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## A report on asthma genetics studies in Pakistani population

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## Abstract

Pakistan is globally sixth most populous, economically developing south Asian country with tremendously increasing trend of urbanization. This increase in urbanization along with consanguineous marriages trend in Pakistani nationals might contribute as most important factors of increasing asthma prevalence.

Up-till now, a few studies related to asthma genetics have been conducted in Pakistan. These studies suggest that the SNP variants like (rs2569190, rs2569191), (rs2243250, rs2227284), (rs1800896), (rs1881457, rs20541, rs1800925), (rs2280091, rs2787094, rs528557), (rs1131882) in CD14, IL-4, IL10, IL-13, ADAM33 and TBXA2R genes respectively and the SNPs (rs3816470, rs6503525, rs3859192, rs12603332) on chromosomal region 17q21 are significantly associated in Pakistani population whereas the haplotype "CCTCAG" of SNPs (rs12936231, rs7216389, rs7216558, rs9894164, rs1007654 and rs7212938) in 17q21 and 'AAGTCG' of SNPs (rs2280089, rs2280090, rs2280091, rs44707, rs528557, and rs612709) in ADAM-33 region are protective factor against asthma susceptibility.

These studies will definitely contribute in understanding genetic basis of asthmatic complications in Pakistan and large population cohort size and sub-ethnic studies in future will give more meaningful conclusions to predict possible asthma susceptible genomic variants in sub-ethnic and general population of Pakistan.



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## Introduction

Asthma is a non-communicable major chronic disease of lungs, characterized by inflammation and narrowing of airways with excessive production of mucus resulting in ultimate breathing difficulty, wheeze and cough. Frequent and recurrent asthmatic exacerbations cause sleeplessness, daytime fatigue, reduced activity levels and work absenteeism [1].

Asthma prevalence is rapidly increasing worldwide and according to WHO reports asthma along with COPD will be the third leading cause of deaths globally by the year 2020 [2]. Pakistan is listed 6<sup>th</sup> most populous country [3] and more than twenty million adult Pakistani population is facing asthmatic complication [4]. The prevalence of allergic diseases is quite high in Pakistan but the diagnosed cases of asthma are about 9.5% [5] and its prevalence is further increasing in Pakistan along with other Asian Pacific and Eastern Mediterranean countries [6]. Although asthma is a common but multi-factorial complex disorder believed to be induced by the interaction of both environmental and genetic factors [7]. Association of more than 100 genetic loci with the susceptibility of asthmatic complications have been reported [8] but the results are not consistent in different ethnic populations [9,10]. Due to the human migrations and intermixing of multiple ethnic populations, current global populations represent the high degree of genetic diversity which impacts the individual genomic variant allele frequency. Thus, how genomic variations are utilized in genetic association may be different in different populations and in different regions. The disease severity and frequency of asthmatic complications also vary among different ethnic and racial communities. An understanding of population based genomic variations involved in disease manifestation might constitute future genetic biomarkers to predict asthma risk and progression in individuals from specific ethnicities [7,11].

## Methods

### Literature Survey and Selection Criteria

This review report was intended to gather an up-to-date information about asthma genetic studies in Pakistani population. For this purpose the research articles on asthma genetics in Pakistani population were explored through Google, PubMed, Web of Science. Conference abstracts and other scientific materials which are not

cited in PubMed were also traced through ResearchGate.

## Discussion

### Status of asthma genetics studies in Pakistan

In 2011, Micheal and his colleagues from “COMSATS Institute of Information Technology, Islamabad, Pakistan”, were the first who identified two SNP variants in CD14 gene (i.e., C159T rs2569190 and A1145G rs2569191) that were associated with atopic asthma and allergic rhinitis in 340 study participants of Pakistan (120 controls, 110 atopic asthma, 110 allergic rhinitis). CD14 is an important functional molecule of innate immune system which expresses on the surface of granulocytes, macrophages, monocytes and B lymphocytes. It is functionally carrier and receptor of microbe ligands. Upon ligand binding, CD-14 induces the production of IL-12 which is required for maturation of naive T-cells to TH1 cells. Micheal and colleagues reported that both the SNP variants were in Hardy-Weinberg equilibrium and also strongly associated with atopy (C159T;  $P = .02$  and A1145G;  $P = .01$ ) but after stratification they found that the variant A1145G ( $P = 0.02$ ) was associated with atopic asthma while C159T was associated with patients of allergic rhinitis [12]. In 2012, the same research group reported the genetic association of IL-4 gene SNP variants with atopy in Pakistani population. In that particular study, they genotyped three SNPs [C-33T (rs2070874), T+2979G (rs2227284), C-589T (rs2243250)] in IL-4 Cytokine in 334 volunteers (120 controls, 108 atopic asthma, 106 allergic rhinitis). IL-4 Cytokine is reported as the mediator of allergic response in immune response. This study predicted two SNP variants rs2243250 and rs2227284 significantly associated with both allergic rhinitis and asthma whereas association of rs2070874 was non-significant in both categories [17]. The same group again reported in October 2012 that IL-13 is a potential risk factor in susceptibility of allergic rhinitis (AR) and atopic asthma. Out of three SNP variants i.e., rs1881457 (A-1512C; 5' UTR), rs847 (T+2749C; 3' UTR) and rs20541 (G+2044A; exon 4) which were genotyped, the SNP variant rs1881457 was significantly associated with atopy in overall studied participants and also independently associated with AR and atopic asthma on population stratification. Association of other two variants was not significant in genotypic model whereas a significant difference in

