
The *CHI3L1* rs4950928 polymorphism is associated with asthma-related hospital admissions in children and young adults

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Background: Asthma exacerbations are the commonest cause of medical admissions in childhood. These have a significant effect on quality of life and are a major financial burden on worldwide healthcare services. A range of gene–environment interactions may influence the course and severity of asthma in children and their response to medication. The *Chitinase 3-like 1* (*CHI3L1*)-131C>G genotype (rs4950928) is associated with increased asthma susceptibility and severity in adults.

Objectives: To study the interactions of the *Chitinase 3-Like-1* functional promoter SNP rs4950928 and its role on asthma exacerbations in a population of children and young adults with asthma.

Methods: A cross-sectional survey was undertaken using medical records and direct interviews of 1,071 children and young adults with asthma, aged 3 to 22 years, from Scotland. Saliva samples were collected for genotyping. Binary logistic regression was used to calculate odds ratios (ORs) and *P*-values for measures of asthma exacerbations.

Results: The minor -131G allele confers protection against asthma-related hospital admissions (OR = 0.62; 95% CI 0.41–0.92; *P* = .018) in children and young adults with asthma.

Conclusions: Our study shows that rs4950928 is significantly associated with hospital admissions in children and young adults; screening for rs4950928 may predict asthma-related hospital admissions, and through individually defined treatment management plans, potentially reduce health care costs.

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INTRODUCTION

Asthma exacerbations are the commonest cause of medical admissions in childhood and have significant effects on quality of life.¹ Asthma-related hospital admissions are a major financial burden on health care systems in developed countries.^{2–4} Exacerbations represent periods of enhanced airway inflammation and remodeling⁵ and are a marker of pulmonary decline.⁶ In humans, chitinase and chitinase-like proteins are highly expressed in lungs of patients with asthma but not in healthy lungs.⁷ The gene *CHI3L1* codes for the protein chitinase 3-like-1 (*CHI3L1*), which is a 40-kDa protein expressed in the bronchial smooth muscle cells, submucosa, subepithe-

lium, epithelium, alveolar macrophages, neutrophils, and other nonrespiratory cells.^{8,9} The *CHI3L1* gene is 10 exons long and is located on chromosome 1q31-q32.

Chitinase 3-like-1 binds with high affinity to chitin and chitin-oligosaccharides through a preserved hydrophobic substrate-binding cleft.¹⁰ Chitin is the second most abundant polysaccharide in nature; it is found in most living organisms, including bacteria, insects, and fungi.¹¹ Chitinase 3-like-1 also interacts with glycosamines such as heparin and hyaluronan, and it binds to collagen types 1, 2, and 3.^{8,12} Chitinase 3-like-1 is only produced under inflammatory conditions and may be correlated to an increase in C-reactive protein.⁸ When expressed, *CHI3L1* is capable of increasing the rate of mitosis through activation of mitogen-activated protein kinase and phosphoinositide 3-kinase signaling cascades in fibroblasts, and by working synergistically with insulin-like growth factor-1. Chitinase 3-like-1 also plays a role in matrix preservation through inhibition of cytokine-stimulated release of Matrix metalloproteinases 1, 3 and 13, in *CHI3L1*-stimulated arterial chondrocytes and skin fibroblasts.⁸ Because of these exacerbating responses, *CHI3L1* has been described as a sentinel molecule, responsible for picking up and binding to chitin, and triggering an immune-mediated response.¹¹

In adults, the *CHI3L1* -131C→G single-nucleotide polymorphism (SNP) rs4950928 is associated with increased *CHI3L1* levels, increased susceptibility and severity of

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asthma, bronchial hyperresponsiveness, and reduced pulmonary function,⁵ whereas the minor -131G allele confers protection against exacerbations of asthma.⁵

However, the role of these polymorphisms on asthma exacerbations and, in particular, asthma-related hospital admissions in children, has not been explored.

