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Molecular Medicine: Bridging the Gap between Basic and Clinical Sciences

A physician's ultimate goal is to help in building healthy society and helping mankind by alleviating diseases. The task cannot be completed alone and but need a coordinating efforts of a team of experts. Clinicians provide care to suffering humans through their skills, vast knowledge, experience and expertise in their decision making. They deal with real problems of real life which are based on the scientific evidences. One can also recount the way the clinical medicine is evolving in last few decades with patient management moving from bedside to heavy reliance on laboratory and technology support. In fact, we can see that our clinical acumen is improving because of technological advances. At the same time doctors are still being appreciated for being humane to people. Insufficient data from appropriate clinical studies and evidence-based medicine presently limit the applications of molecular medicine in clinical practice. Moreover, lack of awareness of each other's field advances limits our utilization of available resources optimally.

The buzz word nowadays in medical education is integrated medical care and teaching. The task is difficult but not impossible. The molecular medicine has provided the true base for integrating basic and clinical sciences. The rapid pace of basic science research greatly exceeds the rate at which these findings are being translated into clinical application.

Our conventional medical curriculum disregards the role of basic science in human suffering and there is deep perception of it being of purely research interest. For this our society is also partly responsible as the subject of Biology is not given much importance to students in school. One important change required is making the subject more relevant to students. This can be achieved by arranging talks by experts, visit to labs and showing application through practical demonstrations.

For medical schools, it should be emphasized that incorporation of conceptual and clinical aspects of molecular medicine in undergraduate and postgraduate curricula and a continuing education of medical professionals is necessary for the quality medical care. The emphasis should be put on bedside-orientated molecular medicine. The prerequisite is translational research aimed to the improvement of healthcare of individual patients and the population as a whole.

The Indian Journal of Genetics and Molecular Research (IJGMR) provide a platform for interaction between basic and clinical research scientists. In this issue, Volume 2, we bring such an attempt of integrating medicine by including clinical case, epidemiological study as well as role of genetic polymorphism in common disease causation.

Dr Kuldeep Singh,
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Jodhpur

Indian Journal of Genetics and Molecular Research

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Original Article

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A Study on Distribution of ABO and Rh (D) Allele Frequencies among Bishnoi, Sunar, and Kumhar of Haryana

Shweta Yadav*, Abhay Singh Yadav**

Abstract

The present investigation was planned on three endogamous groups of Haryana viz. Bishnoi, Sunar and Kumhar, and the distribution of serological traits like ABO and Rh (D) blood groups was determined. In the ABO blood group system the frequency of A allele ranged from 0.09-0.24, that of B allele ranged from 0.24-0.40 and of O allele from 0.36-0.67. In Rh (D) blood group system the frequency of d allele ranged from 0.26-0.35 while the frequency of D allele varied from 0.65-0.74. The frequency range of traits studied conformed to the range of other populations of North West India studied earlier.

Keywords: ABO; Allele frequency; Endogamous groups; Rh (D) blood group.

Introduction

Singh has identified 82 communities residing in Haryana.[1] Although these communities are quite widely distributed yet only sporadic studies are available with regard to the distribution of ABO and Rh (D) blood groups in different endogamous groups of Haryana.[2-13] The present investigation was planned to obtain the original data on these two serological markers of three endogamous groups, *viz.* Bishnoi, Sunar and Kumhar, of Haryana.

Subjects and Methods

Subjects

The study was approved by the Institutional Ethics Committee of the Kurukshetra University, Kurukshetra. Blood samples from a total of 300 individuals of both sexes from three endogamous groups (Bishnoi, Sunar and Kumhar) were collected. A total of 100 unrelated individuals of both sexes (50 males and 50 females) were studied for each caste group. Donor subjects were selected randomly from all over Haryana.

Methods

Vacuum tubes containing EDTA (Vacutainer, Becton Dickinsen, France) were used for intravenous blood sample collection from the subjects. ABO and Rh (D) blood group systems were typed using whole blood by slide method following the standard techniques of serology and manufacturer's directions enclosed with the different blood grouping reagents. The allele frequency in the ABO blood group system was calculated according to Yasuda The frequency of d allele was estimated by square root method.[14]

Results and Discussion

ABO blood group

The phenotypes and gene frequencies of ABO blood group are given in Table 1. In the ABO blood group system the frequency of A allele was found to be highest in Kumhar (0.24) and lowest in Bishnoi (0.09). The allele frequency of B allele was highest in Kumhar (0.40) followed by Sunar (0.33) and Bishnoi (0.24). While the allele frequency of O allele

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Table 1: Phenotypes and gene frequencies of ABO blood group in three endogamous groups of Haryana

Population group		ABO Phenotype				ABO Allele frequency			χ^2 value
		A	B	AB	O	A	B	O	
Bishnoi	Obs.	17	40	2	41	0.09	0.24	0.67	3.0224
	Exp.	12.87	37.92	4.32	44.89				
Sunar	Obs.	18	45	10	27	0.15	0.33	0.52	0.0033
	Exp.	17.85	45.21	9.90	27.04				
Kumhar	Obs.	26	48	14	12	0.24	0.40	0.36	2.4874
	Exp.	23.04	44.80	19.20	12.96				

