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SERPINA1 gene polymorphisms in a population-based ALSPAC cohort

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Abstract

Background: There is an association between persistent preschool wheezing phenotypes and school-age asthma. These wheezing/asthma phenotypes likely represent clinical entities having specific genetic risk factors. The SERPINA1 gene encodes α_1-antitrypsin (AAT), and mutations in the gene are important in the pathophysiology of pulmonary diseases. We hypothesized that there might be an association between SERPINA1 gene polymorphisms and the risk of developing wheezing/school age asthma.

Objective: To examine 10 single nucleotide polymorphisms (SNPs) of SERPINA1 (rs6647, rs11832, rs17580, rs709932, rs1243160, rs2854254, rs8004738, rs17751769, rs28929470, and rs28929474) and relate them to childhood wheezing phenotypes and doctor-diagnosed asthma in the population-based Avon Longitudinal Study of Parents and Children (ALSPAC) cohort.

Methods: Wheeze data, reports of physician-diagnosed asthma and data on the SERPINA1 gene SNPs, were available for 7964 children. Binary logistic regression was used to assess the associations between allele prevalence and wheezing and asthma phenotypes. *P* values were adjusted to account for multiple hypotheses using the Benjamini-Hochberg false discovery rate.

Results: Only within a subgroup of children with asthma who had no prior diagnosis of preschool wheeze was there a trend for association between rs28929474 (Glu342Lys, Pi*Z causing AAT deficiency; $P = .0058$, adjusted $P = .058$). No SNP was associated with wheezing and asthma in those with preschool wheeze.

Conclusion: Analyzed SNPs in SERPINA1 are not associated with wheezing/asthma phenotypes. Only rs28929474, the most common pathologic SNP (Pi*Z) in the SERPINA1 gene, might be associated with a risk of developing school-age asthma without exhibiting preschool wheeze.

KEYWORDS
α_1-antitrypsin, ALSPAC, asthma, gene, SERPINA1, SNPs, wheezing phenotypes

David S. DeLuca and Edita Poluzioroviene contributed equally to this work.

1 | INTRODUCTION

Preschool wheeze is a common problem worldwide causing a poor quality of life and frequent use of health care systems and may be related to asthma and chronic obstructive pulmonary disease (COPD) later in life.[1] Most preschool wheeze remits by school age.[2] However, wheeze may persist into later childhood and adulthood. It is estimated that about one-third of school-age children manifest recurrent wheezing.[3] Recurrent wheezing in infancy may be associated with reduced lung function later in life, especially if there are acute attacks of wheeze, exposure to tobacco smoke, and aeroallergen sensitization.[4] Most asthmatics start wheezing in early childhood.[5,6] Patients with COPD may have early life symptoms and airflow obstruction,[7,8] and there are associations between COPD-associated genes and transient early symptoms of wheeze.[8]

Currently, it is difficult to predict if early childhood wheeze will remit or is the precursor of persistent wheezing/asthma. Wheeze phenotypes can also change within an individual over time. Therefore, understanding of the heterogeneity of wheeze and distinguishing wheeze phenotypes is of critical importance for developing interventions. Certain wheeze phenotypes appear to be associated with genetic factors and/or specific early life influences like atopy, tobacco smoke exposure, frequent infections, and others.[9]

In this study, we aimed to investigate the potential role of SERPINA1, mutations in which are associated with the risk of pulmonary diseases. SERPINA1 is located on chromosome 14q32.1, and encodes a serine protease inhibitor (α_1-antitrypsin, AAT). SERPINA1 is highly polymorphic gene, with more than 125 single nucleotide polymorphisms (SNPs) reported in public databases. Among most common SNP alleles are the normal protease inhibitor Pi*M allele and its subtypes (PiM1Ala213, PiM1Val213, PiM2Arg101His, and PiM3Glu376Asp), and the deficient alleles Pi*S (Glu264Val) and Pi*Z (Glu342Lys) associated with lower serum AAT levels.[9] Specifically, the homozygous Z mutation of the SERPINA1 gene, which is associated with severe deficiency of circulating levels of AAT (only about 10% of normal), is a risk factor of early-onset emphysema and COPD, especially in cigarette smokers.[10] The American Thoracic Society (ATS)/European Respiratory Society (ERS) and the World Health Organization (WHO) suggest that a diagnosis of asthma is one of the clinical indications for AAT deficiency testing.[11]

