ARTICLE

Genetic Testing of Minors for Alpha$_1$-Antitrypsin Deficiency

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Background: Alpha$_1$-antitrypsin deficiency (AATD) is a genetic disorder primarily affecting the lungs and liver of affected individuals, causing severe panlobular emphysema and cirrhosis.

Objective: To describe the demographics and feasibility of a home test for AATD in children and adolescents.

Design: Case series of parents who test their children for AATD.

Setting: Nonprofit supported program in which participants telephoned or e-mailed requests for alpha$_1$-antitrypsin testing.

Participants: All persons younger than 18 years whose parents or guardians chose to test for AATD from January 1, 2002, to October 1, 2004.

Interventions: Home-administered finger-stick blood spot test for alpha$_1$-antitrypsin genotype and questionnaire.

Main Outcome Measures: The alpha$_1$-antitrypsin genotypes and questionnaire responses.

Results: The Alpha Coded Testing Study tested 422 children and adolescents with a confidential test for AATD. Testing was suggested by a family member in most (76.7%) of the cases and was responsible for the many carrier (*PIMZ* and *PIMS*) genotypes (51.9%) in the study. Interest in testing was equally distributed among all ages. Test confidentiality was seen as an important reason to test (64.1% with a Likert scale score of 4-5 on a 5-point scale). Parents and guardians of the minors suggested that testing benefits (mean [SD] Likert score, 3.5 [1.4] on a 5-point scale) were higher than risks (mean [SD] Likert score, 1.7 [1.2]) (*P*=.001).

Conclusion: Parents value genetic testing of their children at risk for AATD when testing can be done in a confidential setting.

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ALPHA$_1$-ANTITRYPSIN (AAT) is an abundant plasma glycoprotein that inhibits neutrophil elastase. Individuals who inherited *AAT* genes associated with deficiency are at high risk for the development of chronic obstructive pulmonary disease and cirrhosis. The prevalence of AAT deficiency (AATD) in the United States is between 1 in 2857 and 1 in 5097, occurring mainly in white populations of European lineage, with an incidence similar to that of cystic fibrosis.[1-4] Cigarette smoking substantially decreases the age of onset of chronic obstructive pulmonary disease in individuals with AATD.

Early identification of AATD allows affected individuals to learn about their condition, make educated decisions regarding lifestyle choices, anticipate insurance and medical needs, and assess career choice options. However, the most important decision may concern smoking behavior. Because tobacco smoking often begins during adolescence, genetic testing of children at risk for AATD has the potential to affect lung health.

From November 1972 to September 1974, 200 000 Swedish newborns were screened for AATD; 183 children had a severe deficiency.[4] When studied in late adolescence, only 3% of those identified smoked cigarettes.[5] However, in targeted studies[6] of the parents, objective measures of psychological stress were encountered. When added to the potential for genetic information misuse in the absence of symptoms by employers or insurance companies, the 2003 American Thoracic Society/European Respiratory Society statement concluded that testing of minors should not be performed in the absence of a family history of AATD.[7]

The goal of this article is to report the demographics of children and adolescents, and the perceptions of their parents, testing for AATD through the Alpha Coded Testing (ACT) Study.

METHODS

The ACT Study began January 16, 2001, to query issues surrounding genetic testing for AATD. The study and all questionnaires were

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Table 1. Age Distribution and Genotypes of Tested Individuals

Genotype*	Age, y						Total (N = 422)†
	0-3 (n = 79)	4-6 (n = 70)	7-9 (n = 71)	10-12 (n = 66)	13-15 (n = 83)	16-18 (n = 153)	
PIMM	33	32	28	36	39	20	**188** (44.5)
PIMS	6	4	6	6	7	4	**33** (7.8)
PIMZ	36	31	35	19	36	29	**186** (44.1)
PISS	1	1	0	2	0	0	**4** (0.9)
PISZ	0	1	2	3	0	0	**6** (1.4)
PIZZ	3	1	0	0	1	0	**5** (1.2)

*The *PIMM* genotype is present in approximately 92% of the US population and produces a normal serum level of alpha$_1$-antitrypsin (AAT). The *PIMS* (5.7%) and *PIMZ* (2.3%) genotypes carry 1 deficient gene and serum levels are intermediate between *PIMM* and the genotypes *PISZ* (0.1%) and *PIZZ* (0.02%), which have severe reductions in serum AAT concentrations.[9]

†Data are given as number (percentage).

approved by the Medical University of South Carolina Institutional Review Board for Research with Human Subjects, and a Certificate of Confidentiality was obtained from the National Institutes of Health. Study participation was advertised as an option for AAT testing by the Alpha-1 Foundation and the Alpha-1 Association, 2 nonprofit organizations dedicated to AAT detection. Participants were required to telephone, e-mail, or visit a study booth at an Alpha-1 Education Day for study materials. Individuals wanting an *AAT* genotype for themselves or their minor children administered a home finger-stick test for blood spot analysis.[8] Consent forms, informational brochures, and a study questionnaire accompanied all mailings. Results of testing were returned only to the requesting individual, who then had the option of telling others about the test results. Participants had the option of having their name and contact information deleted from the study 3 weeks after receiving results. The other option was to maintain consent for further study of testing outcomes for 5 years. Results were mailed with genotype-specific support information. For the first 20 months of the study, a posttest questionnaire and postage-paid envelope were mailed.