Obs.= Observed, Exp.= Expected

Table 2: Phenotypes and gene frequencies of Rh (D) blood group in three endogamous groups of Haryana

Population group	Rh (D) Phenotype		Rh (D) Allele frequency	
	Rh $(D)^+$	Rh $(D)^-$	D	d
Bishnoi	93	7	0.74	0.26
Sunar	89	11	0.67	0.33
Kumhar	88	12	0.65	0.35

was lowest in Kumhar (0.36) it was found to be highest in Bishnoi (0.67). The chi-square values for the distribution of ABO blood group system were found to be non-significant in all the three castes indicating a homogeneous distribution of the trait.

The frequency of allele A in the different caste populations of North West India has been reported to range from 0.066 in Yadav[13] to 0.667 in Brahmin of Himachal Pradesh.[15] The frequency of allele A (0.09-0.24) in the present study fits well in the range recorded previously. Earlier studies on the North West Indian populations reported that the frequency of allele B vary from 0.185 in Sunar[6] to 0.566 in Sikh Harijans of Moga.[16] The frequency of B allele (0.24-0.40) in present study was in agreement with the previous work. Previously, the frequency of allele O has been found to vary from 0.170 in Sikh Harijans of Moga[16] to 0.689 in Maratha of Deccan Plateau[17] and the frequency of the O allele (0.36-0.67) as found in the present study falls well within the range of earlier studies.

Rh (D) blood group

The phenotypes and gene frequencies of Rh (D) blood group are given in Table 2. The gene frequency for d allele was highest in Kumhar (0.35) and lowest in Bishnoi (0.26). Earlier studies have reported that the frequency of d allele varies from 0.000 in Kamboj[6] to 0.420 in Jat[8] in various populations of Haryana. Thus, the frequency range (0.26-0.35) of d allele recorded in the present study fitted well in the range reported in the past studies.

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Review Article

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Association of ADAM33 Gene Polymorphisms with Genetic Susceptibility to Asthma in Asian Populations: A Meta-Analysis

Priya Tripathi*, Shally Awasthi**

Abstract

Method: The aim of present study was to assess the association of causative gene polymorphisms of ADAM33 in Asian population using Meta-analysis approach.We performed a literature search using the MEDLINE citation database and references in the identified reports. Data were analyzed using software Stata 11.2(Stata Corp, College Station, Texas, US). Thirteen studies and twelve ADAM33 gene polymorphisms were selected for meta-analysis, which included 3,270 patients and 2,922 controls. **Results:** On comparing data for "M" (Mutant allele) with the susceptibility to asthma as compared to the "L" (wild allele), four SNPs named as, S2, ST+5, T1 and Q-1 were observed to be associated with asthma. Likewise, on calculating "MM" (homozygous mutant genotype) *vs* "LL" (homozygous normal genotype), SNPs S2 and ST+5 showed association. After calculating, "LM" (heterozygous genotype) + "(MM *vs* LL)", SNP ST+5 was found to be associated and lastly when we compared "MM" vs "(LL+LM)", SNPs T1, S2 and ST+5 were found to be associated with asthma. **Conclusion:** To our knowledge, this is the first and most comprehensive genetic meta-analysis showing association of ADAM33 gene polymorphisms (Q-1, S2 and T1) with asthma in Asian population.

Keywords: Asian population; Meta-analysis; Single nucleotide polymorphisms; Association study; Case-control studies.

Introduction

Asthma is the most common chronic disease, effecting children and adults. It is predictable that around 300 million people in the world currently have asthma.[1] It is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.[2] Masoli *et al* published an article showing global burden of asthma, in which they have nicely represented prevalence of asthma in worldwide population on adults and children.[1]

While the exact role of ADAM33 in the pathogenesis of asthma is vague, studies have shown association of ADAM33 and its related SNPs with asthma. In the first report of ADAM33 as an asthma candidate gene in two Caucasian populations from the UK and the USA, Van Eerdewegh *et al*, identified a locus on the short arm of chromosome 20 and assessed 135 polymorphisms of 23 genes in this region and reported ADAM33 gene to be significantly associated with asthma.[3] A number of studies are available with very diverse results, suggesting ADAM33 SNPs role in asthma.[3-25] Recently Sharma *et al*, reviewed ADAM33 gene association with asthma on published literature[25], however results were not similar in all studied populations, some studies showed positive association of ADAM33 polymorphisms with asthma and another different set of studied populations were not associated with asthma.

