Whole Exome Analysis Associates Hemicentin1 with Lung Function, Pointing Towards a Potential Role in IPF

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RATIONALE: As a heterogeneous respiratory disease, idiopathic pulmonary fibrosis (IPF) is likely to be driven by distinct pathological and biological processes, many that will have a genetic component. Commonly used methods, such as genome wide association studies (GWAS), are unable to identify causal rare variants, whereas whole exome sequencing (WES) allows us to link rare protein-coding variants to physiological phenotypes in a systematic way. The potential to uncover novel genes and pathways driving important physiological factors such as lung function is tantalising. METHODS: UK Biobank (UKBB) exome sequence from 141,738 UK Biobank unrelated participants of European ancestry with FEV1/FVC ratio z-score available were used for this analysis. Collapsing analysis of rare (minor allele frequency <0.1%) protein truncating variants (PTV) in a linear regression model correcting for age and gender was performed to find associations between systemic dose reduction and FEV1/FVC ratio z-score. RESULTS: Of the 141,738 UK Biobank exome sequenced participants we found 289 carriers of rare (MAF<0.1%) PTV in the gene encoding Hemicentin1 (HMCN1). These individuals had a significantly higher FEV1/FVC ratio Z-score (p-value = 4.94x10^{-13}). The location of the PTVs were equally distributed across the whole gene. We leveraged public transcriptomics data and explored if HMCN1 is associated with known pathological lung conditions. We discovered that whole tissue expression of HMCN1 is significantly increased in Idiopathic Pulmonary Fibrosis (IPF) patients, and that patients with the highest HMCN1 expression exhibit a distinct gene expression pattern in comparison to patients with low HMCN1 expression. Ingenuity pathway analysis identified TGFβ, TGFBR1 and SMAD7 as potential up-stream regulators of HMCN1, suggesting increased TGFβ signalling might drive the observed expression pattern in patients with increased HMCN1 expression. HMCN1 has been described to be regulated by TGFβ in cardiac fibroblast and kidney podocytes, and we found that TGFβ regulated HMCN1 in normal human fetal lung fibroblasts in a dose and time dependent manner. CONCLUSIONS: We have identified that carrying a HMCN1 PTV is associated with increased FEV1/FVC z-score. Clinically, we also found that HMCN1 expression is significantly increased in individuals diagnosed with IPF and that high HMCN1 expression is associated with a gene expression profile consistent with increased TGFβ signalling, a pathway known to be important in lung
fibrosis. These observations demonstrate the power of WES to uncover rare functional variants that influence complex respiratory traits and diseases, with the potential to identify new therapeutic targets and biomarkers for disorders of great unmet need.

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