allele frequencies relative to control samples was observed for G+2044A in case of AR [ $p=0.04$ , OR 1.46 (0.99-2.15)] [23].

Data of a study on genetic associations of 33 SNP variants (in 21 genes) with asthmatic population of Pakistan have been reported in a conference proceedings published by Nusrat and colleagues in November 2013. From the literature they selected the SNP variants which were reported as associated with asthma susceptibility in different populations. They recruited 333 asthma and 220 control volunteers from Rawalpindi, Islamabad and Lahore. 26 SNPs were genotyped by Sequenom Mass ARRAY iPLEX platform and seven others in TaqMan assay. The study revealed that G allele of rs2280091 (*ADAM-33*;  $P = 0.03$ , 95% CI 0.50–0.97, OR 0.69,) and A allele of rs1131882 (*TBXA2R gene*;  $P = 0.05$ , 95% CI 0.52–1.01, OR 0.73,) might be protective factor for asthma while G allele of rs1800896 (*IL10 gene*;  $P = 0.04$ , 95% CI 1.01–1.88, OR 1.38) and the T allele of rs1800925 (*IL-13*;  $P = 0.03$ , 95% CI 1.04–2.02, OR 1.45) may be potential variant for asthma risk in Pakistani population [29].

TNF- $\alpha$  cytokine is known for its central role in inflammation and bronchial hyper-responsiveness. Its up-regulation in asthma patients consequently results in increased airways secretions and bronchoalveolar lavage (BAL) fluid. Several polymorphisms of TNF- $\alpha$  are known for possible asthma susceptibility role in different ethnicities with conflicting results. In 2014, Saba and co-authors analyzed TNF-alpha gene SNP (rs1800629) variant in 329 asthmatic and 151 healthy controls through allele specific primers amplification. Volunteers were recruited from OPD respiratory clinics of Islamabad, Rawalpindi and Lahore, Pakistan. In statistical analysis, they did not find any significant role of this SNP variant in asthma susceptibility in Pakistani population [33].

Recently, Mariam and colleagues from Asthma research group of Punjab University, Lahore reported the genetic association of chromosomal region 17q21 with asthma susceptibility in Lahore. 17q21 is a known as potential asthma causative region because of its replicative results of significant association in different ethnic populations [35,46,47]. The researchers analyzed twelve SNPs of 17q21 in a case-control study consisting of 300 participants (200 asthmatics, 100 controls). The

12-plex of genomic SNPs was analyzed by using single base extension/mini-sequencing methodology and ABI-3130XL automated genetic analyzer. The statistical analysis revealed that rs3816470 variant was significantly associated ( $p = 8.89 \times 10^{-5}$ , Odd Ratio = 3.082 [1.755-5.41]) in general whereas rs6503525 and rs3859192 were significantly associated with when positive family history of asthma was also included in the analysis. Six polymorphisms (rs12936231, rs7216389, rs7216558, rs9894164, rs1007654 and rs7212938) in 93 kb genomic block were in moderate linkage disequilibrium with each other and haplotype analysis of this block predicted the protective role of haplotype "CCTCAG" ( $p = 3.56 \times 10^{-2}$ ,  $\chi^2 = 4.415$ ) against asthma susceptibility [35].

Recently in 2015, the association of "C allele" of rs12603332 variant with asthma development in urban asthma population of Lahore –Pakistan was disclosed by same asthma research group of Punjab University in a poster abstract [39]. The SNP variant is known to be involved in altering E2A regulatory motif which leads to disruption in lymphocytes development because development of B-lymphocytes and T-lymphocytes is E2A transcription factor dependents. 300 study participants (200 asthma patients, 100 Controls) were recruited from Lahore. The selected SNP variant showed a trend toward association in overall case-control study, the allele "C" was statistically insignificant for early age asthma onset while it was significant while taking urbanization as a covariate. This study also predicted the strong trend of association with male asthma patients. Strong association with both urban population and male gender might be because of relatively more exposure to environmental pollutants [39].