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A candidate gene case–control approach, investigating polymorphisms, is generally taken to examine genetic risk factors for particular disease. Since asthma is a heterogeneous multifactorial disease, there is large number of candidate genes, which are involved in respiratory disorders like, COPD, allergic rhinitis, allergic dermatitis etc.[26-28] There is an improbability about the nature and number of genes involved in the development of asthma, due to lack of reproducibility of genetic case–control studies.[29] In the association studies, there are possibilities that some positive results might be specious and some negative findings might be a consequence of low statistical power. It could be due to their smaller sample size or methodological liabilities, such as the selection of an appropriate control group.[30] Meta-analysis might be a means of determining reflective results. Like, combining samples from several studies could make greater power than from individual studies or might increase trends for association in small individual studies. Meta-analysis might be useful to identify the causative gene polymorphisms with consistency and to quantify with accuracy the genetic risks. We conducted a complete meta-analysis of all ADAM33 gene polymorphisms in Asthma in Asian populations. Therefore the aim of present study was to assess the association of causative gene polymorphisms of ADAM33 in Asian population.

Materials and Methods

For study identification and selection of applicable studies, a literature search of the PubMed database was conducted to identify all articles that examined the association of the ADAM33 gene polymorphisms with asthma using clinically evident case-control study design. The terms "ADAM33", "ADAM33 gene and asthma", and "ADAM33 gene polymorphisms" were used as search criteria. The search results were limited to humans. All the studies that were published before March, 2012 were considered for primary screening. For meta-analysis inclusion and exclusion criteria were following:

Inclusion criteria

The articles written in English were only considered. To assess the aptness of the studies for inclusion in this meta-analysis, the publications were read in their entirety. Abstracts, editorials and review articles were excluded. All the case–control studies included in this meta-analysis had met the following criteria:

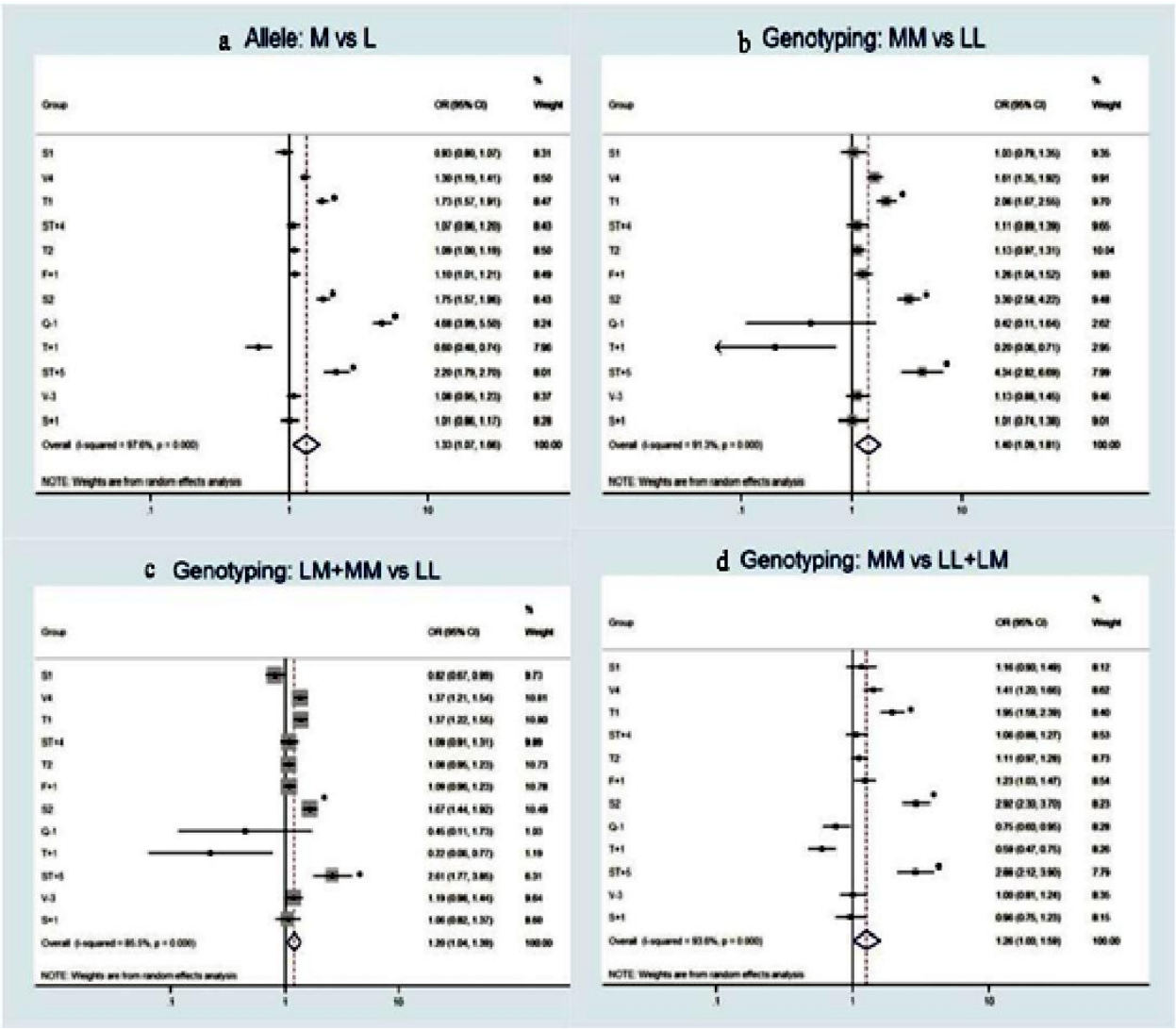
1) Asthma was diagnosed by physician/ pulmonologist who were experts in allergic diseases with characteristic symptoms, accompanied by preferred guidelines for asthma.
2) Studies contained original data (to ensure independence among studies), and
3) Studied that provided sufficient genotype data to calculate an odds ratio (OR).

