

Rare respiratory disease gene carriers actually have increased lung function

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New research has revealed the healthy carriers of a gene that causes a rare respiratory disease are taller and larger than average, with greater respiratory capacity.

The disease, alpha1-antitrypsin deficiency (AATD) can result in severely reduced lung capacity due to emphysema. It is found in about 1 in 2,000 people, and occurs when an individual inherits a defective gene copy from both parents.

The findings from the University of Bristol study, published in the *Journal of Medical Genetics*, may have important implications for physical fitness training, and for the treatment of lung function disorders and short stature.

The researchers studied the AATD gene in relation to human health conditions in around 20,000 participants. They found carriers of the defective gene copy of the AATD gene have important enhanced respiratory capacity of about 10%. Additionally, on average, carriers display a significantly greater height (1.5cm) and size.

Professor Ian Day from the School of Social and Community Medicine was one of the study's senior authors. He said: "Over the past several thousands of years, the deficiency gene seems to have been positively selected, and is mainly found in north Europe, as have gene variants for larger height and size generally. These observations in carriers identify pathway effects that may be of relevance in the fields of physical fitness,

and in therapeutic approaches to modify lung function or short stature.

"Our study suggests some treatment involving the alpha1-antitrypsin pathway might be able to make important modification of height in growth disorders. Hundreds of different common genetic combinations that influence height have been identified, which is itself a highly heritable trait. The most notable of these common genetic variant is HMGA2, which exerts about a 0.3cm effect on height. The AATD variant, which is present in about 4% of the population, exerts a height effect of 1.5cm. A drug treatment targeting this pathway might be able to get a much greater effect."

Alpha1-antitrypsin is already a therapeutic agent used for replacement therapy in deficient individuals suffering from respiratory disease. There is an opposite effect of the deficiency gene in carriers (i.e. enhanced respiratory capacity) compared with full deficiency (i.e. severely diminished respiratory capacity). This opposite effect may potentially be used to enhance respiratory capacity in selected disease contexts through therapeutic mimicry of the carrier status.

More information: Teri-Louise North et al. A study of common Mendelian disease carriers across ageing British cohorts: meta-analyses reveal heterozygosity for alpha 1-antitrypsin deficiency increases respiratory capacity and height, *Journal of Medical Genetics* (2016).
[DOI: 10.1136/jmedgenet-2015-103342](https://doi.org/10.1136/jmedgenet-2015-103342)

Provided by University of Bristol

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