Scotland has one of the highest risks of exacerbation in the United Kingdom. In 2002, 5 hospital admissions per day were attributable to childhood asthma exacerbation.¹³ Asthma UK reports that Tayside has the highest risk of hospital admission, with the exception of Shetland in Scotland. Children in Tayside are 2.5 times more likely to have an exacerbation than children in the Borders,¹⁴ making this population ideal for the investigation of polymorphisms associated with childhood asthma exacerbations.

METHODS

We recruited children and young adults (aged 3–22 years) with physician-diagnosed asthma in Tayside and Dumfries, Scotland, between June 2003 and October 2008. The dataset includes information about demographic, anthropometric, and clinical details from 1,071 individuals attending clinics in 29 primary care practices and 3 secondary care asthma clinics. The study was approved by the Tayside Committee on Medical Research and Ethics. Informed written consent was obtained from the patient or parent/guardian as relevant.

The methods have previously been described in detail.^{15,16} In brief, the patients were seen in the asthma clinic setting, where a detailed history, clinical examination, and review of medical notes were conducted. Information was collected on school absences, use of oral steroids, and asthma-related hospital admissions over the previous 6 months. In children with asthma, school absences, use of short courses of oral steroids, and asthma-related hospital admissions represent well-validated measures of asthma exacerbations. We have previously developed a combined exacerbation score, involving yes or no responses for any of these 3 measures of exacerbations over a 6-month period of reporting, which have been validated through previous publications.^{15–18} The asthma prescribing level was determined in accordance with the British Thoracic Society¹⁹ guidelines for physician-led management of asthma, as follows: step 0, no use of inhaled albuterol on demand within the past month; step 1, inhaled albuterol on demand; step 2, regular inhaled steroids plus inhaled albuterol on demand; step 3a, regular inhaled long-acting beta-agonists (salmeterol or formoterol) plus inhaled steroids with inhaled albuterol on demand; step 4, regular inhaled long-acting beta-agonists plus inhaled steroids plus oral montelukast with inhaled albuterol on demand. From these data, a global index of asthma severity was derived through construction of a composite variable. The use of inhaled short-acting beta-agonists (bronchodilators) was categorized as follows: 0, rarely or never required; 1, required a few times per week but less than once daily; 2, required daily; 3, multiple doses over a 24-hour period on a regular basis.

Genotyping for SNP rs4950928 was performed using a Taqman SNP genotyping assay c_27832042_10 (Applied Biosystems Europe, Warrington, United Kingdom). Allelic discrimination was assessed using an Applied Biosystems 7700 sequence detection system.

All statistical analyses were performed by using SPSS for Windows version 16 (SPSS Inc, Chicago, Illinois). Binary logistic regression was used to calculate odds ratios (ORs) and *P* values for measures of asthma exacerbations. To calculate the ORs for comparison of overall risk, asthma-related hospital admission, school absences, and oral steroid intake were grouped as present (minimum once over the previous 6 months) or absent. The total asthma exacerbation response was calculated as any of these measures during the same period and was grouped as present or absent.

Sex, presence of eczema, and exposure to tobacco smoke were included as covariates. The frequency of exacerbation-related hospital admissions, school absences, short course of oral steroids, and overall asthma exacerbations during the previous 6 months were compared between the CC genotype and the -131G allele.

RESULTS

The population characteristics of 1,071 young white individuals with physician-diagnosed asthma derived from both primary and secondary care are described in Table 1. Individuals range from 3 to 22 years of age (mean, 10.4 years; SD 4.0); 59.1% are male. One-third of participants were exposed to tobacco smoke in their environment over the previous 6 months.

Over the previous 6 months, 37.3% of the 1,071 participants had at least 1 exacerbation requiring either a hospital admission, a short course of oral steroids, a school absence, or a combination of 2 or more of these; 12.4% of participants had at least 1 hospital admission in the previous 6 months; 21.1% had been prescribed a short course of oral steroids; and 31.7% reported a school absence because of their asthma exacerbation.

