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Alpha-1 Antitrypsin Deficiency as an Incidental Finding in Clinical Genetic Testing

To the Editor:

Sequencing of gene panels or whole exomes has become increasingly common for the diagnosis and management of genetic disorders. These tests frequently uncover variants in genes unrelated to the clinical condition, termed “incidental” or “secondary” findings. An additional and rapidly growing source of incidental findings is direct-to-consumer genetic testing. Many of the variants discovered will be of uncertain clinical significance (1). However, there is potential to find variants with severe adverse health

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effects. The American College of Medical Genetics published recommendations for reporting secondary findings, including a limited list of disease genes, with periodic updates (2). However, this list does not include cystic fibrosis or alpha-1 antitrypsin deficiency (AATD), two relatively common genetic disorders encountered by specialists in pulmonary medicine.

AATD is associated with a greatly increased risk for emphysema and, less so, bronchiectasis, in adults. Liver disease may present in childhood or adulthood. Alpha-1 antitrypsin is encoded by the gene *SERPINA1* on chromosome 14. AATD-related lung disease follows an autosomal recessive inheritance pattern. Severe AATD is usually caused by two copies of the protease inhibitor (PI)*Z allele of the *SERPINA1* gene (PI*ZZ genotype). AATD is one of the most common genetic conditions in the United States, with an estimated prevalence of 1 in 3,000 to 1 in 5,000 (3). Studies have identified multiple rare null alleles that yield no detectable serum protein (4). These would be expected to increase risk of lung disease but not liver disease. Compound heterozygosity for the PI*SZ genotype is an established risk factor for chronic obstructive pulmonary disease (COPD) (5). Heterozygous carriers of the PI*Z allele (PI*MZ) have an increased risk of airflow obstruction, especially in cigarette smokers (6), although not to the same degree as PI*ZZ individuals.

Herein, we describe three patients with AATD detected incidentally through different genetic tests, including the discovery of a novel null allele. This study was approved by the institutional review board at Partners Healthcare.

Case 1 is a 45-year-old nonsmoking male physician who underwent exome sequencing as a commercial promotion, revealing PI*SZ genotype (Table 1). He denied symptoms of lung or liver disease. He has a great uncle with COPD, who had not been tested for AATD. Pulmonary function tests (PFTs) and liver function tests were normal.

Case 2 is a 32-year-old male nonsmoker of Ashkenazi Jewish ancestry, with no symptoms or family history of lung or liver disease.

Table 1. Two Individuals with Alpha-1 Antitrypsin Deficiency Incidentally Discovered through Genetic Sequencing

	Case 1	Case 2
Age, yr	45	32
Sex	Male	Male
Alpha-1 antitrypsin genotype	PI*SZ	PI*Z-Null†
Alpha-1 antitrypsin level, μM	9.2	4.8
Alpha-1 antitrypsin level, mg/dl	48	25
FEV ₁ , L (% predicted)	4.68 (112)	5.21 (104)
FVC, L (% predicted)	6.08 (117)	6.27 (100)
FEV ₁ /FVC ratio	0.77	0.83
Total lung capacity, L (% predicted)	7.49 (104)	6.77 (82)
D _{CO} , ml/min/mm Hg (% predicted)	29.6 (90)	38.4 (97)

†Sequencing showed *SERPINA1* heterozygosity, with one PI*Z allele and a complex frameshift mutation, g.94378591_94378598delGCAGCTTCinsTGTTTTT (NC_000014.9), between amino acid positions Glu346 and Ala348. This mutation leads to a premature stop codon at amino acid position 353, leading to a null allele, confirmed by isoelectric focusing of serum, which showed only Pi Z protein. This null allele had not been previously described and has been reported to the National Center for Biotechnology Information dbSNP database as rs864622043.

During preconception counseling after his wife was found to be a carrier for an unrelated condition, he underwent clinical sequencing of a multigene panel. Sequencing showed one PI*Z allele and a complex frameshift mutation leading to a novel null allele (Table 1). PFTs and liver function tests were normal.

Case 3 is a 49-year-old nonsmoking adopted woman with a history of recurrent respiratory illnesses and mild exertional dyspnea; she was diagnosed with “asthmatic bronchitis” in her 20s. She was curious about her birth parents and purchased a direct-to-consumer genetic testing kit, revealing PI*ZZ genotype. Because she was generally feeling well, she took no action. Two years later, after meeting an individual with AATD, she underwent clinical testing (Table 2). PFTs showed mild airflow obstruction and a reduced DL_{CO}. Chest computed tomography (CT) scan revealed mild bilateral lower lobe bronchiectasis.

She petitioned to have her birth records unsealed and found her birth mother and other blood relatives, many of whom were subsequently tested. Her two sisters were both found to have severe AATD. Her birth father (deceased) had a history of lung disease but had never been tested. Sister 1 is a 45-year-old nonsmoker with a mild productive cough and annual episodes of bronchitis. Chest CT scan revealed a few small bullae in the left lower lobe. Sister 2 is a 50-year-old nonsmoker. She had pneumonia at age 6 months. She has a history of recurrent respiratory illnesses during the winter and a minimally productive cough. She had wheezing and was diagnosed with asthma at age 45.

We describe three index cases with AATD discovered incidentally through different genetic testing methods. Two cases were asymptomatic with no evidence of organ dysfunction, but the third case and her two sisters had symptomatic respiratory disease.

Given the relatively common frequency of AATD, there will continue to be many individuals with incidental diagnoses made through clinical or direct-to-consumer genetic testing. Even without symptoms, these individuals may present to primary care providers and pulmonary specialists. Therefore, it is important for clinicians to be familiar with AATD. Early identification of AATD is important, because interventions such as smoking cessation and intravenous augmentation therapy can limit emphysema

progression (7). Although not on the panel of genes defined by the American College of Medical Genetics, we contend that the finding of AATD is a medically actionable result.