Exclusion criteria

The following were excluded:

1) reports containing overlapping data,
2) reports in which the number of null and wild genotypes could not be ascertained,
3) reports in which genotype distributions in the control population were not in accord with Hardy-Weinberg (H-W) expectations, and
4) reports in which family members had been studied, such as those involving transmission disequilibrium studies (because such analyses were based on linkage considerations),
5) Gender specific study and,
6) Control subjects were unrelated individuals without symptoms and family history of asthma, selected randomly from the same geographic region.

Figure 1: Schematic representation of the ADAM33 gene on chromosome 20. (A) Chromosome 20 showing ADAM33 gene position 20p13. (B) Region covered by polymorphisms done on Asian population and covered size in Kb. (C) Exons and size in base pairs (D) domain structure (E) Functions of ADAM33 domain



Data extraction

The following informations were extracted from each study: name of the first author, year of publication, country, journal, racial descent of study population, demographics, number of cases and controls, genotyping methods, genotype and allele distributions and confirmation of diagnosis. If allele frequencies were not given, they were calculated from the corresponding genotype distributions.

Statistical analysis

Data were analyzed using software Stata 11.2(Stata Corp, College Station, Texas, US). For each polymorphisms of ADAM33 gene, meta-analysis was performed to examine the overall association for the allele contrast, the contrast of homozygotes, and the recessive, dominant and additive models. To measure the strength of genetic association for each gene variant, the odds ratios (ORs), together with the 95% confidence interval (CI) and the corresponding P value (the P value being significant if <0.05) were calculated. Heterogeneity between the studies was examined by Q-statistic, which is a weighted sum of squares of the deviations of individual

study OR estimates from the overall estimate.[31,32] The heterogeneity was considered statistically significant with P<0.10. Quantification of the heterogeneity was done with the I^2 metric (I^2 = (Q - df)/Q), which is independent of the number of studies in the meta-analysis.[33] This explains the variance of effect estimate attributable to heterogeneity and its values falls between 0–100%, with higher values denoting greater degree of heterogeneity (I2 = 0–25%, no heterogeneity; I2 = 25–50%, moderate heterogeneity; I2 = 50–75%, large heterogeneity; I2 = 75–100%, extreme heterogeneity).[31,32] The random-effects pooled ORs were calculated by the DerSimonian and Liard method.[34] As the studies are both clinically and methodologically diverse, heterogeneity between studies is an expected outcome.[35] If heterogeneity existed between studies, a pooled OR was estimated by the random-effects model, because this model assumes a genuine diversity in the results of the studies, incorporating the calculations of inter-study variability and provides wider CIs.[32] In this article, the results from the random-effects model are reported only. To assess the publication bias for allele contrasts, the Egger regression test for funnel plot asymmetry[31,32,36] and the begs- Mazumdar test, which is based on Kendall's tau[37], were carried out.

Results

Study inclusion

The initial search with the key words and subject terms identified a total of 19 studies. Of these, based on the penetrating criteria, fourteen articles were taken.[4-9,11-16,38,39] Due to unavailability of the genotype data, one study was excluded.[12] Finally, thirteen studies[4-9,11,13-16,38,39] were considered for the meta-analysis on twelve ADAM 33 gene polymorphisms namely, S1, V4, T1, ST+4, T2, F+1, S2, Q-1, T+1, ST+5, V-3, and S+1. **Figure 1** represents schematic representation of the ADAM33 gene on chromosome 20, gene position on chromosome 20p13, region covered by polymorphisms done on Asian population and covered size in Kb and gives an overview of gene exons and size in base pairs, domain structure and their functions.

We only included Asian populations for meta-analysis. All studies taken were in Hardy– Weinberg equilibrium (HWE). Genotype determination in the included studies was carried out by polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) method in seven studies[4-5,11,13,15,16,38,39] and in other studies it was done by allele specific polymerase chain reaction with fluorescence melting curve[6], using single based extension and electrophoresis[9], using direct sequencing [14] and using Taqman and PCR-RFLP methods.[7] In our personal communication genotyping (SNPs, Q-1, T1, T2, and S1) was done using PCR-RFLP method. We gave common name to studied SNPs' genotypes and allele as; mutant allele= M, wild type allele= L, homozygous normal genotype= LL, heterozygous genotype=LM, homozygous mutant genotype=MM.

Summary statistics

Characteristics of the included studies on ADAM33 gene polymorphisms are shown in **Table 1**. The genotype distributions and the allele frequencies on all included Asian populations' sample size are mentioned in **Table 2**. Study specific genotypic and allelic data are provided in **supplementary file 1**.

