Integrative Genomic and Metabolomic approach to diagnose rare Mendelian diseases in Qatar

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Background

Rare Mendelian diseases is hampered by the low diagnostic yield where a great proportion of patients remain undiagnosed. OMICs-approaches have been proven useful in complementing genetic findings and bridging the diagnostic gap. Metabolomics is an emerging field involving the characterization of small molecules known as metabolites and their association with disease-related pathways. Along with an extensive genomic analysis pipeline, we integrated metabolomic data from 20 patients that have unknown genetic cause

Objectives

- **Develop an integrative genomic and metabolomic approach with emphasis on metabolite-phenotype relation**
- **Determine whether metabolomics would explain the pathophsyiology or molecular etiology of diseases**

Methodology

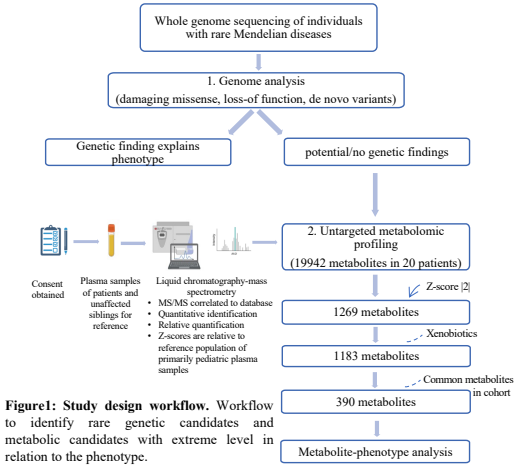


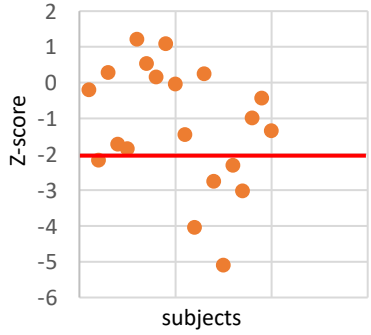
Figure1: Study design workflow. Workflow to identify rare genetic candidates and metabolic candidates with extreme level in relation to the phenotype.

Clinical presentation

- 5 patients with hypothyroidism/thryoid dysfunction
- Two siblings from a consanguineous family and a novel genetic finding in CSPG4 (p.Asp457Gly) presenting with developmental delay, severe hypotonia, laxity of joints, and myoclonic encephalopathy with seizures

Results

A) Oxalate levels in cohort



B) Enrichment pathway analysis

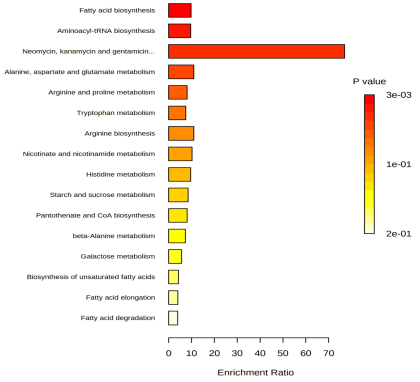
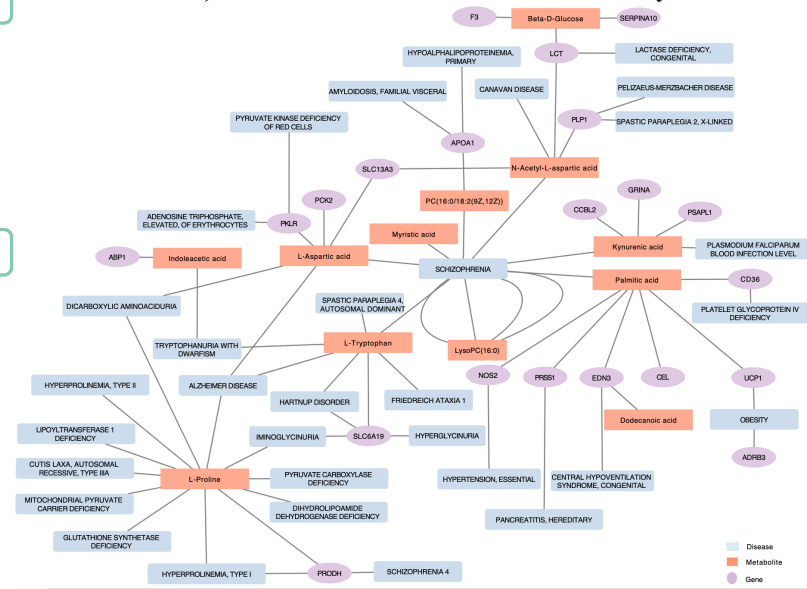


Figure A) Downregulation observed in 5 patients with hypothyroidism or thyroid dysfunction **B)**Metabolic perturbations shared between the two affected siblings reveals perturbation in tryptophan metabolism (downregulation). Tryptophan forms Kynurenic acid, a glutamate receptor antagonist that prevents excitotoxicity and seizures[1]. **C)**Network analysis exploring metabolite-gene-disease interaction using 2-fold differentially expressed genes from CSPG4(p.Asp457Gly) zebrafish model and shared metabolic perturbations with z-score >1.5 or <-1.5 between the siblings. Network analysis revealed association between the differentially expressed genes and metabolites. Three genes, GRINA, KYAT3/CCBL2, and PSAPL1, associated with kynurenic acid were differentially expressed. Other metabolite-gene-disease associations relating to siblings' phenotype are are Proline-PPIB-Osteogenesis imperfectatype IX, Proline-PRODH-Schizophrenia, and N-acetylasparate-PLP1-Spasticparaplegia & Pelizaeus-Merzbacher disease

C)Metabolite-Gene-Disease network analysis



Conclusion

The use of metabolomics alongside genomics shows promising results in diagnosing rare Mendelian diseases by identifying novel biomarkers, uncovering the pathophysiology of a disease, and most importantly, validating genetic results.

References/Aknowledgement

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References:

1.Schwarcz, Robert, and Trevor W Stone. "The kynurenine pathway and the brain: Challenges, controversies and promises." Neuropharmacology vol. 112,Pt B (2017): 237-247. doi:10.1016/j.neuropharm.2016.08.003