**Supplemental Materials and Methods:**

***Materials:*** Human AAT ELISA Kit was purchased from Abcam. Recombinant human AAT, chromogenic substrate for elastase and monoclonal anti-AAT antibody were purchased from Sigma-Aldrich. Recombinant human neutrophil elastase was purchased from AppliChem.

***Plasma samples:*** Plasma samples were obtained from Papworth Hospital Research Tissue Bank with ethical approval from Research Ethics Service and Research Ethics Committees (REC reference: 08/H0304/56+5).Plasma samples were collected in EDTA tubes. IPAH and CTEPH patients were recruited from a specialist pulmonary hypertension center (Papworth Hospital, UK) and the diagnosis was based on international criteria. Samples were excluded if active infection was present at the time of blood sampling. The baseline characteristics of the groups were recorded closest to the time of blood sampling.

***Preparation of plasma samples for immunoblotting:***  PierceTM Albumin/IgG removal Kit was used to prepare plasma samples for immunoblotting following manufacturer’s instruction.

***AAT ELISA:*** Human AAT *in vitro* competitive ELISA was carried out according to manufacturer’s instructions.

***Elastase-inhibition assay.*** Human elastase (130 Unit/ml) was diluted 100-fold in assay buffer (20 mM Tris-HCl, pH 7.4, 100 mM NaCl, 0.1% PEG8000 and 0.2% BSA). AAT standards were prepared by diluting the AAT stock in assay buffer to obtain the final concentrations of 34, 26, 17, 11, 6 and 2 μg/ml, respectively. The dilution of plasma was optimized to ensure the OD reading fell within the linear range of the inhibition (Supplemental Figure 1), and a 200-fold dilution was chosen to use in final assay. The inhibition assay was carried out in a 96 well plate, with each well containing 30 μl of a standard or a diluted plasma sample, 10 μl of 100x diluted elastase, and 200 μl of 800 μM chromogenic substrate to ensure the substrate was in large excess. The reaction was carried out at 37 °C for 1 hour before the plate was read at OD405nm. The remaining elastase activity was reflected by the increase in absorbance at 405 nm compared with buffer alone controls. The percentage of elastase inhibitory activities in the diluted plasma samples was calculated as: [(ODwithout plasma - ODwith plasma)/ODwithout plasma]x100.

***Statistical analysis****:* The differences in phenotypic variables between groups were compared using a Fisher’s exact test for categorical data, and a Mann-Whitney *U* (2 groups) test or Kruskall-Wallis test (3 groups) for continuous data. A false discovery rate adjusted P-value was used to account for multiple testing. Differences in plasma AAT levels between groups were compared using an unpaired t-test. A *P*-value of <0.05 was considered significant.

Supplemental Figure 1. Standard of AAT in the elastase inhibition assay to illustrate the linear range of the inhibition.