

Why is Chromosome 17q21 linked to Asthma?

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Abstract

Asthma is an inflammatory disorder of the airways associated with increased airway responsiveness and airway remodeling. Several genome wide association studies (GWAS) and non-GWAS studies have demonstrated a strong genetic linkage of chromosome 17q21 genes with asthma in populations of diverse ethnic backgrounds. In particular, SNPs in the 17q21 region are found within a large linkage disequilibrium (LD) block that contains not only the orosomucoid like-3 (*ORMDL3*) gene, but also includes other 17q21 genes i.e. gasdermin B (*GSDMB*), IKAROS family zinc finger 3 (*IKZF3*), and zona pellucida binding protein 2 (*ZPBP2*). Studies of mice expressing increased levels of the human *ORMDL3* gene have demonstrated that these mice have spontaneous increased airway remodeling and airway responsiveness in the absence of airway inflammation. Further functional studies are needed to investigate whether some or all of these four genes could contribute to the pathogenesis of asthma.

Keywords: Asthma; Chromosome 17q21

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Introduction

Asthma is a complex inflammatory disorder of the airways associated with the infiltration of inflammatory cells, increased airway responsiveness and airway remodeling [1]. Several genome wide association studies (GWAS) and non-GWAS studies have demonstrated a strong genetic linkage of chromosome 17q21 genes with asthma in populations of diverse ethnic backgrounds [2-7]. Several genetic epidemiologic studies have reported single nucleotide polymorphisms (SNPs) in the 17q21 locus to be associated with the expression levels of orosomucoid like-3 (*ORMDL3*) gene. In particular, one SNP (rs7216389) in the 17q21 region has showed the strongest association with childhood and adult asthma in different ethnic populations and is indicated as the potential causal variant [3,8,9]. The rs7216389 SNP is found within a large linkage disequilibrium (LD) block that contains not only the **ORMDL3** gene, but also includes other 17q21 genes i.e. gasdermin B (*GSDMB*), IKAROS family zinc finger 3 (*IKZF3*), and zona pellucida binding protein 2 (*ZPBP2*). This suggests that these genes could be acting alone or in combination towards asthma pathophysiology. Another SNP located near the *ORMDL3* gene (rs12603332) has also been linked to asthma in several case-control population studies [8,10,11]. Interestingly, a strong association was observed between the rs12603332 SNP and asthma patients with IgE levels exceeding 100 IU/ml in three ethnic populations [8]. A schematic representation of the spatial relationship of genes in the 17q21 region is shown in **Figure 1**.

Although several genetic studies link chromosome 17q21 with asthma, there are limited functional studies investigating how each of these four genes contribute to the pathogenesis of asthma.

ORMDL3 is an allergen-inducible endoplasmic reticulum (ER) gene expressed in airway epithelial cells. *ORMDL3* activates ATF-6 α pathway during ER unfolded response and induces sarco/endoplasmic reticulum Ca²⁺ ATPases pump (SERCA2b) to regulate ER-mediated Ca²⁺ signaling and cellular stress response [12,13]. *ORMDL3* acts as a mediator of sphingolipid homeostasis [14,15] and can also regulate eosinophil trafficking, recruitment and degranulation [16]. Studies of mice generated to express increased levels of human *ORMDL3* have also demonstrated that *in vivo* *ORMDL3* activates ATF6 α (but not Ire1 or PERK), and that this is associated with increased expression of SERCA2b. SERCA2b regulates calcium flux, protein synthesis, gene expression, and metabolism and has been implicated in airway remodeling in asthma. In addition, *ORMDL3* transgenic mice have increased airway remodeling and airway responsiveness without increased airway inflammation [13]. Thus, there is biological evidence that *ORMDL3* may be one of the genes on chromosome 17q21 contributing to the pathogenesis of asthma.

Several studies show that asthma-associated variants of 17q21 alter the transcription levels of *ORMDL3* and *GSDMB*. While several genetic studies have clearly demonstrated that *ORMDL3*

