IRF-1 SNPs influence the risk for childhood allergic asthma: A critical role for pro-inflammatory immune regulation.

Allergic and non-allergic childhood asthma has been characterized by distinct immune mechanisms. While interferon regulating factor 1 (IRF-1) polymorphisms (SNPs) influence atopy risk, the effect of SNPs on asthma phenotype-specific immune mechanisms is unclear. We assessed whether IRF-1 SNPs modify distinct immune-regulatory pathways in allergic and non-allergic childhood asthma (AA/NA). In the CLARA study, asthma was characterized by doctor's diagnosis and AA vs NA by positive or negative specific IgE. Children were genotyped for four tagging SNPs within IRF-1 (n = 172). mRNA expression was measured with qRT-PCR. Gene expression was analyzed depending on genetic variants within IRF-1 and phenotype including haplotype estimation and an allelic risk score. Carrying the risk alleles of IRF-1 in rs10035166, rs2706384, or rs2070721 was associated with increased risk for AA. Carrying the non-risk allele in rs17622656 was associated with lower risk for AA but not NA. In AA carrying the risk alleles, an increased pro-inflammatory expression of ICAM3, IRF-8, XBP-1, IFN-, RGS13, RORC, and TSC2 was observed. NOD2 expression was decreased in
AA with risk alleles in rs2706384 and rs10035166 and with risk haplotype. Further, AA with risk haplotype showed increased IL-13 secretion. NA with risk allele in rs2070721 compared to non-risk allele in rs17622656 showed significantly upregulated calcium, innate, mTOR, neutrophil, and inflammatory-associated genes. IRF-1 polymorphisms influence the risk for childhood allergic asthma being associated with increased pro-inflammatory gene regulation. Thus, it is critical to implement IRF-1 genetics in immune assessment for childhood asthma phenotypes.

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