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Thymic Stromal Lymphopoietin and IL7R Variants are Associated with Persistent Atopic Dermatitis

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Keywords

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DATA AVAILABILITY

Datasets related to this article can be found within the online data repository hosted by Mendelay at DOI: 10.17632/sgnkksb36x.1 under the title: "Datasets for 'Thymic Stromal Lymphopoietin and IL7R Variants are Associated with Persistent Atopic Dermatitis.'"

CONFLICT OF INTEREST

David Margolis is a consultant for Pfizer, Leo, and Sanofi with respect to studies of atopic dermatitis and serves on an advisory board for the National Eczema Association. Joy Wan receives research funding from Pfizer, Inc for work unrelated to this study. No other authors state financial conflicts of interest with respect to this investigation.

TO THE EDITOR

Atopic dermatitis (AD) is a common inflammatory skin disease which manifests as itchy, red patches appearing early in life (Abramovitz et al.,2005;Margolis et al.,2014b). Previous studies have associated TSLP, a cytokine which promotes the differentiation of type 2 helper T cells, and specifically the single nucleotide polymorphism (SNP) rs1898671 (TSLP:g.110408002C>T), with the prevalence and persistence of AD (Gao et al.,2012;Margolis et al.,2014a). TSLP exerts its action via a heterodimeric receptor complex composed of IL-7Rα (encoded by the gene *IL7R*) and TSLPR (encoded by *CRLF2*) (Fornassa et al.,2015).

Study of *TSLP* and its receptor is important for understanding the genetic architecture of AD and identifying potential therapeutic targets (Margolis et al.,2014a). Prior studies of *TSLP* and *IL7R* have been limited to the examination of tagging SNPs (Gao et al.,2012; Hoffjan et al.,2009). In this report, we fully sequenced the *TSLP* and *IL7R* genes in a large longitudinal cohort of white and African American individuals with AD to gain more complete insight into their association with AD persistence.

Data were obtained from the Pediatric Elective Eczema Registry (PEER), a longitudinal cohort of children with mild-to-moderate AD, for whom disease control was assessed via self-report every 6 months for up to 10 years. Disease was considered persistent if the participant did not report “complete disease control” over the past six months and did not use prescription cream. Multiple measurements of this outcome were recorded over time for each participant. Next generation sequencing (NGS) of *TSLP* and *IL7R* was conducted on 739 individuals in PEER. Only the *TSLP* and *IL7R* genes were targeted for sequencing. Association between the outcome measure and individual SNPs was evaluated using generalized estimating equations (Berna et al.,2020). Full methods are described in the Supplement. Written, informed consent was obtained from all enrolled children. This study was approved by the Institutional Review Board of the University of Pennsylvania.

703 individuals described themselves as either white (n=379) or African American (n=324). Participant demographics are presented in Table 1. For the *TSLP* gene, 161 distinct SNPs were identified, 30 with MAF≥1%. Within the *IL7R* gene, 428 distinct SNPs were identified, 144 with MAF≥1%. Figure 1 presents associations of *TSLP* and *IL7R* SNPs with the persistence of AD over time in the full cohort and separately by race. The rs10073816 SNP (TSLP:g.110413489G>A) retained statistical significance after multiple testing correction in the full cohort (p=0.001). rs61423440 (TSLP:g.110408482G>C) and rs60340825 (TSLP:g.110408483T>A) also retained significance, after correction, in the full cohort (p=0.001,p=0.001,respectively). Within *IL7R*, the rs11567725 SNP (IL7R:g.35865962A>G) was associated with increased AD persistence in the full cohort, after correction (p=0.0003).

Rs10073816 was associated with more persistent AD and is not in strong linkage disequilibrium (R^2>0.6) with other *TSLP* SNPs with MAF≥1%, with the exception of rs2289277 (TSLP:g.110409067C>G), R^2=0.61, an SNP not associated with AD persistence (Supplementary Figure 1). eQTL analysis provided in GTEx demonstrates that rs10073816

is negatively associated with TSLP mRNA expression in sun-exposed skin, non-sun-exposed skin, and cultured fibroblasts (p=8.6e-39,1.1e-35,5.3e-18,respectively).