Main results

Thirteen studies and twelve ADAM33 gene polymorphisms were selected for meta-analysis, which included 3,270 patients and 2,922 controls. After combining all data for meta-analysis of ADAM33 gene polymorphisms named as S1, V4, T1, ST+4, T2, F+1, S2, Q-1, T+1, ST+5, V-3, and S+1, four of the twelve SNPs were significantly associated with asthma in meat-analysis (**Figure 2**) with a maximum odds ratio (OR)

Table 1: characteristic of the studies of ADAM33 gene polymorphisms and asthma on Asian population

S. no.	Population	Cases	Control	Polymorphisms	References
1	Northern Chinese	412 (48.30% female); mean age 7.74 ± 2.78 years	397 (48.36% female); mean age 7.52 ± 2.95 years	F+1, T+1, T2, T1, V4 and Q-1	Qu *et al*, 2011[11]
2	East Chinese Han	150 (54.0% female); age range 13-75 in years	74 (56.8% female); age range 20-69 in years	F+1, ST+4, S1, S2, T1 and T2	Jie *et al*, 2011[8]
3	Chinese	329(43.16% female); age in years, median(range); 39.88 (13-69)	316 (47.78% female); age in years, median(range); 43.0(22-69)	F+1, S2, T2 and V4	Chi *et al*, 2011[6]
4	Indian	175 (30.9% female); mean age 33.7 ± 11.3years	235 (20.6% female); mean age 31.9 ± 9.2	F+1,V4, ST+4, ST+5 and S2	Tripathi *et al*, 2011[15]
5	Indian	211 (32.2%female); mean age 74.39 ± 45.76 months	137 (29.9% female); mean age 73.61 ± 42.56 months	F+1,V4, ST+4, ST+5 and S2	Awasthi *et al*, 2011[4]
6	South Indian	100 (45% female); age range: 6 months to 80 years	50 (12% female); age range: 6 months to 80 years	T1	Bijanzadeh *et al*, 2010[5]
7	Chinese Han	181 (37.02%female); mean age 36.69 ± 11.53 years	151 (35.76% female); mean age 37.18 ± 10.60 years	V4, T+1, T2, T1, S1 and Q-1	Su *et al*, 2008[13]
8	Thai	200 (42% female); mean age 29.86 years	100 (54% female); mean age 26 years	ST+4, S2 and V4	Thongngarm *et al*, 200814
9	Japanese	504 (male: female ratio = 1.0 : 1.29); mean age 48.7,16–91 years	651 (male : female ratio = 2.56 : 1.0); mean age 44, 18–83 years	F+1, S2, ST+4, T1, T2, V-3 and V4	Hirota *et al*, 2006
10	Korean	326 (59.82%female); median (range); 48(11-78) in years	151 (47.02% female) median (range); 27(10-74) in years	S1, T1 and V4	Lee *et al*, 2004[9]
11	Chinese	296 (48.31%female); average age 43.32 years	270; (46.67%female) average age 41.91 years	F+1, T1, S+1	Wang *et al*, 2000[16]
12	Indian	386 (68.4%female) mean age 18.7 ± 15.9 years	390 (76.2% female) mean age 22.87 ± 14.54 years	V-3, S+1 and T+1	Tripathi *et al*, 2012[38]
13	Indian	386 (68.4%female) mean age 18.7 ± 15.9 years	390 (76.2% female) mean age 22.87 ± 14.54 years	Q-1, T1, T2 and S1	Awasthi et al, 2012 [39]

Table 2: The distribution of the A disintegrin and metalloprotease 33 (ADAM33) genotypes and the allelic frequency for asthmatic patients and controls (values in parentheses are the corresponding percentages) on Asian populations