To date, little is known about any relationship between SERPINA1 gene polymorphisms and childhood wheeze. We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort to test the hypothesis that there are associations between common SERPINA1 gene polymorphisms, childhood wheezing phenotypes, and asthma. We selected ten SERPINA1 SNPs (rs6647, rs11832, rs17580, rs709932, rs1243160, rs2854254, rs8004738, rs17751769, rs28929470, and rs28929474) because of previous studies linking these SNPs to pulmonary function.[3,5,6]

2 | MATERIALS AND METHODS

2.1 | ALSPAC cohort

ALSPAC is a longitudinal, population-based birth cohort established in Avon, United Kingdom, which recruited 14 701 children born between 1 April 1991 and 31 December 1992. Ethical approval was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. The details of the ALSPAC cohort have been published previously[12] and available at: http://www.bristol.ac.uk/alspac with a fully searchable data dictionary http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/

2.2 | Study cohort

Out of total 14 771 children, wheezing and physician-diagnosed asthma data were available for 12 303 (83.3%), of which 7964 (64.73%) had data on the SERPINA1 SNPs. The wheeze phenotypes were as follows[13]: (a) never/infrequent wheeze at 6 months with declining prevalence of sporadic wheeze thereafter, (b) transient early wheeze, prevalent up to 18 months, declining to low prevalence from 42 months, (c) prolonged early wheeze with a peak prevalence at 30 months, declining to low prevalence from 69 months, (d) intermediate onset wheeze had a low prevalence up to 18 months, rising rapidly to high prevalence from the age of 42 months, (e) late onset wheeze prevalent up to 42 months, rising to higher prevalence thereafter, and (f) persistent wheeze prevalent at 6 months and thereafter.

Never/infrequent wheeze phenotype had the lowest subsequent prevalence of physician-diagnosed asthma and was considered as the reference population.

2.3 | Genotyping

ALSPAC children were genotyped using the Illumina HumanHap550 genotyping platforms at the Wellcome Trust Sanger Institute, Cambridge, UK and the Laboratory Corporation of America, Burlington, NC, US.

Only SNPs above 1% allele frequency, a call rate above 95%, and nonviolating Hardy-Weinberg equilibrium ($P < 5 \times 10^{-7}$) were retained. Genotype imputation was performed using the Markov Chain Haplotyping (MACH) software[14] and the CEU reference panel (HapMap release 22, phase II NCBI B36). Details of the data generation process are available online http://www.bristol.ac.uk/media-library/sites/alspac/migrated/documents/gwas-data-generation

2.4 | Statistical analysis

Data were processed with R statistical software package (version 3.4.2, 2017-09-28) (The R Foundation for Statistical Computing, Vienna, Austria). We used poLCA for R[15,16] to determine the different wheezing phenotypes based on questionnaire responses. A six-class based model was chosen as this found to be optimal previously[13] and returned the lowest AIC values in our analyses. Logistic regression was used to analyze the associations of different

TABLE 1 Distribution of wheezing phenotypes between children from ALSPAC cohort

Wheezing phenotype	N total	Sex, N (%)		OR (95% CI)[a]	*P* value
		Male	Female		
Never/infrequent	5308	2524 (62.1)	2784 (71.4)	0.567 (0.505-0.636)	<.001
Preschool-onset remitting	1326	753 (18.5)	573 (14.7)	1.614 (1.354-1.925)	<.001
Mid-childhood-onset remitting	405	256 (6.3)	149 (3.8)	1.962 (1.523-2.527)	<.001
School-age-onset persisting	222	114 (2.8)	108 (2.8)	0.972 (0.672-1.406)	.882
Late childhood-onset persisting	287	163 (4)	124 (3.2)	1.575 (1.169-2.122)	.002
Continuous	416	253 (6.2)	163 (4.2)	2.146 (1.651-2.789)	<.001
Total	7964	4063 (51.0)	3901 (49.0)		

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Odds ratio, 95% confidence interval (Univariate logistic regression, Wald statistic).