TSLP variant rs10073816 was more strongly associated with AD persistence when controlling for IL7R variant rs11567725 in both the full cohort (OR,0.646;95%CI,0.525–0.796;p=3.961e-5) and African American population (OR,0.609;95%CI,0.409–0.908;p=0.0148).

Our study demonstrates considerable variation in *TSLP* and *IL7R*; however, little is associated with AD persistence. We identify variants previously unassociated, to our knowledge, with AD, including rs61423440 and rs60340825 (MAF<5%), associated with a 4-fold increase in AD persistence, and rs10073816 (MAF=50.1%), associated with a 1.4 fold increase in AD persistence. The rs10073816 association was only observed in the full cohort, likely because this population is larger than the African American or white populations alone.

Our rs10073816, rs61423440, and rs60340825 associations have not, to our knowledge, been observed in other studies, even though a number of analyses of *TSLP* have been conducted (Gao et.al.,2012;Lou et al.,2019;Margolis et.al.,2014a;Ziegler,2012). The primary difference between our study and previous reports is that we used NGS to identify variants.

Identified TSLP variants are located in non-coding regions, suggesting that TSLP variation in AD is linked to altered protein quantity, not structure. The *TSLP* gene is transcribed into two proteins—a long isoform which is proinflammatory and a short isoform which is anti-inflammatory (Fornassa et al.,2015). The fact that rs10073816 is associated with decreased TSLP mRNA production and not in LD with any variants equally associated with AD persistence suggests that its effect on AD persistence may be causal. Since AD is thought to be an inflammatory disorder and rs10073816 is associated with decreased production of TSLP, it is likely that rs10073816 is associated with decreased production of TSLP's short isoform.

It is reasonable to think that *IL7R*, a component of the TSLP receptor, could be associated with AD persistence. One SNP, rs11567725 (MAF~1%), was associated with increased AD persistence. Our data imply that further study of *IL7R* may not uncover variants, at a clinically important frequency, associated with AD. The fact that variants in *IL7R do* modulate AD persistence suggests that this receptor protein may still be a valuable therapeutic target in AD.

This report's primary limitation is that SNPs in the *TSLP* and *IL7R* genes with MAF<1% were not analyzed. These SNPs may be associated with variation in AD severity and important in understanding the etiology of genetically distinct forms of AD. Although our sample size is large for a full-gene sequencing study (>700 individuals), these rare variants were difficult to analyze due to limited statistical power. However, our primary interest was the identification of ***clinically-actionable mutations***; rare variants are less useful in clinical practice. We therefore *a priori* only evaluated common SNPs.

In summary, we have conducted NGS of the *TSLP* and *IL7R* genes and identified that *TSLP* variants rs10073816, rs61423440, and rs60340825 are associated with more persistent AD. The rs10073816 variant is very common in the population, associated with decreased TSLP mRNA production, and not in strong LD with any variants equally likely to affect AD persistence. *IL7R* had only one mutation, rs11567725, associated with AD persistence. *IL7R* variants may modulate the effect of *TSLP* variants, for the association of rs10073816 with AD persistence is strengthened when controlling for rs11567725. This study strongly supports additional investigation of the TSLP pathway in AD, encourages further study of therapeutics targeting *TSLP* and *IL7R*, and promotes the case for including *TSLP* in genetic risk models for AD persistence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AD	atopic dermatitis
CI	confidence interval
FLG	filaggrin
LoF	loss of function
TSLP	thymic stromal lymphopoietin
PEER	Pediatric Eczema Elective Registry
MPS	massively parallel sequencing
MAF	minor allele frequency
GEE	generalized estimating equations

