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The undiagnosed disease burden associated with alpha-1 antitrypsin deficiency genotypes

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Only 6.4% of those with genotype-defined alpha-1 antitrypsin deficiency had been diagnosed with this serious disease in UK Biobank. Genotype-guided diagnosis could help to identify the thousands of people in the UK with this partially preventable disease. https://bit.ly/3dMu5Ng

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ABSTRACT Alpha-1 antitrypsin deficiency (AATD), mainly due to the PI*ZZ genotype in *SERPINA1*, is one of the most common inherited diseases. Since it is associated with a high disease burden and partially prevented by smoking cessation, identification of PI*ZZ individuals through genotyping could improve health outcomes.

We examined the frequency of the PI*ZZ genotype in individuals with and without diagnosed AATD from UK Biobank, and assessed the associations of the genotypes with clinical outcomes and mortality. A phenome-wide association study (PheWAS) was conducted to reveal disease associations with genotypes. A polygenic risk score (PRS) for forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio was used to evaluate variable penetrance of PI*ZZ.

Among 458 164 European-ancestry participants in UK Biobank, 140 had the PI*ZZ genotype and only nine (6.4%, 95% CI 3.4–11.7%) of them were diagnosed with AATD. Those with PI*ZZ had a substantially higher odds of COPD (OR 8.8, 95% CI 5.8–13.3), asthma (OR 2.0, 95% CI 1.4–3.0), bronchiectasis (OR 7.3, 95%CI 3.2–16.8), pneumonia (OR 2.7, 95% CI 1.5–4.9) and cirrhosis (OR 7.8, 95% CI 2.5–24.6) diagnoses and a higher hazard of mortality (2.4, 95% CI 1.2–4.6), compared to PI*MM (wildtype) (n=398 424). These associations were stronger among smokers. PheWAS demonstrated associations with increased odds of empyema, pneumothorax, cachexia, polycythaemia, aneurysm and pancreatitis. Polygenic risk score and PI*ZZ were independently associated with FEV_1/FVC <0.7 (OR 1.4 per 1-SD change, 95% CI 1.4–1.5 and OR 4.5, 95% CI 3.0–6.9, respectively).

The important underdiagnosis of AATD, whose outcomes are partially preventable through smoking cession, could be improved through genotype-guided diagnosis.