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Title: Rare alpha-1 antitrypsin mutations in the Irish population

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Body: AAT deficiency (AATD) results from mutations in the SERPINA1 gene, classically presenting with early-onset emphysema and liver disease. The most common mutation responsible for AATD is the Z mutation. AAT deficiency is under-diagnosed and prolonged delays in diagnosis are common. ERS and ATS guidelines advocate the screening of all COPD, poorly-controlled asthma, and cryptogenic liver disease patients, as well as first degree relatives of known AATD patients. 8,000 individuals have been screened following ATS/ERS guidelines as part of the Irish national targeted detection programme. AAT levels were determined by immunonephelometry. AAT phenotyping was performed by isoelectric focussing. Rare and novel mutations were identified by DNA sequencing of the SERPINA1 gene. A number of rare SERPINA1 mutations including I, F, V, Xchristchurch, Zbristol, and Mmalton were identified. The I mutation (Arg39Cys) was present at a relatively high frequency (0.0038) in the targeted population, with over 60 cases described. Three Null SERPINA1 mutations were detected, including two novel mutations. In addition, the first individuals in Ireland homozygous for a Null mutation and for the Mmalton mutation were identified. Current testing of suspected AATD cases is often limited and can miss rare and novel clinically significant SERPINA1 mutations. The rare mutations described in this study were not detected by a commonly used genotyping assay; however, the low AAT levels prompted their correct identification using more detailed genetic analysis. Our findings underline the need for a comprehensive diagnostic work up of all patients with low AAT levels including phenotyping, genotyping and if necessary, sequencing of the SERPINA1 gene.