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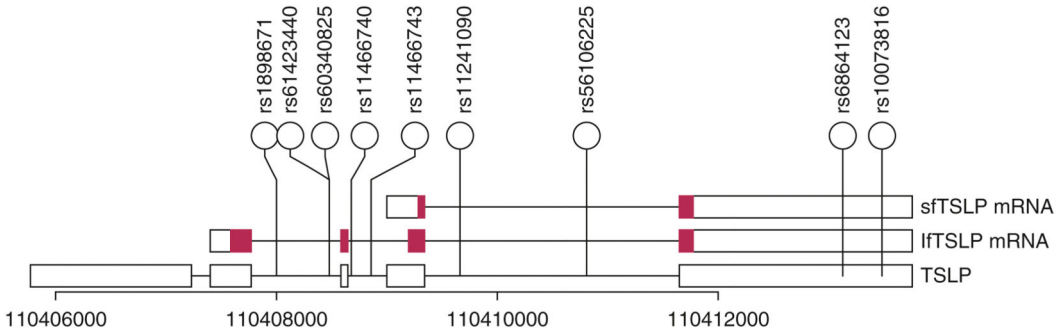
a

		Full cohort (n = 703)			African American (n = 324)			White (n = 379)		
Genomic Placements	SNP	Odds of Healing (95% CI)	uncorrected p-value	MAF	Odds of Healing (95% CI)	uncorrected p-value	MAF	Odds of Healing (95% CI)	uncorrected p-value	MAF
NC_000005.9: g.110413489G>A	rs10073816	0.727 (0.601,0.879)	0.001	0.5	0.749 (0.511,1.098)	0.139	0.594	0.857 (0.68,1.08)	0.190	0.420
NC_000005.9: g.110408002C>T	rs1898671	1.568 (1.269,1.938)	3.09E-05	0.236	1.902 (1.094,3.307)	0.023	0.099	1.205 (0.938,1.548)	0.144	0.354
NC_000005.9: g.110409666A>G	rs11241090	0.535 (0.328,0.874)	0.012	0.057	0.749 (0.428,1.311)	0.312	0.120	2.75 (2.138,3.537)	3.33E-15	0.003
NC_000005.9: g.110408673G>A	rs11466740	0.511 (0.308,0.849)	0.009	0.056	0.749 (0.428,1.311)	0.312	0.120	2.932 (2.346,3.663)	0	0.001
NC_000005.9: g.110408867G>A	rs11466743	0.513 (0.273,0.964)	0.038	0.035	0.731 (0.366,1.46)	0.374	0.074	2.932 (2.346,3.663)	0	0.001
NC_000005.9: g.110410818T>C	rs56106225	0.49 (0.245,0.979)	0.044	0.029	0.636 (0.321,1.261)	0.195	0.059	1.195 (0.166,8.592)	0.859	0.004
NC_000005.9: g.110413133A>G	rs6864123	0.411 (0.185,0.91)	0.028	0.024	0.657 (0.291,1.482)	0.311	0.051	0 (0,0)	0	0.001
NC_000005.9: g.110408482G>C	rs61423440	0.23 (0.094,0.562)	0.001	0.011	0.366 (0.148,0.908)	0.030	0.023	–	–	0
NC_000005.9: g.110408483T>A	rs60340825	0.23 (0.094,0.562)	0.001	0.011	0.366 (0.148,0.908	0.030	0.023	–	–	0

