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## Chromosome 17q21 SNP and Severe Asthma

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### Keywords

severe asthma; 17q21; *ORMDL3*

Asthma is a complex disease that is influenced by poorly understood genetic and environmental factors<sup>1</sup>. A genome-wide association study (GWAS) of 994 cases and 1243 controls from the UK and Germany found strong associations ( $P < 10^{-12}$ ) for SNPs at the 17q21 locus and childhood asthma using family and case-control panels<sup>2</sup>. The association between these SNPs and gene transcript levels in Epstein-Barr virus-transformed lymphoblastoid cell lines from the asthmatic children identified *ORMDL3* as a candidate gene for asthma. One of the SNPs, *rs7216389*, located within a highly conserved region containing an element homologous to the proinflammatory transcription factor C/EBP $\beta$  was associated to both asthma and *ORMDL3* transcript levels with the highest degree of statistical significance in the initial study (uncorrected  $P = 9 \times 10^{-11}$ )<sup>2</sup>.

The initial GWAS findings have subsequently replicated in a number of studies involving ethnically diverse populations and the variants were reported to contribute to early-onset asthma and interacting to early-life environmental tobacco smoke exposures<sup>3</sup>.

A study published recently identified an association of *rs7216389* variant with disease severity in early-onset asthma<sup>4</sup>. In the study, asthmatic cases were stratified according to asthma severity and they were classified into mild, moderate and severe asthmatics following national and international guidelines. Severe asthmatics were not recruited through severe asthma clinics; however, the study proposed *rs7216389* is involved in early-onset severe asthma.

Severe or “difficult/therapy-resistant” asthma refers to asthma that is poorly controlled in terms of persistent symptoms, episodic exacerbations and persistent and variable airway obstruction despite the use of high doses of inhaled corticosteroids, long-acting bronchodilators and short  $\beta_2$  agonists<sup>5</sup>. Studying individuals with an extreme phenotype can be very powerful when isolating the genetic determinants underlying a disease. Using this strategy we have consequently examined the role of *rs7216389* in severe asthma.

The case group consisted of 397 severe asthmatic adults identified through specialist severe asthma clinics at two UK centres, Royal Brompton Hospital, London and the Glenfield Hospital, Leicester. Asthma was defined using the international GINA (Global Initiative for Asthma: <http://www.ginasthma.com>) guidelines and the ATS criteria for refractory asthma<sup>5</sup>.

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For 226 subjects, the asthma age of onset was available. Childhood asthma-onset was present in 114 samples and adulthood asthma-onset in 112 subjects. The male to female ratio was 1:2, the mean age was 48.95 years (Standard Deviation 13.55) and mean IgE (kU/L) was 291.72 (Standard Deviation 456.09). We derived 1429 previously genotyped healthy UK adult controls from the 1958 British Birth Cohort study. The 1958 British birth cohort includes 17,638 males and females with sex ratio 1:1 enrolled in the Perinatal Mortality Survey at the time of their birth during 1 week in March 1958 across England, Wales and Scotland<sup>6</sup>. A DNA collection was obtained during a follow-up in 2002 to 2004<sup>7</sup>. Genome-wide genotyping data from the Illumina HumanHap550 Beadarray on 1430 subjects were deposited by the Wellcome Trust Sanger Institute<sup>8</sup>.

Blood samples from cases were collected and DNA was extracted using whole blood DNA extraction protocols (Promega Wizard® Genomic DNA purification kit). TaqMan® SNP Genotyping Assays (Applied Biosystems 7300 Real-Time PCR System, 40 cycles of 10 min at 95 °C, 15 sec at 92 °C and 1 min at 60 °C) were used for the allelic discrimination (primer and probe sequences available upon request). Controls of known genotype were included.

Deviation from Hardy Weinberg equilibrium (HWE) was calculated for the allele frequencies. Genotype and allele frequencies were compared between cases and controls by Fisher's exact test and logistic regression. Associations between the genotypes and IgE were also examined by Kruskal-Wallis test.

The genotyping success rate for *rs7216389* was 97%. No significant deviation from HWE was detected ( $P > 0.05$ ). The *rs7216389* SNP was found to be significantly associated with severe adult asthma (OR 1.42, CI: 1.21-1.67,  $P = 1.8 \times 10^{-5}$ ) (Table 1). In our study the frequency of the T allele in the asthmatic adults was 56%, which is lower than that reported by Moffatt *et al.* (62%)<sup>2</sup>. When the data was stratified according to the disease age of onset, a significant association between SNP *rs7216389* and severe asthma was reported only in the childhood-onset asthmatics (OR 2.02, CI: 1.53-2.68,  $P = 4.5 \times 10^{-6}$ ) (Table 1). Interestingly, the frequency of the T allele in cases of childhood onset was 67%, similar to the figure reported by Moffatt *et al.*<sup>2</sup> Adult-onset of the disease did not show any significant associations for this SNP ( $P = 0.853$ ) and minor allele frequency (T allele) was 49%, comparable to the control group (47%) (Table 1). No associations were found between genotypes and IgE levels. The results highlight the differences in the genetic components of childhood and adulthood asthma-onset.

Our results confirm the role of the *ORMDL3* genomic area as a locus conferring susceptibility to childhood asthma-onset of the most severe type of the disease. In combination with the recent published studies in ethnically diverse populations it highlights the importance of the *ORMDL3* and other genes from the Chromosome 17q21 region in the development of this complex disease. Further studies are required to investigate the functional role of this polymorphism and its involvement in early-onset asthma that could contribute in elucidating the mechanisms underlying asthma and could be applied for therapeutic interventions.

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Genotype frequencies and association test results for *rs7216389* with severe asthma, childhood-onset and adult-onset asthma susceptibility.

**Table 1**

	Genotype frequencies (N)				MAF	P	OR (95% CI)
	CC	TC	TT	CC vs TC vs TT			
Controls	0.283 (405)	0.487 (696)	0.229 (328)	0.47			
Severe asthmatics	0.179 (69)	0.519 (200)	0.301 (116)	0.56	$1.8 \times 10^{-5}$	1.42, (1.21-1.67)	
Childhood-onset asthmatics	0.089 (11)	0.482 (59)	0.429 (44)	0.67	$4.5 \times 10^{-6}$	2.02, (1.53-2.68)	
Adult-onset asthmatics	0.259(29)	0.500 (56)	0.241 (27)	0.49	0.853	1.07, (0.78-1.47)	

MAF=minimum allele frequency, CI=Confidence Intervals