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ORMDL3 but not neighboring 17q21 gene LRRC3C is expressed in human lungs and lung cells of asthmatics

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Keywords: ORMDL3, LRRC3C, asthma

Abbreviations:

AHR	Airway hyperreactivity
ASM	Airway smooth muscle
ATF6 α	Activating transcription factor 6 α
BAL	Bronchoalveolar lavage
GSDMA	Gasdermin A
GSDMB	Gasdermin B
IBD	Inflammatory bowel disease
LRRC3C	Leucine rich repeat containing 3C
ORMDL3	ORM1-like-3
SERCA2b	Sarco/endoplasmic reticulum Ca ²⁺ ATPase 2b
SNP	Single nucleotide polymorphism
PBMC	Peripheral blood mononuclear cell
ZPBP2	Zona Pellucida Binding Protein 2

To the Editor:

The chromosome 17q21 region has strong linkage to asthma in genetic association studies.¹ This region contains a cluster of nine genes, including ORMDL3, GSDMB, LRRC3C, GSDMA, ZPBP2, IKZF3, GRB7, ERBB2, and PGAP3 of which the role of ORMDL3 and GSDMB have been most studied in relation to the pathogenesis of asthma¹. Although ORMDL3 expression in human CD4 cells^{E1,E2} and epithelial cells² is well documented there are currently no studies examining its expression in human lungs from asthmatics which is the focus of this study. As ORMDL3 is linked in genetic association studies to asthma^{1,E3}, but not to allergic rhinitis³, ORMDL3 expression in the lung rather than its ability to regulate Th2 responses^{E1} (which are present both in asthma and allergic rhinitis) may potentially be more important to its role in the pathogenesis of asthma. The pathway(s) mediating the linkage of ORMDL3 to asthma are currently unknown, but there is *in vitro* and *in vivo* evidence in mouse models to support effects of ORMDL3 on airway smooth muscle and AHR⁴, sphingolipids⁵, ceramide⁵, ATF6 α ², SERCA2b², cytokines/chemokines², and adhesion molecules^{E4} as potential candidates. In contrast to studies investigating the biology of ORMDL3 in relation to the pathogenesis of asthma, there are currently no published studies examining whether LRRC3C, a neighboring gene located immediately next to ORMDL3 on chromosome 17q21 (**Figure 1A-C**), is expressed in asthmatic lung or lung cells which is a second focus of this study.

The chromosome 17q21 locus has not only been implicated in the pathogenesis of asthma but also in the pathogenesis of inflammatory bowel disease (IBD)^{E5,E6} and auto-immune disease^{E7}. Studies of IBD and chromosome 17q21 have demonstrated that LRRC3C is linked to IBD and that levels of LRRC3C expression in colon are linked to chromosome 17q21 SNPs⁶. In addition, genetic epidemiologic studies of asthma have demonstrated that a SNP rs4794820 located in chromosome 17q21 within LRRC3C (**Figure 1C**) was significantly associated with severe asthma compared to mild to moderate asthma⁷, as well as with atopic asthma and lower PC₂₀⁸ while a second SNP rs2872507 (**Figure 1A**) linked to LRRC3C expression in IBD⁶ was associated with poor ICS response in asthma⁹. LRRC3C has two exons (**Figure 1C**) and encodes a 275 amino acid predicted membrane protein with one predicted transmembrane region^{E8}. In addition to LRRC3C expression in colon², a RNAseq data set in normal humans demonstrates highest levels of LRRC3C expression in testis^{E9}.

Interestingly another chromosome 17q21 gene ZPBP2 is not only highly expressed in testis^{E10,E11}, but is also expressed in bronchial epithelial cells and linked to asthma in mouse model studies^{E10,E11}. As there are no studies investigating whether ORMDL3 and its neighboring gene LRRC3C are expressed in human lungs from asthmatics in this study we investigated this possibility.