Recently, the Alpha-1 Foundation (8) and the European Respiratory Society (9) have each published clinical practice guidelines for AATD, with both recommending an initial baseline lung function evaluation that includes measurement of diffusing capacity. Although more sensitive for the detection of emphysema and bronchiectasis, the role for chest CT scans in the evaluation of the patient with AATD is not as clear (10). Laboratory and ultrasound testing for cirrhosis and hepatocellular carcinoma is recommended. Patients should be advised to avoid cigarette smoking and hepatotoxins. Genetic counseling and testing of at-risk family members is important. The European Respiratory Society document recommends that patients with AATD be managed in specialized centers and includes a table of centers in Europe (9). The Alpha-1 Foundation maintains a similar list of U.S. centers that can be accessed at www.alpha1.org/Alphas-Friends-Family/Resources/Find-an-Alpha-1-Specialist. ■

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Table 2. Index Case with Alpha-1 Antitrypsin Deficiency Incidentally Discovered by Direct-to-Consumer Genetic Testing, and Her Two Sisters

	Case 3	Sibling 1	Sibling 2
Age, yr	49	45	50
Sex	Female	Female	Female
Alpha-1 antitrypsin genotype	PI*ZZ	PI*ZZ	PI*ZZ
Alpha-1 antitrypsin level, μ M	6.3	6.3	6.9
Alpha-1 antitrypsin level, mg/dl	33	33	36
FEV ₁ , L (% predicted)	3.38 (90)	3.61 (107)	3.0 (101)
FVC, L (% predicted)	5.01 (104)	5.26 (126)	3.9 (106)
FEV ₁ /FVC ratio	0.67	0.69	0.77
Total lung capacity, L (% predicted)	7.49 (109)	7.23 (121)	7.7 (141)
DL _{CO} , ml/min/mm Hg (% predicted)	20.4 (60)	24.5 (80)	19.8 (71)

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Extent of Overuse of Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease

To the Editor:

We read with great interest the paper by Rinne and colleagues that was recently published in the *Journal* (1). The authors investigated the impact of guideline changes on indications for inhaled corticosteroids (ICS) among veterans with chronic obstructive pulmonary disease (COPD). Undoubtedly, the 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) update dramatically reduced the number of guideline-concordant ICS prescriptions, as ICS use was restricted to patients with “real” exacerbations in the previous year irrespective of the degree of obstruction. Rinne and colleagues used data from the Veterans Affairs (VA) Corporate Data Warehouse and found that out of 42,478 patients, 15,286 (36%) met the GOLD 2015 ICS prescription criteria, and only 9.4% of patients met 2017 ICS prescription criteria. The discordance rates roughly doubled when the authors used 2017 versus 2015 criteria. In the German prospective real-life DACCORD (Die ambulante Versorgung mit langwirksamen Bronchodilatoren: COPD-Register in Deutschland [Outpatient Care with Long-Acting Bronchodilators: COPD Registry in Germany]) study, at baseline, among 5,827 patients with spirometry-proven COPD, 33.7% had ICS-containing therapy, but only 18% were GOLD 2011 A-B-C-D group concordant (2).

Exacerbations are relatively infrequent events in COPD. For example, DACCORD prospectively followed 3,137 patients over 2 years and found that as few as 26.2% and 23.2% had exacerbations in the first and second year, respectively, and 62% had no exacerbations at all (3). In a very different cohort (SPIROMICS [Subpopulations and Intermediate Outcome Measures in COPD Study]), 51% of the patients had no exacerbations during a 3-year period (4). In real life and in register studies, the small number of patients who experience two exacerbations a year limits GOLD 2017–concordant ICS prescriptions to patients with the only approved indication, which is prevention of frequent exacerbations.

Rinne and colleagues state that ICS overuse is very common in patients with COPD. However, beyond the usual limitations of retrospective register studies (not fully mentioned by the authors), other important limitations apply. Adding ICS to long-acting β agonists is a very effective way to reduce exacerbations in an exacerbation-prone cohort of patients. For example, in the VIVACE (Impact of Salmeterol/Fluticasone Propionate versus Salmeterol on Exacerbations in Severe COPD) study (5), we showed a 35% reduction. In this cohort, every third exacerbation was prevented while the subjects were under ICS treatment. Thus, if an ICS-treated patient had no or less than two exacerbations in the year before entering the study, it cannot be automatically assumed that the ICS treatment was discordant. According to recent data, ICS treatment seems to be especially effective in preventing exacerbations in patients with some degree of eosinophilia even if they are nonfrequent exacerbators. Eosinophilia was beyond the focus of the VA register study by Rinne and colleagues, as was asthma–COPD overlap, another important segment of the analyzed VA population that is hardly distinguishable in a register study. According to the commonly held hypothesis, patients with asthma–COPD overlap also benefit from an ICS treatment. Furthermore, retrospective patient history data on exacerbations, an important determinant of the COPD treatment approach, may not be fully reliable in real life, or even in a randomized controlled trial that includes a COPD population. This may be one of the explanations for the important reductions of exacerbation rates in the placebo arms of previous COPD trials. Recently, members of the GOLD 2017 Scientific Committee highlighted the fallacy of staging pretreated patients with COPD (such as those whose information was obtained from the VA Corporate Data Warehouse by Rinne and colleagues) for the purpose of ICS treatment recommendations (6).

We agree with the statement regarding the overuse of ICS in COPD; however, a word of caution is needed before assessing the extent of the overuse. ■

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