The 1,071 recruited participants were genotyped for the SNP rs4950928. The overall effect of the rs4950928 genotype on exacerbations in individuals with asthma is described in Table 2. The CC genotype was present in 60.2% (*n* = 645) of participants, heterozygous mutation (CG) in 35.2% (*n* = 377), and homozygous mutation (GG) in 4.6% (*n* = 49) participants. The genotype distributions of all SNPs were in accordance with the Hardy-Weinberg equilibrium (*P* > .05) in each set of samples.

Of our population, 60.2% are homozygous for the risk allele; 39.69% of this risk group reported exacerbation in the previous 6 months (Table 1). Of the participants, 79.3% were on regular inhaled corticosteroids with or without long-acting beta agonists and leukotriene receptor antagonist, and 81.87% of the population have reported using their bronchodilator short-acting beta agonist occasionally over the previous 6 months (Table 1). From a population of children and young

Table 1. Characteristics of BREATHE Study Participants with Asthma (n = 1,071)

Age	Range, 3–22 (mean, 10.4; SD, 4.0)
Sex (males: females)	633 (59.1%): 438 (40.9%)
CHI3L1 functional promoter SNP rs4950928 (%) (CC: CG:GG)	645 (60.2%): 377 (35.2%): 49 (4.65%)
Exposure to smoke (yes/no) (n = 1,071)	357/714 (33.3%)
Mean percent predicted FEV1 (SD)	96.1 (15.2)
Mean percent predicted FVC (SD)	92.3 (14.1)
Mean FEV1/FVC (SD)	0.88 (11.2)
BTS asthma treatment steps ^a (n = 1,069)	1 = 221; 2 = 594; 3 = 254
Inhaled bronchodilator use ^b (n = 1,070)	0 = 125; 1 = 751; 2 = 166; 3 = 28
Median inhaled corticosteroid dose (beclomethasone dipropionate equivalent)	200 µg
Hospital admissions (yes/no) over previous 6 months because of exacerbations (n = 1,071)	133/938 (12.4%)
Oral steroid intake (yes/no) over previous 6 months due to exacerbations (n = 1,071)	226/845 (21.1%)
School absence (yes/no) over previous 6 months due to exacerbations (n = 1,071)	339/732 (31.7%)
Overall exacerbations (yes/no) over previous 6 months ^c (n = 1,071)	400/671 (37.3%)

^a Step 1 = no/occasional use of inhaled albuterol; Step 2 = step 1 + inhaled steroids; step 3 = step 2 + inhaled long-acting β_2 agonists with or without montelukast.

^b Inhaled bronchodilator use: 0 = none, 1 = occasional, 2 = daily, 3 = excessive use.

^c Defined as any one of the following in previous 6 months: school absences, courses of oral steroids, or hospital admissions.

adults with mild to moderate asthma, 14.57% reported exacerbations requiring hospital admission.

Among the participants with the CC genotype, 39.69% reported at least 1 measure for asthma exacerbations in the previous 6 months: 14.57% reported hospital admission, 33.3% school absence, and 22.79% use of oral steroids. Among the participants with the -131G allele, 33.80% reported an exacerbation in the previous 6 months; 9.15% reported hospital admission, 29.11% reported a school absence, and 18.55% reported use of oral steroids because of exacerbation of asthma.

The -131C allele (CC) was associated with hospital admissions attributable to exacerbations ($P = .02$) when compared

with the minor -131G allele (CG or GG). The odds ratio for CG/GG was 0.62, indicating that the minor allele may have a protective role, reducing the need for asthma-related hospital admissions. The CC genotype was significantly associated with total exacerbations ($P = .05$).