To determine whether ORMDL3 and LRRC3C mRNA were expressed in the lungs of asthmatics we extracted total RNA from postmortem human lungs of asthmatics (n=12) and control non-asthmatics (n=14)(clinical characteristics described in **Supplement Table 1**) which was processed for RT-qPCR (all methods described in the **Supplementary Online Repository**)^{E1-E21}. ORMDL3 mRNA was readily detected in the lung samples from both asthmatics (10/12 or 83% of asthmatics had detectable ORMDL3 mRNA) and normal controls (11/14 or 78% of controls had detectable ORMDL3 mRNA) with levels trending but not statistically significantly higher in the asthma lungs compared to control lungs (**Figure 1D**). As prior studies have demonstrated that the 17q21 association with asthma is mainly driven by haplotype H1 SNPs rs8076131 and rs4065275^{E1} located in close proximity and present in approximately 61% of childhood allergic asthmatics and 49% of controls^{E1}, we genotyped the asthma and control lungs to determine the proportion of lungs expressing the ORMDL3 asthma risk allele haplotype H1 SNP AA rs8076131^{E1}. The presence of the AA SNP rs8076131 was associated with detectable lung ORMDL3 mRNA in 7/7 asthmatics (100%) and 7/9 controls (78%) who had this SNP (**Fig 1E**).

In contrast to detecting ORMDL3 expression in asthma lungs, LRRC3C mRNA was not detected in any of the lungs from either asthmatics (0/12 asthmatics detectable LRRC3C mRNA) or controls (0/14 controls detectable LRRC3C mRNA)(**Figure 1F**). As the chromosome 17q21 SNP rs2872507 has been linked to expression of LRRC3C in colon tissue as assessed by gene expression assay², we also genotyped the asthma and control lungs to determine whether the SNP rs2872507 would influence our ability to detect LRRC3C mRNA in human lungs. The lung genotyping demonstrated that the rs2872507 GG (risk allele for asthma)⁹ was detected in 3/10 (30%) of the asthma lungs, and 8/13 (61%) of the control lungs (**Figure 1F**), none of whose lungs expressed LRRC3C mRNA. All of the lung samples were genotyped for a second SNP rs4794820 and had the AG allele (data not shown)

making comparisons between the risk allele (GG) and non-risk allele (AA) not possible. As a LRRC3C positive control for our RT-qPCR, we measured LRRC3C mRNA in a human LRRC3C cDNA clone, and identified high Cycle threshold (Ct) values at seven different clone concentrations of LRRC3C cDNA (0.01 to 10^5 ng/ μ L) (**Figure 1G**).

In addition, to investigating whether ORMDL3 and LRRC3C mRNA were expressed in human lung we also examined whether they were expressed in primary human lung cells pertinent to the pathogenesis of asthma including primary bronchial epithelial cells, BAL macrophages, and PBMCs from both normal and asthmatics as previously described^{E12,E13}. We readily detected expression of ORMDL3 mRNA in asthmatics in all cell types studied (bronchial epithelial cells, BAL macrophages, PBMC) (**Figure 2A-C**). In contrast, no LRRC3C mRNA was detected in either primary bronchial epithelial cells (**Figure 2D**), BAL macrophages (**Figure 2E**), or PBMCs (**Figure 2F**) in both asthmatics and normals.

In summary, this study demonstrates that ORMDL3 mRNA can readily be detected in the lungs as well as lung cells of asthmatics. In contrast, expression of LRRC3C mRNA, the gene neighboring ORMDL3 on chromosome 17q21, cannot be detected in the same lung samples, or in lung cells such as epithelial cells, macrophages, or PBMCs. These studies suggest that in unselected subjects, ORMDL3 is expressed at significant levels in the human lung and in selected lung cells pertinent to the pathogenesis of asthma. In contrast, LRRC3C was not detected in human lung suggesting that LRRC3C may be more important to intestinal diseases such as IBD⁶ than asthma. Further study is needed to determine whether there are SNPs that regulate LRRC3C expression and whether in such a preselected smaller subset of asthma or control lungs LRRC3C expression could be detected or not. Overall, this study demonstrates that ORMDL3 is significantly expressed in the lungs of asthmatics underscoring the potential importance of lung cell expression of ORMDL3 to the pathogenesis of asthma.