SNPs	Populations	Distribution of ADAM33 SNP's genotypes						Frequency of ADAM33 SNPs alleles			
		LL, n (%)		LM, n (%)		MM, n (%)		L, n (%)		M, n (%)	
		Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
S1	East Chinese Han, Chinese Han, Korean, Indian	613 (59.63)	418 (54.64)	236 (22.96)	229 (29.93)	179 (17.41)	118 (15.42)	1462 (71.11)	1065 (69.61)	594 (28.89)	465 (30.39)
V4	Northern Chinese, Chinese, Indian, Thai, Japanese, Korean	896 (36.23)	873 (43.72)	1107 (44.76)	840 (42.06)	470 (19.01)	284 (14.22)	2899 (58.61)	2584 (64.75)	2047 (41.39)	1408 (35.25)
T1	Northern Chinese, East Chinese Han, South Indian, Chinese Han, Japanese, Korean, Chinese, Indian	1078 (46.61)	1393 (65.55)	826 (35.71)	584 (27.48)	409 (17.68)	148 (6.96)	2982 (64.46)	3370 (79.29)	1644 (35.54)	880 (20.71)
ST+4	Indian, Thai, Japanese,	313 (25.47)	330 (27.16)	593 (48.25)	579 (47.65)	323 (26.28)	306 (25.19)	1219 (49.59)	1239 (50.99)	1239 (50.14)	1191 (49.01)
T2	Northern Chinese, East Chinese Han, Chinese, Chinese Han, Japanese, Indian	822 (42.33)	863 (44.26)	501 (25.80)	510 (26.15)	619 (31.87)	577 (29.59)	2145 (55.23)	2236 (57.33)	1739 (44.77)	1664 (42.67)
F+1	Northern Chinese, East Chinese Han, Chinese, Indian, Chinese, Japanese	858 (41.43)	912 (43.55)	908 (43.84)	924 (44.13)	305 (14.73)	258 (12.32)	2624 (63.35)	2748 (65.62)	1518 (36.65)	1440 (34.38)
S2	East Chinese Han, Chinese, Indian, Thai, Japanese,	695 (44.93)	878 (57.61)	575 (37.17)	540 (35.43)	277 (17.91)	106 (6.96)	1965 (63.51)	2296 (75.33)	1129 (36.49)	752 (24.67)
Q-1	Northern Chinese, Chinese Han, Thai, Japanese,	7 (0.72)	3 (0.32)	204 (20.84)	158 (16.84)	768 (78.45)	777 (82.84)	218 (11.13)	164 (8.74)	1740 (88.87)	1712 (91.26)
T+1	Northern Chinese, Chinese Han, Indian	14 (1.43)	3 (0.32)	214 (21.86)	140 (14.93)	751 (76.71)	795 (84.75)	242 (12.36)	146 (7.78)	1716 (87.64)	1730 (62.22)
ST+5	Indian	44 (11.40)	98 (25.13)	155 (40.16)	196 (50.26)	187 (48.45)	96 (24.62)	243 (31.48)	392 (50.26)	529 (68.52)	388 (49.74)
V-3	Japanese, Indian	216 (25.68)	340 (33.17)	425 (50.54)	454 (44.29)	200 (23.78)	231 (22.54)	857 (50.95)	1134 (55.32)	825 (49.05)	916 (44.68)
S+1	Chinese, Indian	157 (23.02)	159 (24.09)	361 (52.93)	337 (51.06)	164 (24.05)	164 (24.85)	675 (49.49)	655 (49.62)	689 (5051)	665 (50.38)

Mutant allele= M, wild type allele= L, homozygous normal genotype= LL, heterozygous genotype=LM, homozygous mutant genotype=MM.

Figure 2: Forest plots on studied SNPs
a)M vs L; b) MM vs LL; c) LM+MM vs LL and d) MM vs LL+LM ; where Mutant allele= M, wild type allele= L, homozygous normal genotype= LL, heterozygous genotype=LM, homozygous mutant genotype=MM.

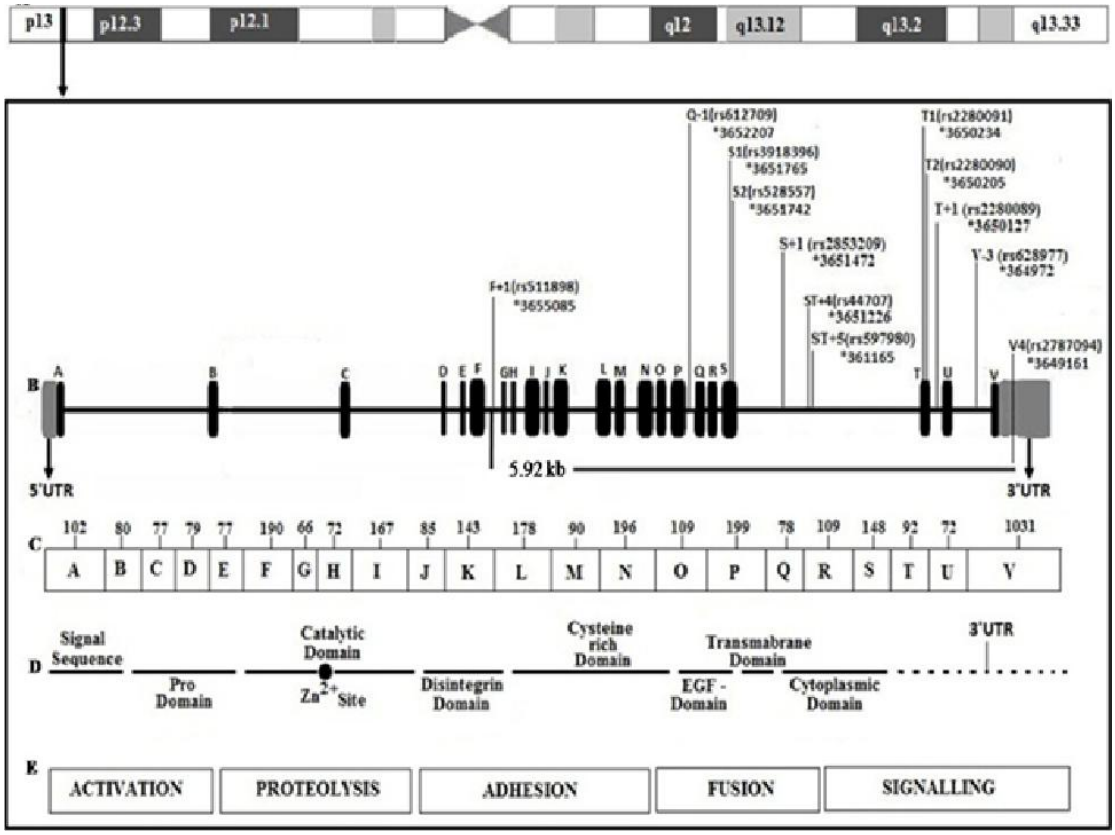


Table 3: Association of Taken ADAM33 gene polymorphisms for meta-analysis in different populations