We did not observe any significant association between the risk (-131C) of SNP and oral steroid intake attributable to asthma exacerbations (OR 0.77; 95% CI 0.57–1.05; $P = .11$), or asthma-related school absences (OR 0.82; 95% CI 0.63–1.07; $P = .16$) over the previous 6 months. We tested for the interaction between the risk allele and individual measures of exacerbation. We did not observe any significant interactions between the risk genotype and requirement of oral steroids or school absences because of exacerbations as well as overall exacerbations. We also tested the hypothesis that an interaction occurs between the genotype and asthma medication use. We did not observe any significant interactions between the risk genotype and inhaled steroid dosage, or increased use of short-acting beta agonist when required.

We tested the gene–dosage effect for the risk allele for each treatment step for long-term control of asthma. However, no significant effect was observed, indicating a lack of gene–dose relationship with this SNP.

DISCUSSION

Our study is the first to show that *CHI3L1* SNP rs4950928 is significantly associated with asthma-related hospital admissions in children and young adults with asthma. The odds ratio for the presence of 1 or 2 -131G allele (CG or GG) was less than 1, indicating that the minor allele may confer protection against asthma-related exacerbations.

Chupp et al⁹ associated increased quantities of CHI3L1 in the serum and the lungs with severity of asthma in an adult population. Ober et al⁵ later reported that *CHI3L1* is a susceptibility gene for asthma and that CHI3L1 can be used as a biomarker for asthma and decline in lung function. This was derived from an adult population of Hutterites and from the COAST cohort.⁵ Increased quantities of serum CHI3L1 has been observed in Chinese patients with asthma, and the level has been correlated with asthma exacerbations.²⁰ Contrary to these findings Wu et al²¹ have reported an absence of any association with three chitinases, from a cohort of 422 children recruited across the United States.²¹ The rs4950928 *CHI3L1* polymorphism was not investigated by Wu et al. An association between CHI3L1 and atopy was identified in Korean children, but no association was found with asthma.²² Rathcke et al²³ investigated the *CHI3L1* polymorphisms in a population of 6,514 Danish adults. Of this population, 540 had asthma, 300 of whom were defined as atopic asthma. In contrast to other studies, these researchers observed an association between the minor G allele, atopic asthma, and self-reported physician-diagnosed asthma. *CHI3L1* has not been identified in any genome-wide association study as an asthma susceptibility risk. *CHI3L1* SNPs were, however, investigated through a genome-wide association study of serum CHI3L1 levels, known to be elevated in patients with severe

Table 2. Overall Effect of *CHI3L1* Functional Promoter SNP rs4950928 Genotype (codominant and mutant varieties) on Hospital Admissions, Oral Steroid Intake, and School Absences Attributable to Asthma Exacerbations, and Overall Asthma Exacerbations, in Children and Young Adults

	<i>CHI3L1</i> functional promoter SNP rs4950928			OR (95% CI)	P value
	CG/GG	CC	Total		
Hospital admission because of asthma exacerbations				0.62 (0.41–0.92)	.018 ^a
No	387	551	938		
Yes	39	94	133		
Total	426	645	1,071		
School absence due to asthma exacerbations				0.82 (0.63–1.07)	.159
No	302	430	732		
Yes	124	215	339		
Total	426	645	1,071		
Oral steroid intake due to asthma exacerbations				0.77 (0.57–1.05)	.108
No	347	498	845		
Yes	79	147	226		
Total	426	645	1,071		
Overall asthma exacerbations				0.77 (0.60–1.00)	.053
No	282	389	671		
Yes	144	256	400		
Total	426	645	1071		

Abbreviations: OR, odds ratio; CI, confidence interval.

^a P values were calculated by binary logistic regression corrected for age, sex, personal eczema, and exposure to tobacco smoke.

asthma.²⁴ This study is an attempt at replicating the initial findings of Ober et al.⁵ We did not investigate serum or lung concentrations of *CHI3L1* as a marker for severity. The odds ratios for all measures of exacerbation were less than 1, in conjunction with the previously reported observation of the protective role of rs4950928. We did not find any direct association between *CHI3L1* and asthma severity. Unlike the adult populations investigated in both these previous studies, we found no association between lung function and *CHI3L1*. This correlates with the COAST cohort. A likely explanation for this is the characteristic reversibility of lung function in childhood asthma. Our identification of an association between *CHI3L1* and exacerbations may explain the exertion on asthma risk from *CHI3L1* as hypothesized by Ober et al.⁵ We did not collect any data regarding exacerbation triggers in this study, although these data would be important in exploring the clinical and therapeutic impact of *CHI3L1*.

