7.16 Identification and characterisation of SERPINA1 Null mutations Causing Severe Alpha-1 Antitrypsin Deficiency

Ronan C. Heeney (1, 4), Geraldine Kelly (1), Daniel Fraughen (4), Orla Cahalane (2), Ilaria Ferrarotti (3), Noel G. McElvaney (4), Cedric Gunaratnam (4) and Tomás P. Carroll (1, 4)

(1) Alpha-1 Foundation Ireland, Beaumont Hospital, Dublin 9. (2) Beaumont Hospital, (3) University of Pavia, Italy. (4) RCSI Education & Research Centre, Beaumont Hospital

Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder which can lead to lung, liver, and skin disease. In Ireland, the most common pathological mutation is Z, found in 1 in 25 Irish people. Rare null or nonsense (SERPINA1) mutations are associated with a complete absence of AAT.

>23,000 individuals have been screened following ATS & ERS guidelines in a national targeted detection programme. Serum Alpha-1 antitrypsin (AAT) quantification is by turbidimetry. AAT phenotyping is by isoelectric focusing with allele-specific genotyping, when required. Rare and novel mutations are identified by SERPINA1 gene sequencing.

Isoelectric focusing revealed an apparent normal (M) phenotype pattern in 10 individuals with lower than expected AAT levels. Seven individuals had apparent SS or ZZ phenotypes but unusually low serum AAT. One individual had no detectable AAT on phenotyping.

SERPINA1 gene sequencing confirmed the presence of 10 M/Nulls, 2 S/Nulls, 4 Z/Nulls, and 1 Null/Null cases. Six different null mutations have been described among the 17 confirmed cases $Q0_{bolton}$, $Q0_{dublin}$, $Q0_{porto}$, $Q0_{cork}$, $Q0_{amersfoort}$, and $Q0_{lisbon}$

Null mutations are underreported due to unique diagnostic challenges. A multi-faceted approach including phenotyping, allele-specific genotyping, SERPINA1 sequencing, and the ability to interpret dissonant results is required to achieve an accurate AATD diagnosis.

Conflict of Interest: *None to declare*