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FIGURE LEGENDS

Figure 1. ORMDL3 and LRRC3C mRNA expression in human asthma and control lungs

(A) Chromosome 17q21 localized genes with ORMDL3 and LRRC3C in red. SNP rs2872507, rs8076131 and rs4794820 (small black arrows). (B) ORMDL3 gene structure (coding exons in black boxes) and SNP rs8076131 (black arrow). (C) LRRC3C gene structure (two coding exons in black boxes) and SNP rs4794820 (black arrow). (D) ORMDL3 and LRRC3C mRNA expression in human asthma and control lungs. (E) ORMDL3 mRNA expression in human lung by SNP rs8076131 genotype. (F) LRRC3C mRNA expression in human lung by SNP rs2872507 genotype. (G) Cycle threshold (Ct) levels of LRRC3C mRNA at different human LRRC3C cDNA clone concentrations.

Figure 2. ORMDL3 and LRRC3C mRNA expression in human asthma and control cells

(A) ORMDL3 mRNA expression in primary human bronchial epithelial cells. (B) ORMDL3 mRNA expression in primary human BAL macrophages. (C) ORMDL3 mRNA expression in human PBMCs. (D) LRRC3C mRNA expression in primary human bronchial epithelial cells. (E) LRRC3C mRNA expression in primary human BAL macrophages. (F) LRRC3C mRNA expression in human PBMCs.

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Conflict of Interest

The authors have no conflicts of interest to disclose related to this research. These include consultant arrangements, speakers' bureau participation, stock or other equity ownership, patent licensing arrangements, employment, or expert witness testimony.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