b



c

Genomic Placements	SNP	Full cohort (n = 703)			African American (n = 324)			White (n = 379)		
		Odds of Healing (95% CI)	uncorrected p-value	MAF	Odds of Healing (95% CI)	uncorrected p-value	MAF	Odds of Healing (95% CI)	uncorrected p-value	MAF
NC_000005.9: g.35865962A>G	rs11567725	0.461 (0.302,0.702)	0.0003	0.014	0.586 (0.357,0.963)	0.0348	0.026	0.725 (0.64,0.82)	3.57E-07	0.005
NC_000005.9: g.35873077T>A	rs11567758	0.382 (0.163,0.892)	0.0261	0.021	0.57 (0.249,1.302)	0.1824	0.045	–	–	0
NC_000005.9: g.35862627G>A	rs11567713	0.382 (0.164,0.893)	0.0263	0.021	0.569 (0.249,1.302)	0.1821	0.045	–	–	0
NC_000005.9: g.35858295A>G	rs11567696	0.382 (0.164,0.893)	0.0264	0.021	0.57 (0.249,1.302)	0.1824	0.045	–	–	0
NC_000005.9: g.35862385C>T	rs11567710	0.382 (0.164,0.893)	0.0264	0.021	0.57 (0.249,1.302)	0.1824	0.045	–	–	0
NC_000005.9: g.35864692G>A	rs11567721	0.382 (0.164,0.893)	0.0264	0.021	0.57 (0.249,1.302)	0.1824	0.045	–	–	0
NC_000005.9: g.35866650G>C	rs11567732	0.382 (0.164,0.893)	0.0264	0.021	0.57 (0.249,1.302)	0.1824	0.045	–	–	0
NC_000005.9: g.35870625A>C	rs11567746	0.382 (0.164,0.893)	0.0264	0.021	0.57 (0.249,1.302)	0.1824	0.045	–	–	0
NC_000005.9: g.35871831G>A	rs11567752	0.382 (0.164,0.893)	0.0264	0.021	0.57 (0.249,1.302)	0.1824	0.045	–	–	0
NC_000005.9: g.35875954C>A	rs7704710	0.489 (0.258,0.927)	0.0284	0.036	0.779 (0.409,1.484)	0.4477	0.077	–	–	0
NC_000005.9: g.35877759G>	rs16902514	0.489 (0.258,0.927)	0.0284	0.036	0.779 (0.409,1.484)	0.4477	0.077	–	–	0

d

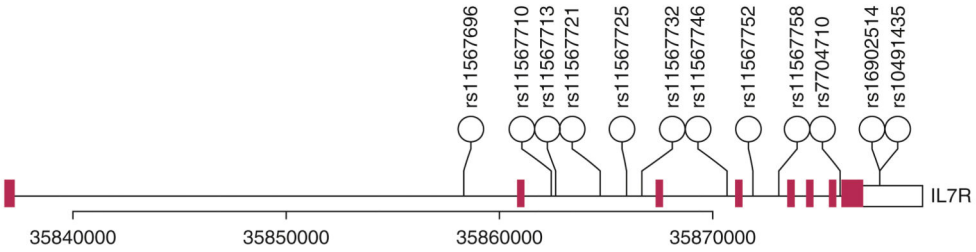


Figure 1. Evaluation of TSLP and IL7R SNPs.

(a) Association of TSLP SNPs with outcome, ordered by number of allele occurrences. Only variants with raw p values in the pooled analysis ≤ 0.05 and MAF ≥ 1% are reported. Presented p values are all raw. Bolded SNPs have p-values which satisfy Bonferroni correction in the pooled analysis (adjusted p = 0.00167). Genomic placements are from sequence GRCh37.p13 chr 5. (b) Schematic representation of human TSLP based on Fornassa et al. (hg 19), with locations of SNPs from the table above. Blue regions are coding. (c) Association of IL7R SNPs with AD persistence. Only variants with raw p values

in the pooled analysis ≤ 0.05 and MAF ≥ 1% are reported. Presented p values are all raw. Bolded SNPs have p-values which satisfy Bonferroni correction in the pooled analysis (adjusted p = 0.00035). Genomic placements are from sequence GRCh37.p13 chr 5. (d) Schematic representation of human IL7R based on the NCBI gene database (hg 19), with locations of SNPs from the table above. Blue regions are coding.

Table 1.

Participant Demographics

	Full cohort, n (%)	African American, n (%)	White, n (%)	p value (African American vs. White)
Number	703	324	379	
Age of AD onset, mean (SD)	1.98 (2.74)	2.14 (2.85)	1.84 (2.65)	0.162
Sex: male, n (%)	332 (47.23)	136 (41.98)	196 (51.72)	0.012
Asthma, n (%)	382 (54.34)	182 (56.17)	200 (52.77)	0.408
Seasonal Allergies, n (%)	494 (70.27)	228 (70.37)	266 (70.18)	~1
Observation time in months, mean (95% CI)	117.3 (115.8,118.8)	116.9 (115.2,118.8)	117.7 (115.8,119.4)	0.549