SNPs with wheezing phenotypes and doctor-diagnosed asthma at 15 years. *P* values were adjusted to account for multiple hypothesis by using the Benjamini-Hochberg false discovery rate (FDR).[17]

3 | RESULTS

3.1 | Study cohort characteristics

The largest subgroup of children was never/infrequent wheeze (n = 5308, 66.64%, Table 1). In this subgroup, there were significantly more females than males. The second largest subgroup was preschool-onset remitting wheeze (n = 1326, 16.64%). The distributions of children with remaining wheeze phenotypes were as follows: continuous (n = 416, 5.22%), mid-childhood-onset remitting (n = 405, 5.08%), late childhood-onset persisting (n = 287, 3.60%), and school-age-onset persisting (n = 222, 2.78%). There were significantly more males than females in all wheeze groups, except for school-age-onset persistent wheezers.

Six of 7964 (0.08%) children were homozygous and 357 (4.48%) heterozygous for the Pi*Z (rs28929474) AAT genotype. Moreover, 29 (0.36%) had homozygous PiSS and 924 (11.6%) heterozygous Pi*S (rs17580) AAT genotype. Both are similar to the population the frequency previously estimated for England (1.47% for Pi*Z and 4.57% for Pi*S).[13]

3.2 | SERPINA1 SNPs among children with asthma

3828 of 7964 (48.2%) subjects had a doctor's assessment of asthma status at 15 years of age, of whom 896 were diagnosed with asthma, and 2932 were nonasthmatics. Among never/infrequent wheezers during early childhood (n = 2596), 309 had asthma and 2287 did not. Three SNPs rs11832 (adjusted *P* = .073), rs1243160 (adjusted *P* = .073) and rs28929474 (adjusted *P* = .0577) showed a statistically nonsignificant trend for association with physician-diagnosed asthma among those preschool non-wheezers (Table 2). The SNP rs28929474 was observed with a minor allele frequency of 0.023 in this cohort, with 357 heterozygous individuals and 6 homozygous for the minor allele.

In contrast, none of the analyzed 10 SNPs were associated with doctor-diagnosed asthma among the 1239 preschool wheezers (Table 3).

TABLE 2 SERPINA1 gene single nucleotide polymorphisms and relative risks for doctor's diagnosed asthma among children without diagnosis of preschool wheeze

SERPINA1 SNPs	Description	Odds ratio	*P* value	Adjusted *P* value
rs6647	M1-Ala213; M1-Val213	0.83	.179	.448
rs11832	3′UTR	0.75	.022	.073
rs17580	S Glu264Val	0.94	.747	.871
rs709932	M2 Arg101His	0.88	.393	.787
rs1243160	Intron variant	0.66	.021	.073
rs2854254	Intron variant	1.06	.647	.871
rs8004738	5′UTR	1.04	.842	.871
rs17751769	Intron variant	1.15	.495	.825
rs28929470	F Arg223Cys	0.91	.871	.871
rs28929474	Z Glu342Lys	2.32	.006	.058

Abbreviations: SNP, single nucleotide polymorphism; UTR, untranslated region.

TABLE 3 SERPINA1 gene single nucleotide polymorphisms and relative risks for doctor's diagnosed asthma among wheezers

SERPINA1 SNPs	Description	Odds ratio	*P* value	Adjusted *P* value
rs6647	M1-Ala213; M1-Val213	0.86	.209	.561
rs11832	3′UTR	0.90	.408	.579
rs17580	S Glu264Val	0.85	.349	.579
rs709932	M2 Arg101His	0.85	.280	.561
rs1243160	Intron variant	0.80	.173	.561
rs2854254	Intron variant	1.15	.271	.561
rs8004738	5′UTR	0.70	.072	.561
rs17751769	Intron variant	0.88	.489	.579
rs28929470	F Arg223Cys	0.75	.579	.579
rs28929474	Z Glu342Lys	0.82	.525	.579

Abbreviations: SNP, single nucleotide polymorphism; UTR, untranslated region.

TABLE 4 SERPINA1 gene single nucleotide polymorphisms and relative risks of wheeze

SERPINA1 SNPs	Description	Odds ratio	*P* value	Adjusted *P* value
rs6647	M1-Ala213; M1-Val213	1.083	.130	.326
rs11832	3′UTR	1.080	.126	.326
rs17580	S Glu264Val	0.954	.535	.575
rs709932	M2 Arg101His	1.180	.008	.084
rs1243160	Intron variant	1.121	.095	.326
rs2854254	Intron variant	0.962	.447	.575
rs8004738	5′UTR	1.083	.342	.575
rs17751769	Intron variant	1.046	.575	.575
rs28929470	F Arg223Cys	1.171	.468	.575
rs28929474	Z Glu342Lys	0.890	.397	.575

Abbreviations: SNP, single nucleotide polymorphism; UTR, untranslated region.

