2.16 Don’t ignore the nonsense: Alpha-1 Antitrypsin Deficiency caused by null mutations

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BACKGROUND: AAT deficiency (AATD) is a hereditary disorder caused by mutations in the SERPINA1 gene, and can lead to COPD, liver, and skin disease. The most common harmful mutation is Z (Glu342Lys, rs28929474) but <200 other pathological variants exist. ATS/ERS guidelines advocate screening COPD, refractory asthma, cryptogenic liver disease and panniculitis cohorts, and first degree relatives of AATD patients.

METHODS: <24,000 individuals have been screened following ATS/ERS guidelines in the Irish national targeted detection programme. AAT is measured quantitatively and qualitatively by isoelectric focusing and by immune turbidimetry respectively. Rare mutations are identified by SERPINA1 sequencing.

RESULTS: We have identified 6 rare Null (Q0) mutations in 17 patients. These mutations include Q0bolton, Q0dublin, Q0porto, Q0cork, Q0amersfoort, Q0lisbon. Individuals with Null mutations presented with bronchiectasis, refractory asthma, and early onset COPD. Two of the mutations were completely novel.

CONCLUSION: Our findings highlight the importance of a comprehensive diagnostic approach to AATD that includes phenotyping, genotyping, and DNA sequencing to accurately identify rare and novel pathological mutations. The advantages of a correct diagnosis of AATD are many, including pulmonary and liver surveillance, increased smoking cessation, specific treatments, family testing, and mitigation against occupational and environmental exposures.

CONFLICT OF INTEREST: The authors declare that they have no conflict of interest.