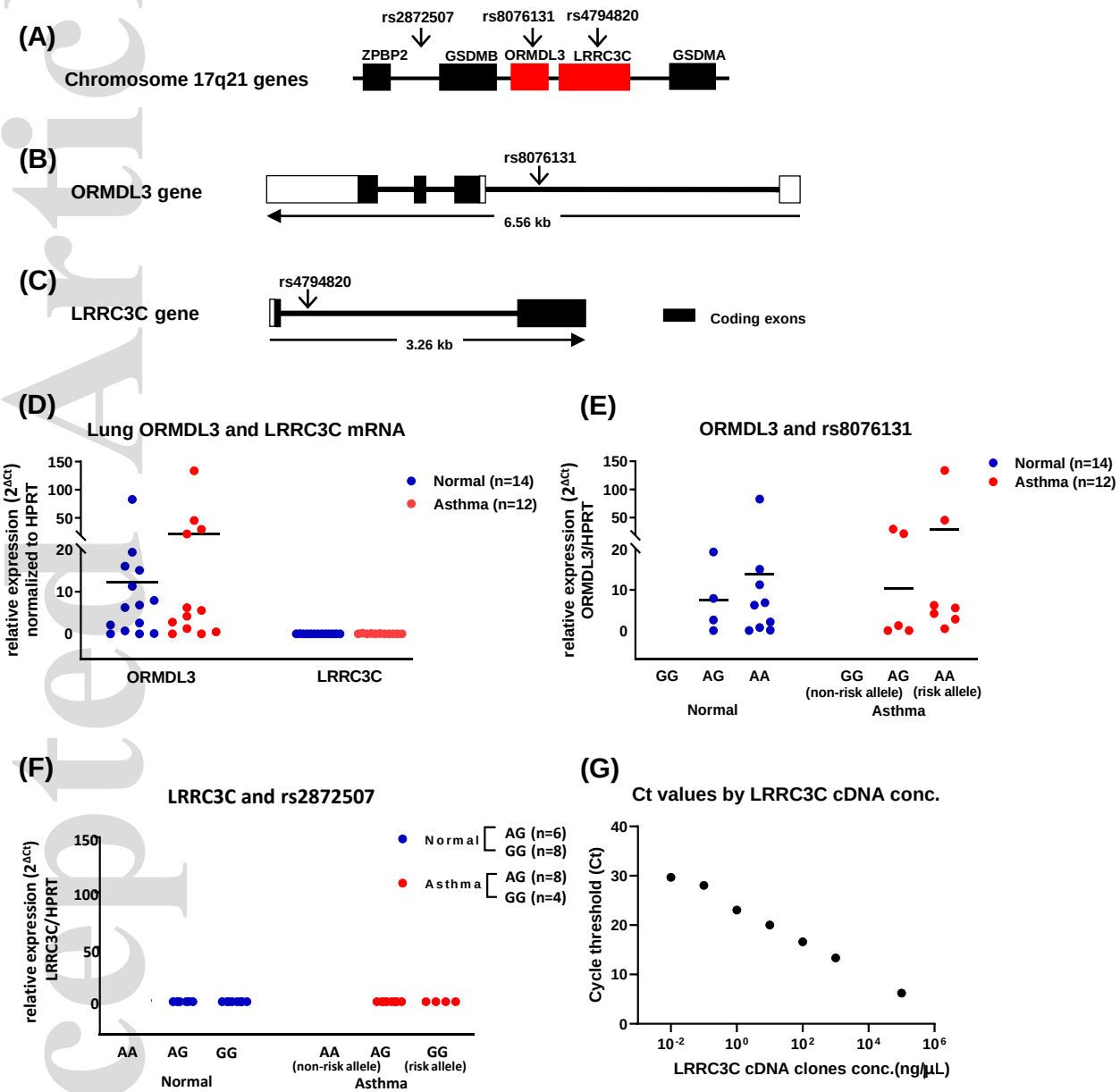


Figure 1.

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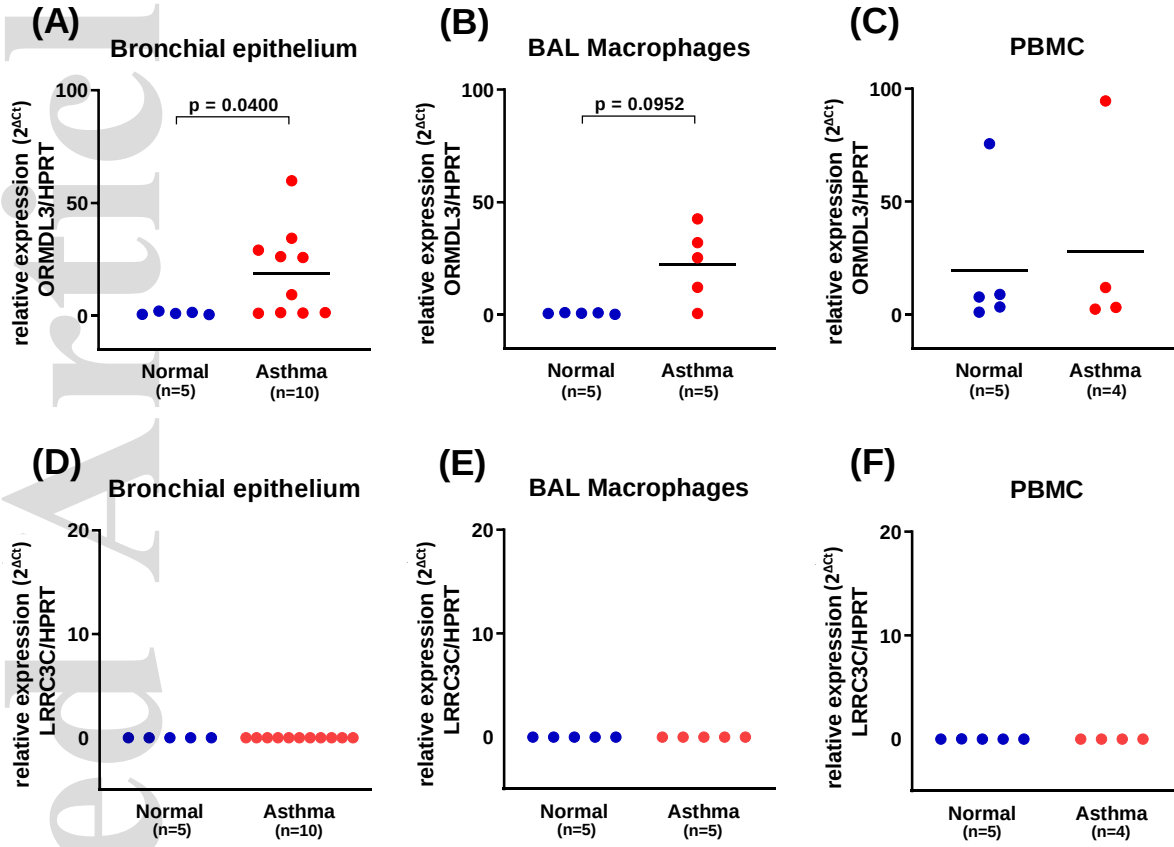