S. no.	Population	C^1/C^2	Polymorphisms												
1			S1	V4	T1	ST+4	T2	F+1	S2	Q-1	T+1	ST+5	S+1	V-3	References
	Northern Chinese	412/397	NA	AR	AR	ND	NA	NA	ND	NA	AR	ND	ND	ND	Qu *et al*, 2011[11]
2	East Chinese Han	150/74	NA	ND	AR	NA	AR	AR	NA	ND	ND	ND	ND	ND	Jie *et al*, 2011[8]
3	Chinese	329/316	ND	NA	ND	ND	NA	NA	AR	ND	ND	ND	ND	ND	Chi *et al*, 2011[6]
4	Indian	175/235	NA	AR	NA	AR	NA	AR	AR	NA	NA	AR	ND	ND	Tripathi *et al*, 2011[15]
5	Indian	211/137	ND	AR	ND	AR	ND	AR	AR	ND	ND	AR	ND	ND	Awasthi *et al*, 2011[4]
6	South Indian	100/50	ND	ND	NA	ND	ND	ND	ND	ND	ND	ND	ND	ND	Bijanzadeh *et al*, 2010[5]
7	Chinese Han	181/151	NA	AR	AR	ND	AR	ND	ND	AR	NA	ND	ND	ND	Su *et al*, 2008[13]
8	Thai (DNG)	200/100	ND	NA	ND	AR	ND	ND	AR	ND	ND	ND	ND	ND	Thongngarm *et al*, 200814
9	Japanese	504/651	ND	NA	AR	NA	AR	NA	AR	ND	ND	ND	ND	NA	Hirota *et al*, 2006
10	Korean	326/151	NA	NA	NA	ND	ND	ND	ND	ND	ND	ND	ND	ND	Lee *et al*, 2004[9]
11	Chinese	296/270	ND	ND	NA	ND	ND	NA	ND	ND	ND	ND	NA	ND	Wang *et al*, 2000[16]
12	Indian	386/390	ND	ND	ND	ND	ND	ND	ND	ND	NA	ND	NA	NA	Tripathi *et al*, 2012[38]
13	Indian	386/390	AR	ND	AR	ND	AR	ND	ND	NA	ND	ND	ND	ND	Awasthi et al, 2012 [39]

1=case; 2=control; NA=not associated; AR=associated with risk of disease asthma; ND=not done; DNG= Details not given

of 4.68 [95% confidence interval (CI) (3.99,5.50)] for Q-1 when we compared M allele with the susceptibility to asthma as compared to the L allele under the random effects model. SNPs S2, ST+5 and T1 were also found to be associated with risk of asthma. [(OR=1.75, 95 % CI=1.57-1.96); (OR=2.20, 95 %CI=1.79-2.70) and (OR=1.73, 95%CI= (1.57-1.91)]

Genotype combinations "MM" vs. "LL", "(LM+MM)" vs "LL" and "MM" vs "(LL+LM)" were made for analysis to find association in all aspects. On calculating MM

Table 1: Distribution of genotype and allele frequency of ADAM33 polymorphisms in asthmatic patients and controls