3.3 | Distribution of SERPINA1 SNPs among wheeze phenotypes

Distribution of the individual SNPs among wheezers shown in Table 4. Out of 10 analyzed SERPINA1 SNPs we found that only rs709932 shows a trend for an association with mid-childhood-onset remitting wheeze (adjusted $P = .084$), with an odds ratio of 1.18. There was no association between this SNP and with any wheeze subgroup.

4 | DISCUSSION

Many children experience severe and/or frequent preschool wheeze and manifest asthma during adolescence. There is evidence of a high level of heritability of wheezing and asthma[18] and therefore studies on the wheezing and the risk-related genes for developing school-age asthma are of potential importance. We hypothesized that there would be relationships between polymorphisms of SERPINA1 gene and the risk of developing wheezing and asthma but could not confirm this.

The role of SERPINA1 SNPs in wheezing and asthma remains poorly understood, with only few studies and conflicting results. Based on the data from Swedish neonatal screening cohort, at age 16- and 22-years, the prevalence of self-reported recurrent preschool wheezing and physician-reported asthma was higher among PiZZ AAT deficient than among age-matched non-AAT deficient individuals.[19] By contrast, other studies failed to find an association between SERPINA1 polymorphisms and reported wheeze.[20]

In line with the latter study, our results show that the presence of deficient Z and S alleles of the SERPINA1 gene does not associate with a risk of childhood wheezing. There was no association between analyzed SERPINA1 SNPs and doctor-diagnosed asthma at the age of 15 years among preschool wheezers. Thus, SERPINA1 polymorphisms, specifically deficient Z and S alleles, are not risk factors for childhood wheezing or preschool wheeze-associated asthma. The rs709932 SNP exhibited a nonsignificant association with mid-childhood-onset remitting and continuous wheezing. This SNP has not previously been linked to wheezing, but has been associated with COPD,[21] so this SNP may merit further investigation.

Viral infections and environmental pollutants (such as smoking) are the dominant triggers of wheezing illnesses during early childhood. Many children who experience preschool wheezing, develop atopic allergic asthma during school age.[22] Specifically, the persisting wheeze phenotypes (school-age onset, late childhood-onset, and continuous) are associated with a later diagnosis of asthma. Nevertheless, viral infections or environmental exposures do not lead to wheezing illness in all children or wheezing results in asthma in all cases,[6,23,24] demonstrating that genotype plays an important role.

We tested for the possible association between SERPINA1 SNPs and diagnosed asthma at age of 15 years among preschool nonwheezers. Out of 10 analysed SNPs, three carried a marginal contribution to a risk for asthma in this group, namely rs11832 ($P = .022$ and adjusted $P = .073$), rs1243160 ($P = .020$ and adjusted $P = .073$) and rs28929474 (causing a Pi*Z AAT deficiency, $P = .0058$ and adjusted $P = .058$). In fact, the variant most positively associated with preschool nonwheezer's school age asthma was the Pi*Z deficiency of AAT whereas rs17580 (causing a Pi*S AAT deficiency) did not make any contribution.

There is a lack of consistent data regarding the association between the Pi*S and Pi*Z deficiency variants of SERPINA1 gene and childhood asthma. Lindmark at al[25] reported that the relationship between Pi*Z AAT and childhood asthma is weak, of the 172 asthmatic children only 12 (7.0%) were positive in the Pi*Z asthma. An increased prevalence of Pi*S or Pi*Z alleles was reported in asthmatic Puerto Rican children[26] whereas another study found no increase in Pi*Z or Pi*S prevalence among asthmatic children.[27] Similarly, von Ehrenstein et al[28] did not find PiMZ to increase the risk of asthma in a large cohort of school children. Vance et al[29] reported no differences in respiratory symptoms or lung function between PiMS and PiMM children.

The main strengths of our study are the large sample size and the frequency of data collection of the ALSPAC cohort.[12] Despite the large number of participants, ALSPAC cohort is still limited regarding the detection of rare variants such as rs28929474 or rs17580. Therefore our results need replication.

In summary, and contrary to our hypothesis, we have shown no significant association between the common SERPINA1 SNPs, with a risk of developing school-age asthma.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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