Figure 2.

SUPPLEMENTARY ONLINE REPOSITORY

ORMDL3 but not neighboring 17q21 gene LRRC3C is expressed in human lungs and lung cells of asthmatics

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SUPPLEMENTARY METHODS

The methods are all described below and in detail in the references^{E1-E21}.

Asthma and control lungs

In brief, postmortem human lungs from asthmatics and controls were procured by the Arkansas Regional Organ Recovery Agency and by the National Disease Research Interchange and delivered to the Lung Cell Biology Laboratory at the Arkansas Children's Research Institute for studies of the expression of ORMDL3 and LRRC3C mRNA at UC San Diego as previously described^{E12}. Subjects were categorized as asthma if they had a physician diagnosis of asthma listed in the hospital medical record and used asthma medications at the time of death (**Supplement Table 1**). Subjects were categorized as non-asthma if they had no physician diagnosis of asthma as well as no asthma medication use listed in the hospital medical record at the time of death. The acquisition of deceased donor tissue was reviewed by the University of Arkansas for Medical Sciences Institutional Review Board and determined not to be human subject research. This study was approved by the University of California, San Diego Human Research Protections program.

Asthma and Control Bronchial Epithelial cells, BAL macrophages, and PBMC

Primary bronchial epithelial cells were isolated from bronchi of postmortem lungs as described.^{E15} In brief, bronchi were dissected and the interior of each bronchus was scraped with a Cell Lifter (Corning Inc.) to obtain bronchial epithelial cells. The bronchial epithelial cells were collected and cultured in CnT-17 media (CellIntec, Bern, Switzerland). These primary bronchial epithelial cells were of >95% purity as assessed by E-cadherin expression on FACS and histologic detection of

ciliated epithelial cells.^{E15} Primary BAL macrophages and PBMCs were obtained as previously described in our laboratory.^{E13, E14}

ORMDL3 and LRRC3C mRNA quantitation

To quantitate ORMDL3 and LRRC3C mRNA in either lungs or cells (epithelial cells, BAL macrophages, or PBMC) from asthmatics and controls, total RNA from each lung or cell sample was processed for RT-qPCR as previously described in this laboratory^{E12}. In brief, all lung samples were treated with RNA-STAT-60 (TelTest), and reverse-transcribed with Oligo-dT and SuperScript II kit (Life Technologies). Quantitative PCR (qPCR) was performed with TaqMan PCR Master Mix and TaqMan primers (Thermo Fisher Scientific) for human ORMDL3 mRNA (Hs00918021_m1) and human LRRC3C mRNA (Hs04935571_m1). The relative amounts of mRNA were normalized to those of housekeeping gene hypoxanthine phosphoribosyltransferase 1 (HPRT1) mRNA.