The chitinase family of hydrolases are associated with TH2-induced inflammation and airway hypersensitivity.⁵ *CHI3L1* increases myofibroblast replication and differentiation through activation of mitogen-activated protein kinase and PI-3K signaling cascades in fibroblast, enhances production of the pro-inflammatory cytokines and chemokines tumor necrosis factor alpha (TNF α), interleukin (IL)-8, RANTES, and eotaxin and increases activity of nuclear factor kappa B (Fig 1).^{8,25} An increase in secretion of these chemo attractants will lead to leukocyte migration. Overexpression of *CHI3L1* may cause increased fibroblast hyperplasia and increased secretion of TNF α , leading to airway smooth muscle hypertrophy and

a possible increase in membrane thickening. Membrane thickening could also be aided by inhibition of matrix metalloproteinases 1, 3, and 13.

As a sentinel molecule, *CHI3L1* binds to substrate and initiates a severe immune response.^{8,11} Cumulative adhesion of chitin and *CHI3L1* substrates in this inflammatory active area may result in a rapid, severe immune response, resulting in asthma exacerbation requiring hospital admission. The *CHI3L1* SNP rs4950928, which is expressed in the inflammatory lung,⁷ may have increased affinity for chitin, thus resulting in higher bronchial epithelial concentrations of chitin. This could increase the exposure of antigen-presenting cells (macrophages and dendritic cells) to chitin, thus mediating a larger TH2 and IL-13-mediated immune response associated with asthma severity and airway remodeling.

Through NF- κ B pathway up-regulation, *CHI3L1* increases leukocyte migration (Fig 1).²⁵ The rs4950928 polymorphism may up-regulate the efficiency of this pathway, which would result in greater quantities of leukocyte migration. As a byproduct of this effect, TNF α secretion would be increased. This could possibly lead to significant levels of airway smooth muscle hypertrophy.²⁶

Possibly for a *CHI3L1*-elicited exacerbation of asthma (Fig 1), a minimal threshold concentration of *CHI3L1*-substrate complex could be exceeded. Individuals with the *CHI3L1* SNP have higher concentrations of *CHI3L1*.⁵ Higher concentrations of *CHI3L1* may lead to accelerated buildup of *CHI3L1* complex, which may lead to increased antigen-presenting cell exposure, and thus heightened immune educa-

