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Untargeted Metabolomic Analysis of Sjögren-Larsson Syndrome Reveals a Distinctive Pattern of Multiple Disrupted Biochemical Pathways

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Background: Sjögren-Larsson syndrome (SLS) is a rare inherited neurocutaneous disease characterized by ichthyosis, spastic diplegia or tetraplegia, intellectual disability, and a distinctive retinopathy. SLS is caused by bi-allelic mutations in ALDH3A2, which codes for fatty aldehyde dehydrogenase and results in abnormal metabolism of long chain aldehydes and alcohols. The biochemical abnormalities in SLS, however, are not completely known and the pathogenic mechanisms leading to symptoms are unclear.

Hypothesis: We hypothesized that SLS patients have abnormal metabolism beyond the known primary lipid defect. To search for secondary biochemical pathways that are disrupted, we performed untargeted metabolomic screening in SLS subjects.

Methods: Fasting blood samples were collected from 20 SLS subjects (11 F, 9 M; ages 4-30 yrs, mean 13.0 ± 7.3) enrolled in the Sterol and Isoprenoid Research Consortium along with age- and sex-matched controls. Plasma metabolites were separated and quantitated by LC-MS/MS. Metabolites were identified and statistically compared using q values and Random Forest analysis.

Results: Metabolomic analysis of SLS plasma detected 1041 total metabolites, including 823 identified metabolites and 218 unknown ones. Of the identified metabolites, 121 (14.7%) quantitatively differed in the overall SLS cohort from controls; 77 metabolites were decreased and 44 were increased. Pathway analysis pointed to disrupted metabolism of sphingolipids, sterols, bile acids, glycogen, purines and certain amino acids such as tryptophan, aspartate and phenylalanine. Random Forest analysis identified a unique metabolomic profile of 30 biochemicals involving 20 pathways that had a predictive accuracy of 100% for discriminating SLS from controls.

Conclusions: These results provide new insight into the abnormal biochemical pathways that likely contribute to disease mechanisms in SLS. The results also identify new potential therapeutic targets and may constitute a biomarker panel for diagnosing SLS and monitoring drug efficacy in future clinical trials.