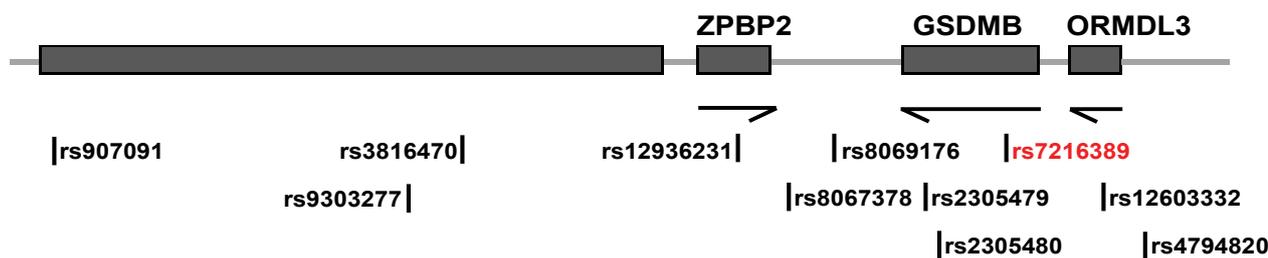


Figure 1 Schematic representation of chromosome 17q21 genes and asthma associated SNPs. Genes found within the 17q21 region includes orosomucoid like-3 (ORMDL3), gasdermin B (GSDMB), IKAROS family zinc finger 3 (IKZF3), and zona pellucida binding protein 2 (ZPBP2). The location of asthma-associated SNPs studied in different ethnic populations are indicated with SNP reference IDs. The rs7216389 SNP (highlighted in red) is found within a large LD block that contains ORMDL3, GSDMB, IKZF3, and ZPBP2.

and GSDMB either individually, or in combination act as associated risk factors for asthma, no functional studies to date have established the biological role(s) of GSDMB in mediating asthma pathogenesis. GSDMB (also known as GSDML) is a novel protein that belongs to the gasdermin (GSDM) family that consists of four human genes: GSDMA, GSDMB, GSDMC and GSDMD [17]. A mouse or rat ortholog of the GSDMB gene has not been identified, and it may have evolved independently in humans through a GSDM gene duplication [18]. The human GSDMB gene consists of 12 exons and four different splice variants have been described, which differ in exons 6 and 7 of the GSDMB gene [19]. GSDMB has been linked to cancer progression and is expressed in human gastric, liver, colon and breast cancer cell lines and carcinomas [17,19]. Although several genetic studies show a strong association of GSDMB with asthma, no functional studies to date have investigated the biological role of GSDMB in asthma and related airway cell types. Interestingly, the rs7216389 SNP highly associated with asthma is localized within the GSDMB gene and demonstrates a strong LD with other 17q21 genes, thus underscoring the need to perform future studies on GSDMB in asthma.

The 17q21 region contains two other genes i.e., IKZF3 and ZPBP2. IKZF3 (Aiolos) belongs to the Ikaros family of zinc-finger proteins which encodes hematopoietic-specific transcription factors involved in the regulation of lymphocyte development [20]. IKZF3 plays a critical role in regulating B and T cell development, and several alternative coding as well as non-coding transcripts variants of IKZF3 have been described [21]. Since various T cell subsets and B cells are well-known to influence the nature and magnitude of the allergic immune response, future studies on IKZF3 could unravel its biological role in asthma pathogenesis. ZPBP2 is a protein coding gene implicated in gamete interaction during fertilization [22]. Diseases associated with ZPBP2 include osteogenesis imperfecta and this gene might not be directly involved in asthma biology.

Environmental exposures have a profound impact on the development and clinical course of childhood asthma. Environmental exposures commonly linked with asthma include tobacco smoke exposure, domestic and farm animals, respiratory viral infections, and occupational exposures [23]. Variants of the 17q21 locus may enhance the association between early respiratory infections and childhood asthma. Respiratory infections with human rhinovirus (HRV) in individuals with the risk genotype for rs7216389 SNP was associated with a >10-fold increase in odds ratio for childhood asthma. The rs7216389 genotype was also associated with increased transcript levels of ORMDL3 and GSDMB, but not IKZF3, in HRV-stimulated PBMCs [24]. The increased risk for early-onset asthma conferred by the 17q21 gene variants was also increased by early-life exposure to environmental tobacco smoke [4]. These studies highlight the interactions between 17q21 gene variants and common environmental risk factors, thus providing insights into the functional role of 17q21 locus in the pathophysiology of asthma.

Conclusion

In conclusion, several genetic epidemiological studies have consistently shown the association of 17q21 locus with asthma, thus highlighting the paramount importance of studying the biological roles of 17q21 genes. Recent experimental evidence has linked ORMDL3 to activation of ATF6 α , altered calcium homeostasis, and sphingolipid synthesis. In addition, ORMDL3 transgenic mice exhibit increased airway remodeling and airway responsiveness suggesting an important role for ORMDL3 in asthma. At present the biological function(s) of the three other genes of this locus, including GSDMB, IKZF3 and ZPBP2 remains unexplored. As current asthma therapies mainly rely on symptomatic relief and anti-inflammatory therapy identifying novel pathways that could be therapeutically manipulated based on a patient's genotype is an important step towards developing a more personalized medicine approach for asthma therapies.

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