Summary statistics were performed using SAS statistical software (SAS Institute Inc, Cary, NC). Mean risk and mean benefit scores were calculated from mean Likert responses for participants who gave answers to all questions. A *t* test was used to compare continuous variables. $P<.05$ was considered significant.

RESULTS

Between January 1, 2002, and October 1, 2004, the ACT Study enrolled 2831 persons who requested a confidential, self-administered, finger-stick test kit, including 422 younger than 18 years. Participation for the 422 minors in the ACT Study was dependent on the following: (1) parent or legal guardian signed consent and (2) return of a completed pretest research questionnaire. **Table 1** shows the age distribution and genotypes of the participants. Of the 422 respondents, 212 (50.2%) were male, 208 (49.3%) were female, and 2 (0.5%) did not respond. Testing for the first time was reported by 386 (91.5%) participants. Individuals in the study requested removal of contact information after results returned in 174 (41.2%) cases.

Respondent race was as follows (data available for 421 respondents): 375 (89.1%) were white, 7 (1.7%) were Hispanic, 2 (0.5%) were Native American, and 1 (0.2%) was Asian; 35 (8.3%) responded as having more than 1 race, and 1 (0.2%) did not state race. As expected for minor testing, the test was recommended most often by a family member (319 [76.7%] of 416 subjects with this information). Recommendations for testing also came from physicians for 24 subjects (5.8%), the participants alone for 11 subjects (2.6%), the media or Internet for 6 subjects (1.4%), other sources for 25 subjects (6.0%), and a combination of sources for 31 subjects (7.5%).

The distribution of responses to a Likert scale query on whether confidentiality was a reason for participation were also obtained. The query answered by 220 participants was as follows: "I enrolled because the test was confidential and results cannot be traced." Test confidentiality was measured on a scale from 0 (not a reason) to 5 (a very important reason). Of the 220 participants, 34 (15.5%) answered 0; 17 (7.7%), 1; 13 (5.9%), 2; 15 (6.8%), 3; 26 (11.8%), 4; and 115 (52.3%), 5. Of the 250 responses to smoking status, 227 (90.8%) were never smokers, 17 (6.8%) reported current smoking, and 6 (2.4%) reported an ex-smoking status. Of the 17 smokers, 10 (58.8%) reported they were very likely (Likert scale score, 4-5) to quit if they received results of being severely deficient in AAT.

Likert responses from 1 to 5 were collected (1 indicates no risk; and 5, high risk) for a series of potential testing risks that included the loss of insurance or increased insurance cost, discovery of true paternity, and encountering religious issues associated with testing. Participants who answered all risk questions (n=162) had a mean (SD) Likert response of 1.7 (1.2). Likert responses for selected questions of benefits of testing were graded from a score of 1 (no benefit) to a score of 5 (important benefit). A mean (SD) score of 3.5 (1.4) was recorded from participants who answered all benefit questions (n=173) for questions including the benefits of establishing diagnosis, screening for other manifestations of disease, finding individuals without abnormal genes, and better understanding family genetics. Participants reported receiving more benefits than risks from AATD testing (P=.001) (**Table 2**).

COMMENT

Testing of children and adolescents for genetic conditions that clinically present later in life is termed *predispositional testing*. In AATD, however, there is a unique gene × environment interaction that is responsible for the most common associated disease: emphysema. The environmental determinants of emphysema include cigarette smoking and dusty environments, both of which are amenable to prevention before the age of 18 years.[10,11] Although most children and adolescents being tested are asymptomatic, the genetic information being provided has the potential to be life changing.

One critical issue addressed by this article is whether genetic testing for AATD is likely harmful or helpful to minors or the family. In the absence of long-term outcomes, the attitudes of the parents were sampled in this large genetic testing study. The only other large study of AATD testing in which parental questionnaires were obtained remains the experience of the Swedish studies[4] of early identification of AATD.

