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Serum protein signatures as a non-invasive tool for monitoring nonalcoholic steatohepatitis (NASH)

While histological examination of the liver allows for precise diagnosis, it can result in abdominal discomfort and bleeding, and may not be able to provide unbiased diagnosis if only a small section of hepatic tissue is examined.

Current diagnostic and prognostic tools for NASH require unreliable, invasive procedures

Nonalcoholic fatty liver disease (NAFLD) is a liver condition that affects 25% of the global population[1]. Nonalcoholic steatohepatitis (NASH) refers to an aggressive form of NAFLD that is predicted to rise exponentially through the year 2030[2]. NASH is characterized by liver steatosis accompanied by liver cell injury and inflammation. NASH may include liver fibrosis and progression to cirrhosis (permanent liver scarring), liver cancer, and functional failure resembling heavy alcohol usage. A central hallmark of NASH is excessive accumulation of fat in the liver[3]. While the precise etiology of NAFLD remains unknown, lipid metabolic pathways, obesity, type 2 diabetes, and genetic susceptibility loci have been identified as potential contributors[4].

Diagnosing the severity of NAFLD and NASH heavily relies on liver biopsy. While histological examination of the liver allows for precise diagnosis, it can result in abdominal discomfort and bleeding, and may not be able to provide unbiased diagnosis if only a small section of hepatic tissue is examined.

Non-invasive techniques for NAFLD diagnosis and prognosis include imaging and measuring the enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST). However, ALT and AST measurements are not sufficiently sensitive or specific[5], and non-invasive imaging modalities are not accurate or precise enough to differentiate between stages of steatosis or fibrosis[6]. Therefore, there is an increasing demand for safe, reliable, and non-invasive diagnostic tools[7,8].

Proteomics as a non-invasive tool for diagnosing and monitoring NASH

Different components of liver pathology of NASH are characterized by distinct sets of protein signatures[3,4,7,8]. While no one protein is sufficient for assessing NASH, multiple blood biomarkers can be combined to improve diagnostic accuracy[8]. Therefore, proteomic approaches present a promising opportunity for identifying protein signatures associated with the different components of NASH pathology.

Proteomic-based monitoring of NASH and other diseases will require a tool that can measure multiple biomarkers simultaneously, while maintaining sensitivity and specificity. To this end, protein screening using the SomaScan® Assay has shown promise for accurate and specific identification of a massive menu of protein biomarkers over a large dynamic range[9].

Using the SomaScan Assay to identify and characterize NASH

In a 2017 study published in Scientific Reports, Wood et al.[10] used the SomaScan Assay to identify biomarkers for susceptibility to NASH in the context of obesity. This study involved 576 adults with extreme obesity divided randomly into a discovery cohort and a validation cohort. The discovery cohort (n=443) was used to identify serum protein biomarkers associated with steatosis. The validation cohort (n=133) was used to test whether the identified serum protein biomarkers could reliably predict steatosis.

Using the SomaScan Assay, Wood et al. surveyed 1129 serum proteins (LOQ=0.3pM, median CV~5%). Eight proteins associated with NASH were identified by multivariate analysis (three positively correlated and five negatively correlated). Using these 8 biomarkers, Wood et al. developed a model for predicting steatosis.

In addition to a proteomics-based approach, the authors also stratified participants based on the presence of a single nucleotide polymorphism in the PNLPA3 gene, a well-characterized genetic risk factor associated with steatosis, and a phenomic classification that assessed 19 known phenotypic variables that are associated with hepatic fat accumulation.

Using mathematical modeling, Wood et al. reported that the proteomic approach using the SomaScan Assay had a higher association with steatosis in the discovery cohort (0.913 AUC) than the genomic (0.596 AUC) or phenomic (0.886 AUC) classifiers. The proteomic approach was also the most successful predictor of NASH in the validation

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cohort. Finally, while combining all three approaches (genomic, phenomic, and proteomic) resulted in the highest predictive value, the proteomic approach alone was more powerful than the genomic and phenomic approaches combined.

While studying susceptibility to NASH in specific disease contexts has been informative, a recent proof-of-concept study by Williams et al.[11] involving 8,566 participants demonstrated that plasma protein levels detected using the SomaScan Assay can also reliably predict hepatic fat accumulation from multiple cohorts regardless of disease context[11]. Similar to the design adopted by Wood et al.[10], but now measuring ~5,000 different proteins, Williams and colleagues developed a model to predict steatosis based on protein levels and validated their model using a sub-group of participants. The authors observed that plasma protein levels measured with the SomaScan Assay more accurately predicted liver fat accumulation when compared to the best available clinical model[11]. In sum, using the SomaScan Assay to determine circulating protein levels can serve to both diagnose and predict the presence of or susceptibility to hepatic steatosis.

The SomaScan Assay and the future of NASH

The studies by Wood et al.[10] and Williams et al.[11] demonstrate that the SomaScan Assay can be reliably used to help diagnose, predict, and monitor NAFLD non-invasively. Future research could help determine whether the SomaScan Assay can also be leveraged to measure changes occurring to NASH-associated protein levels over the course of interventions or to predict the success of interventions in particular patient subpopulations. Additional studies involving genetically diverse, multi-ethnic populations could also provide more comprehensive information regarding ethnicity-specific protein signatures related to liver steatosis. Diagnostic tests for individual NASH biopsy components (steatosis, inflammation, ballooning, fibrosis) are currently under development and will be available soon from SomaLogic, Inc.

To learn how you can get started using the SomaScan Assay for NASH and NAFLD research, visit SomaLogic.com/discovery.

Studies demonstrate the SomaScan Assay can be reliably used to help diagnose, predict, and monitor NAFLD non-invasively.

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Founded in 2000, SomaLogic, a global leader in proteomics, pioneered the SomaScan Platform with unparalleled coverage. Unlike any other technology, the SomaScan Assay enables users to take up to 11,000 protein measurements from just 55 µL of various body fluids like plasma, serum, CSF, and urine.

The proprietary SomaScan Assay measures proteins with high specificity, high throughput, and high reproducibility, which enables the possibility of faster, more precise drug discovery. Our A.I. and machine learning-powered bioinformatics algorithms, operated in tandem with the company's database of more than 750,000 protein samples, helped to create a growing suite of SomaSignal® Tests. These tests provide additional insights into the current health status of patients and the future risk of conditions and diseases. Custom and disease-specific panels are also available for a more targeted approach.

LEARN MORE - https://somalogic.com/somascan-assay-services/

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