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Granularity of *SERPINA1* alleles by DNA sequencing in CanCOLD

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15.5% of subjects in this Canadian cohort were carriers of at least one deficient allele affecting alpha-1 antitrypsin serum levels, but only genotypes resulting in severe deficiency and MZ heterozygotes were associated with COPD phenotypes https://bit.ly/3ekozCf

Cite this article as: Gupta N, Gaudreault N, Thériault S, *et al*. Granularity of *SERPINA1* alleles by DNA sequencing in CanCOLD. *Eur Respir J* 2020; 56: 2000958 [https://doi.org/10.1183/13993003.00958-2020].

ABSTRACT DNA sequencing of the *SERPINA1* gene to detect α_1-antitrypsin (AAT) deficiency (AATD) may provide a better appreciation of the individual and cumulative impact of genetic variants on AAT serum levels and COPD phenotypes.

AAT serum level and DNA sequencing of the coding regions of *SERPINA1* were performed in 1359 participants of the Canadian Cohort Obstructive Lung Disease (CanCOLD) study. Clinical assessment for COPD included questionnaires, pulmonary function testing and computed tomography (CT) imaging. Phenotypes were tested for association with *SERPINA1* genotypes collated into four groups: normal (MM), mild (MS and MI), intermediate (heterozygote MZ, non-S/non-Z/non-I, compound IS, and homozygote SS) and severe (ZZ and SZ) deficiency. Smoking strata and MZ-only analyses were also performed.

34 genetic variants were identified including 25 missense mutations. Overall, 8.1% of alleles in this Canadian cohort were deficient and 15.5% of 1359 individuals were carriers of at least one deficient allele. Four AATD subjects were identified and had statistically lower diffusion capacity and greater CT-based emphysema. No COPD phenotypes were associated with mild and intermediate AATD in the overall cohort or stratified by smoking status. MZ heterozygotes had similar CT-based emphysema, but lowered diffusion capacity compared with normal and mild deficiency.

In this Canadian population-based cohort, comprehensive genetic testing for AATD reveals a variety of deficient alleles affecting 15.5% of subjects. COPD phenotype was demonstrated in severe deficiency and MZ heterozygotes. This study shows the feasibility of implementing a diagnostic test for AATD using DNA sequencing in a large cohort.