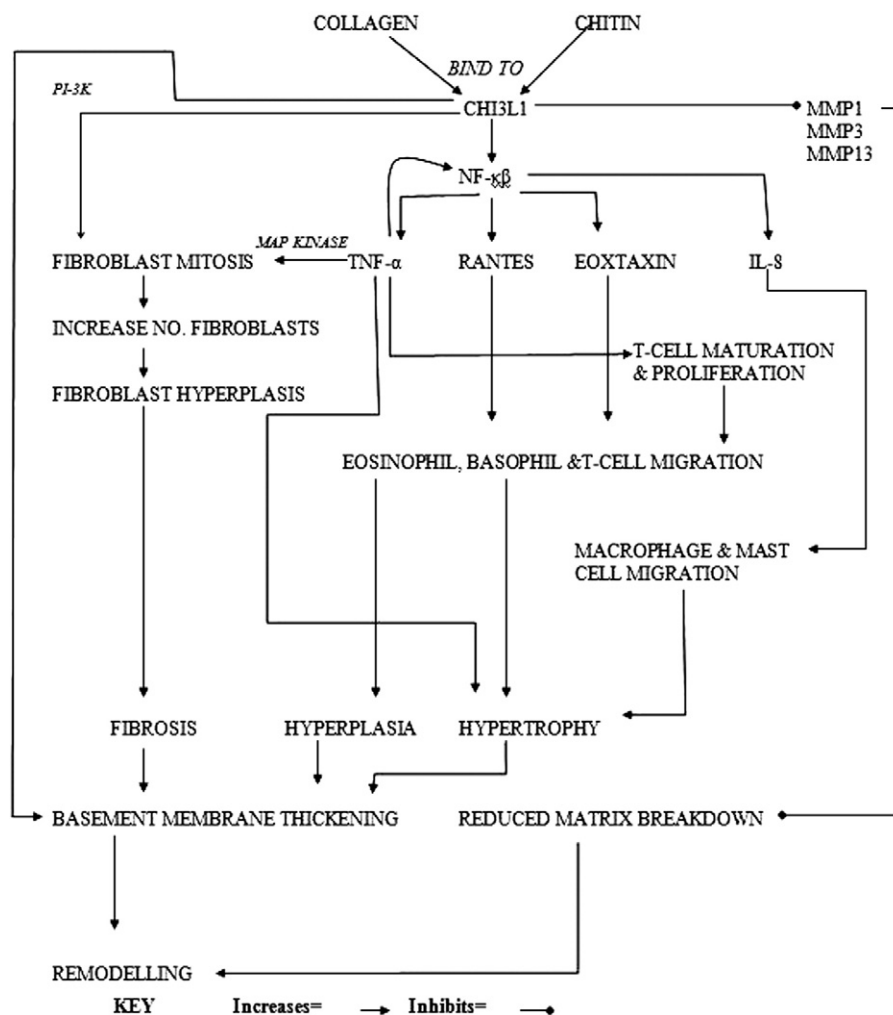


Figure 1. Hypothesized pathogenesis of the CC allele of the rs4950928 functional promoter SNP.

tion. Steroid-based inhalers suppress leukocyte concentrations in the lung, through nuclear factor kappa B inhibition.^{26,27} Thus, possibly carriers of the risk genotype exacerbate more often because of immune education and hyperreactivity overcoming the general immune suppression caused by steroid-based treatment.²⁷

Asthma costs the United Kingdom approximately £996 million per year,⁴ and the United States approximately \$37.2 billion per year.² Approximately 48% of this cost is attributed to hospital admission alone.³ The cost of care of asthma requiring hospital admission is approximately 3-fold greater than the cost of asthma management in the community. The annual average cost per patient in European children between the ages of 0 and 4 was €789, equating to €37,486,179 for admissions alone.³ Identification of children and young adults positive for the risk genotype through genetic screening could improve the quality of life and reduce the healthcare costs of children and young adults with asthma. Postdiagnostic screening

of children and young adults with asthma could alert health-care workers to high-risk patients. These high-risk patients would have an empirical incentive to avoid sensitized triggers. Regular clinics and assessment of condition, including unique, regularly reviewed treatment regimens, are needed. The risk genotype carriers could benefit from alternate treatment regimens such as the introduction of mometasone furoate.²⁸ The regular monitoring of these high-risk patients therefore is likely to dramatically improve their quality of life and significantly reduce the costs attributed to emergency secondary care.

The implementation of postdiagnostic screening for identification of risk genotypes in asthmatic children and young adults has many ethical and economic implications,²⁹ which need to be weighed against the benefit to health care systems and patient benefit. Future clinical trials, determining the outcome of monitoring and treatment variation on the *CHI3L1* risk group, may help us to weigh this benefit. Using

genotyping as a tool for quantifying risk of asthma-related hospital admissions and the understanding of the relationship between *CHI3L1* and asthma thus might focus primary prevention strategies to reduce the burden on emergency care. Of the recruited population, 60.2% were positive for the risk genotype; 23.9% of the cohort were positive for the risk genotype and reported an exacerbation in the previous 6 months. A relatively small reduction in asthma-related hospital admissions therefore may still outweigh screening costs, thus reducing the financial burden on overstretched health care systems.

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