Sveger and Thelin[12] described the attitudes of parents of 4-year-old children with AATD that had been detected in the Swedish birth-testing cohort. They found that 92% of the parents believed the knowledge of AATD did not have a negative effect on their own self-image. Of the parents, 50% had positive attitudes about testing their child, 80% thought the test should be offered to all children, and 94% wanted to test their remaining or future children.[12]

Some negative effects of testing were recorded in the Swedish experience. Although most parents experienced initial concern, poor emotional adjustment was found in 8% of mothers and 6% of fathers at 5 to 7 years after diagnosis. In general, parents of AAT-deficient children had a higher frequency of poor physical and/or mental health compared with control parents. However, by the time the children were 16 years old, the only difference noted was a higher incidence of anxiety in mothers, but not in fathers, of AAT-deficient children.[6]

Parents' smoking habits were examined because of concerns about secondary smoke inhalation. Although parents were advised to stop smoking, it was extremely difficult for them to quit completely.[5] In fact, fathers of the children were smoking at twice the frequency of the control cohorts.

Adolescents in the Swedish cohort (N=50) supported general screening for AATD, with 94% supporting testing during the neonatal period.[13] Of this cohort, 50% reported that knowledge of the results had affected their lives, especially regarding air pollution and smoking, and 88% recognized the importance of avoiding cigarette smoke for optimal lung protection. They found no early adult negative psychosocial consequences from their neonatal screening of AATD, with all participants (N=50) recommending AATD screening. In a separate questionnaire survey, 3% of adolescents from the Swedish cohort (N=150) were smoking compared with 12% of an age-matched nondeficient cohort (N=50).[5]

The American Thoracic Society/European Respiratory Society standards for the diagnosis and management of individuals with AATD recommend testing for newborns, children, and adolescents with unexplained liver disease.[7] The standards' document recommends predispositional testing for siblings of known deficient individuals who would have a 1 in 4 chance or more of being severely deficient and recommends testing if the genetic testing outcome serves as a motivator for the individual to quit cigarette smoking.[7] However, the document recommends against testing of minors independent of these circumstances.

Table 2. The Risks and Benefits of AATD Testing

Category	No. of Participants*	Likert Scale Score, Mean (SD)
Risks		
Losing health insurance	171	2.3 (1.6)
Higher health insurance	169	2.2 (1.5)
Losing your job	170	1.5 (1.1)
Psychological risks associated with genetic knowledge	173	2.1 (1.3)
Religious issues associated with genetic knowledge	169	1.4 (0.9)
Knowledge concerning children's true parents	166	1.4 (1.0)
Increased stress knowing that I have normal genes while a family member has abnormal *AAT* genes	172	1.9 (1.3)
Benefits		
Establishing a diagnosis	181	3.8 (1.5)
Benefit of drug treatment not available without a diagnosis	179	3.6 (1.6)
Genetic knowledge that may be helpful for family members	183	3.8 (1.5)
Networking with others who have the genetic condition	177	3.0 (1.6)
Screening for other manifestations of AATD	181	3.5 (1.5)
Peace of mind if the genetic test result is normal	182	4.0 (1.4)

Abbreviation: AATD, alpha$_1$-antitrypsin deficiency.
*There were differing numbers of responses because of missing data.

One reason that predispositional testing of minors remains controversial for AATD and other genetic conditions is the absence of protective legislation at the federal level to prevent genetic discrimination, particularly regarding health and life insurance costs. Consistent with previous studies in AATD, we found that confidentiality in genetic testing remains a high concern. One of the reasons for high study enrollment is likely the confidentiality protection afforded by the study and its Certificate of Confidentiality. The ACT Study was designed to protect the confidentiality of participants by only disclosing test results to the individual or, in the case of minors, to the parent or guardian. We do not know the extent that parents shared genetic information or its implications with their children, an important determinant of whether models such as this should be advanced. Furthermore, long-term health outcomes of testing remain unknown.

The present study does not reflect the current practice of AAT testing in a community practice setting.[14,15]

One alternative for community testing is a model that has been used in other genetic diseases.[16] If a parent is severely deficient, with a *PIZZ* genotype, test results of the spouse have a high chance of being normal, with a genotype of *PIMM*. In this case, testing of children is unnecessary because all with parental genes will be genotype *PIMZ*. This pattern undoubtedly plays a major role in the many *PIMZ* carriers in this study. Advocates of testing both parents argue that the practice is more cost-effective than testing all children. However, if either parent is not homozygous, the testing model does not provide the genotypes of children and adolescents.

There are several limitations to the study. Because questionnaires were completed at participants' homes, there is a significant amount of missing data, as reflected in the data tables. In addition, we do not know the extent of influence from adolescents on the parental response to these questions. Finally, because of the few severely deficient (*PISZ* and *PIZZ*) responses, and the failure to query after test results were returned, we cannot define differences in responses between genotypes.

Because cigarette smoking and environmental dust exposure can have a significantly negative effect on the health of individuals with AATD and these exposures begin in adolescence, we believe that genetic testing should be accessible to all families in which AATD has been detected. Our study demonstrates that parents and guardians value genetic testing of minors for AATD.

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