LRRC3C mRNA quantitation in a LRRC3C cDNA clone

We used a human LRRC3C cDNA clone (OriGene) as a positive control to detect LRRC3C mRNA, and performed RT-qPCR as described above. Serial dilutions of the LRRC3C cDNA clone (0.01, 0.1, 1, 10, 10², 10³, and 10⁵ ng/μL) were utilized to detect LRRC3C mRNA by qPCR. Cycle threshold (Ct) values were measured at each concentration. As the LRRC3C cDNA clone does not contain a housekeeping gene results are expressed as Ct values.

ORMDL3 and LRRC3C SNP genotyping

To determine the genotypes of the ORMDL3 SNP rs8076131 as well as the LRRC3C SNPs rs2872507 and rs4794820 in each sample, SNP genotyping was performed with 20 ng genomic DNA per sample using a TaqMan SNP genotyping assay (assay ID; C 1385764 20 for ORMDL3 SNP rs8076131; C 11630970 20 for LRRC3C SNP rs2872507; C 29609729 20 for LRRC3C SNP rs4794820)(Thermo Fisher Scientific). All genotyping was conducted using the Mx3000P qPCR system (Agilent Technology).

Chromosome 17q21 SNPs and classification of LRRC3C risk alleles

In IBD the chromosome 17q21 SNP rs2872507 AA allele is the risk allele and linked to expression of LRRC3C in colon tissue^{E16}. In contrast, in asthma the chromosome 17q21 SNP rs2872507 AA allele is the protective allele for asthma^{E17}. Therefore, we classified the LRRC3C genotype of rs2872507 into either the non-risk AA allele (asthma protective), intermediate allele AG, or risk allele GG (asthma non-protective) (**Figure 1F**). Studies of chromosome 17q21 linkage to disease have identified that the chromosome 17q21 disease haplotypes that confers risk for asthma confer protection for IBD and autoimmune disease, whereas the haplotypes that confer risk for IBD and autoimmune disease confer protection for asthma^{E18,E19}. Thus, finding that the risk allele linked to expression of LRRC3C differs in IBD and asthma is not unexpected. It should also be noted that studies of IBD have linked chromosome 17q21 SNP rs2872507 to expression of LRRC3C in colon tissue^{E16}, whereas studies of asthma have linked chromosome 17q21 SNP rs2872507 to asthma and ORMDL3^{E17}, but have not examined whether rs2872507 is linked to expression of LRRC3C. Similarly, studies of chromosome 17q21 SNP rs4794820 (located within the LRRC3 gene)

(**Figure 1C**) have linked this SNP to asthma and ORM^{MDL3}^{E20, E21}, but have not examined whether rs4794820 is linked to expression of LRRC3C.

Statistical Analysis.

All results are presented as mean $\pm$ SEM. A statistical software package (GraphPad Prism) was used for statistical analyses and a p value of <0.05 was considered statistically significant.

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Table 1. Characteristics of Asthma and Control Study Subjects

Characteristic	Control	Asthma
Number of subjects	14	12
Age (mean $\pm$ SEM, range) (years)	42 $\pm$ 22 (8-78)	20 $\pm$ 11 (7-45)
Gender (male/female)(number)	8/6	7/5
β -Agonist MDI (%)	0%	100 %
Inhaled corticosteroids (%)	0%	25 %
Inhaled corticosteroids + LABA (%)	0%	33 %
Oral corticosteroid (%)	0%	8%
Leukotriene inhibitor (%)	0%	17%

LABA: Long Action β -Agonist

MDI: Metered Dose Inhaler

NA: Not Applicable