>A; *ABCD1* c.598G>A) by incorporating RNA sequencing results or biochemical profile with clinical phenotype and family history.
- We retrospectively investigated the biochemical and molecular results of Pompe, Fabry, and Gaucher disease single gene testing to determine the association of the biochemical results with the molecular results, and whether biochemical results would help variant reclassification.

RESULTS

Patient demographic information

Patient cohort	# of cases								
	GAA			GBA			GLA		
	M	F	Total	M	F	Total	M	F	Total
Adult	14	16	30	23	24	47	21	22	43
Pediatric	55	49	99	6	11	17	38	2	40
Total	69	65	134	29	35	64	59	24	83

Correlation of *GAA* variants with biochemical results

Group	*GAA* Variants	# of cases	Ave. enzyme activity (range)
1	Biallelic LP/P (Adult)	17	0.42 (0.21 – 0.75)
	Biallelic LP/P (Ped)	17	0.57 (026 – 1.38)
	Biallelic LP/P (Total)	34	0.50 (0.21 – 1.38)
2	1 LP/P + 1 VOUS	20	1.24 (0.26 – 3.14)
3	2 VOUS	7	1.79 (0.64 – 5.53)
4	1 LP/P + 1 Pseudo	13	1.36 (0.83 – 1.93)
5	2 Pseudo	32	1.36 (0.51 – 2.02)
6	1 LP/P or 1 VOUS or 1 Pseudo	24	1.79 (0.79 – 2.89)
7	1 VOUS + 1 Pseudo	4	1.45 (1.38 – 1.66)

Normal range: >=2.10µmol/L/hr, LP/P: likely pathogenic / pathogenic; VOUS: variant of uncertain significance; Pseudo: pseudodeficiency allele

Correlation of *GBA* variants with biochemical results

GBA Variants	# of cases	Ave. enzyme activity (range)	Ave. Lyso-Gb1 (range)
Biallelic LP/P (Adult)	37	0.49 (<0.26 – 0.95)	110.0 (5.89 - >200)
Biallelic LP/P (Ped)	12	0.90 (<0.26 – 3.49)	120.6 (13.14 - >200)
Biallelic LP/P (Total)	49	0.60 (<0.26 – 3.49)	112.75 (5.89 - >200)
1 LP/P + 1 VOUS	8	0.67 (<0.26 – 1.55)	89.15 (6.56 - >200)
1 LP/P	7	2.49 (1.3 – 5.52)	5.63 (<5 – 6.9)

Correlation of *GLA* variants with biochemical results

GLA Variants	# of cases	Ave. enzyme activity (range)	Ave. Lyso-Gb3 (range)
LP/P (Adult)	18	0.37 (<0.23 – 0.86)	25.55 (1.15 – 130.56)
LP/P (Ped)	15	0.53 (<0.23 – 0.89)	11.19 (1.01 – 69.46)
LP/P (Total)	33	0.44 (<0.23 – 0.89)	19.02 (1.01 – 130.56)
1 VOUS	9	1.71 (0.77 – 3.40)	2.84 (<0.45 – 14.93)

- Enzyme normal range: >=1.10µmol/L/hr; Lyso-Gb3 normal ranger: <=1.11 ng/mL
- Exclude c.427G>A (p.Ala143Thr) variant

CONCLUSION

- Our data set for the three lysosomal storage disorders indicated biochemical results alone are insufficient for variant reclassification albeit it's one of the critical components.
- Additional information from multiple measurements through multiomics, large reference and patient databases, integrated analysis methods, and computational infrastructure is required to further interpret the VOUS variants to ensure improving early diagnosis and personalized treatment.
- Advanced Omics technologies will help discover of additional biomarkers and further elucidate the phenotype-genotype relationship along with tracking response to new therapies.
- Accurate variant classification and interpretation through the incorporation of omics will help personalized genetic counseling to reduce unnecessary medical visits and family anxiety.

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