ADAM33 (A disintegrin and metalloproteinase) is a known asthma susceptible gene due to its probable involvement in airway remodeling, abnormal cells proliferation, and differentiation [9]. In August 2014, Ghazala and colleagues reported the strong association of rs2787094 C/G ADAM-33 gene SNP variant in general Pakistani population. They studied two SNP variants (rs2787094 C/G and rs3918936 A/G) in a case-control study comprising 504 participants (asthma patients 298, controls N=204). In allelic model C allele of rs2787094 SNP was significantly raised in cases ( $<0.0001$ , OR= 2.08 CI=1.45-2.99) and in genotypic

Gene ID	SNP ID	Asthma Phenotype	Association in Pakistani Population	Populations Already Associated	Global MAF	Allele Frequency in Pakistan
CD14	rs2569190	Allergic rhinitis	Significant [12]	Turkish [13], Chinese Han children [14], Korea [15], Norway [16]	T=0.47	0.557
	rs2569191	Atopic asthma	Significant [12]	Norway [16]	G= 0.47	0.557
IL-4	rs2070874	Atopic asthma	Non-significant [17]	China [18,19], Netherlands [20]	T=0.40	0.198
	rs2243250	Atopic asthma	Significant [17]	Turkish [13], Netherlands [20]	T= 0.47	0.198
IL-13	rs2227284	Atopic asthma	Significant [17]	Polish [21], China [22]	G= 0.39	0.625
	rs1881457	Atopic asthma	Significant [23]	UK [24],	C= 0.20	0.245
	rs847	Atopic asthma	Non-significant [23]	-	T= 0.25	0.323
TBXA2R	rs20541	Atopic asthma	Non-significant [23]	Korea [15,25], UK [24], Portugal [26], Japan [27], China [28]	A= 0.27	0.328
	rs1800925	Asthma	Significant [29]	UK [24], Caucasians [30]	T= 0.25	0.25
IL10	rs1131882	Asthma	'A allele' protective factor [29]	Japan [31]	A= 0.23	0.203
TNF-α	rs1800896	Asthma	Significant [29]	South India [32]	G= 0.27	0.318
IKZF3	rs1800629	Asthma	Non-significant [33]	West Asians [34], South Asians [34]	A= 0.09	0.057
LRR3C	rs3816470	Asthma	Significant [35]	southern Chinese children [36]	G= 0.47	0.411
GSDMA	rs6503525	Asthma	Significant for asthma in family history [35]	Australia [37]	C= 0.48	0.453
	rs3859192	Asthma	Significant for asthma in family history [35]	UK [38]	T= 0.39	0.307
ORMDL3	rs12603332	Urban Asthma	Significant [39]	Meta-Analysis [40,41], Mexicans [42], African American [42]	T= 0.46	0.438
ADAM-33	rs2787094	Asthma	Significant [10]	Meta-analysis [43], Japanese women [44], Indian children [45]	C= 0.31	0.271
	rs3918396	Asthma	Deviate from HWE [10]	Turkish [13]	T= 0.05	0.141
	rs2280091	Asthma	'G allele' protective factor [29]	Asia [43]	G= 0.13	0.193
	rs528557	Asthma	Significant [9]	Indian Children [45], Netherlands [20]	G= 0.39	0.422

Table 1: SNPs studied in Pakistani population for association with asthma and comparison of minor allele frequencies

model homozygous CC allele was raised ( $p=0.0015$ ) in case of samples relative to controls. rs3918396 SNP was excluded for further analysis for disease association because it had shown deviation from HWE [10]. In one of our previous study, we have analyzed eight already reported SNP variants [rs2280089, rs2280090, rs2280091, rs597980, rs44707, rs528557, rs612709, rs511898] in 203 Punjabi ethnic population (101 asthma, 102 controls) from Pakistan. In statistical analysis only rs528557 variant was significant for asthma manifestation in both allelic and genotypic model ( $p=0.0189$  and  $0.021$  respectively). The six SNPs [rs2280089, rs2280090, rs2280091, rs44707, rs528557, and rs612709] were in moderate to strong Linkage Disequilibrium and significantly higher prevalence of haplotype 'AAGTCG' in control participants suggested it's protective role against asthma susceptibility ( $p = 0.0059$ ) in the studied population [9]. Table 1 summari-

-zes the status of some SNPs associations with asthma in Pakistan and in some other populations as well as their allele frequency comparison with global MAF.

## Conclusion

These short scope studies targeting several previously reported SNP variants suggest the possible role of specific genetic variants in the susceptibility of asthma in Pakistani population. It was found through these studies that most of the variants associated in other populations are not associated in Pakistani population but some others do show replication in association with the disease in Pakistan too. Although these studies are not enough for the detailed information of the role of different genomic regions and variants in asthma but these will pave the spot-on direction towards discoveries of the causes and therapeutics of the disease and lot of work is to be done in this regard especially in countries

like Pakistan. In this era of advanced technologies, genome based analysis like whole genome/exome analysis might be utilized to identify the potential causative factors associated with multifactorial complex disorders like asthma. Whole Genome/Exome Analysis study on large asthma cohort size is an appropriate route for a detailed investigation to identify asthma susceptible genomic markers and regions.

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