	Trial name	Publication year	Case LL	Case LM	Case MM	Case L allele	Case M allele	Control LL	Control LM	Control MM	Control L allele	Control M allele
id	name											
V4	Tripathi *et al*,	2011	17 (9.71)	70 (40.0)	88 (40.3)	104 (29.7)	246 (29.7)	47 (18.6)	133 (52.5)	73 (28.9)	227 (44.9)	279 (55.1)
V4	Qu *et al*,	2011	141 (34.2)	198 (48.1)	73 (17.7)	480 (58.3)	344 (41.8)	232 (58.4)	134 (33.8)	31 (7.8)	598 (75.3)	196 (24.)
V4	Chi *et al*,	2011	151 (45.9)	133 (40.4)	45 (13.7)	435 (66.1)	223 (33.9)	148 (46.8)	132 (41.8)	36 (11.4)	428 (67.7)	204 (32.3)
V4	Awasthi *et al*,	2010	34 (16.1)	90 (42.7)	87 (41.2)	158 (37.4)	264 (62.6)	33 (24.1)	58 (42.4)	46 (33.6)	124 (45.3)	150 (54.7)
V4	Thongngarm *et al*,	2008	87 (43.5)	94 (47.0)	19 (9.5)	268 (67.0)	132 (33.0)	40 (40.0)	47 (47.0)	13 (13.0)	127 (63.5)	73 (36.5)
V4	Su *et al*,	2008	49 (27.1)	78 (43.1)	54 (29.8)	176 (48.6)	186 (51.4)	113 (74.8)	32 (21.2)	6 (4.0)	258 (85.4)	44 (14.6)
V4	Hirota *et al*,	2006	292 (44.6)	298 (45.5)	65 (9.9)	882 (67.3)	428 (32.7)	198 (40.0)	233 (47.1)	64 (12.9)	629 (63.5)	361 (36.5)
V4	Lee *et al*,	2004	125 (40.3)	146 (47.1)	39 (12.6)	396 (63.9)	224 (36.1)	61 (41.5)	71 (48.3)	15 (10.2)	193 (65.7)	101 (34.4)
S1	Jie *et al*,	2011	130 (86.7)	20 (13.3)	0 (0.0)	280 (93.3)	20 (6.7)	68 (91.9)	6 (8.1)	0 (0.0)	142 (95.5)	8 (4.1)
S1	*Awasthi *et al*,	2012	44 (11.4)	163 (42.2)	179 (46.4)	251 (32.5)	521 (67.5)	95 (24.4)	177 (45.4)	118 (30.3)	367 (47.1)	413 (53.0)
S1	Su *et al*,	2008	140 (77.4)	41 (22.7)	0 (0.0)	321 (88.7)	41 (11.3)	110 (72.9)	41 (27.2)	0 (0.0)	261 (86.4)	41 (13.6)
S1	Lee *et al*,	2003	299 (96.1)	12 (3.9)	0 (0.0)	610 (98.1)	12 (1.9)	145 (96.7)	5 (3.3)	0 (0.0)	295 (98.3)	5 (1.7)
T1	*Awasthi *et al*,	2012	58 (15.3)	170 (44.0)	158 (40.9)	286 (37.1)	486 (63.0)	100 (25.5)	183 (46.9)	107 (27.4)	383 (49.1)	397 (50.9)
T1	Qu *et al*,	2011	140 (34)	185 (44.9)	87 (21.1)	465 (56.7)	359 (43.6)	240 (60.5)	129 (32.5)	28 (7.1)	609 (76.7)	185 (23.3)
T1	Jie *et al*,	2011	118 (78.7)	32 (21.3)	0 (0.0)	268 (89.3)	32 (10.7)	69 (93.2)	5(6.8)	0 (0.0)	143 (96.6)	5 (3.4)
T1	Bijanzadeh *et al*,	2010	50 (62.5)	29 (36.3)	1 (1.3)	129 (80.6	31 (19.4)	35 (70.0)	15 (30.0)	0 (0.0)	85 (85.0)	15 (15.0)
T1	Su *et al*,	2008	63 (34.8)	78 (43.1)	40 (22.1)	204 (56.4)	158 (43.7)	117 (77.5)	29 (19.2)	5 (3.3)	263 (87.1)	39 (12.9)
T1	Hirota *et al*,	2006	134 (27.2)	239 (48.5)	120 (24.3)	507 (51.4)	180 (48.6)	471 (73.0)	68 (26.1)	6 (0.9)	1110 (86.1)	180 (14.0)
T1	Lee *et al*,	2004	265 (84.1)	48 (15.2)	2 (0.6)	578 (91.8)	52 (8.3)	125 (84.5)	22 (14.9)	1 (0.7)	272 (91.9)	24 (8.1)
ST +4	Jie *et al*,	2011	47 (31.3)	79 (52.7)	24 (16.0)	173 (57.7)	127 (42.3)	31 (43.0)	32 (42.0)	11 (15.0)	128 (64.0)	72 (36.0)
ST +4	Tripathi *et al*,	2011	31 (17.7)	78 (44.6)	66 (37.7)	140 (40.0)	210 (60.0)	63 (24.9)	120 (47.4)	70 (27.7)	246 (48.6)	260 (51.4)
ST +4	Awasthi *et al*,	2011	38 (18)	94 (44.6)	79 (37.4)	170 (40.3)	252 (59.7)	37 (27.0)	59 (43.1)	41 (29.9)	133 (48.5)	141 (51.5)
ST +4	Thongngarm *et al*,	2008	63 (31.5)	103 (51.5)	34 (17.0)	229 (57.3)	171 (45.8)	43 (43.0)	42 (42.0)	15 (15.0)	128 (64.0)	72 (36.0)
ST +4	Hirota *et al*,	2004	134 (27.2)	239 (48.5)	120 (24.3)	507 (51.4)	479 (48.6)	156 (24.0)	326 (50.1)	169 (26.0)	638 (49.0)	664 (51.0)
T2	*Awasthi *et al*,	2012	54 (14)	168 (43.5)	164 (42.5)	276 (35.8)	496 (64.3)	101 (25.9)	192 (49.2)	97 (24.9)	394 (50.5)	386 (49.5)
T2	Chi *et al*,	2011	248 (75.4)	79 (24.0)	2 (0.6)	575 (87.4)	83 (12.6)	246 (77.9)	67 (21.2)	3 (1.0)	559 (88.5)	73 (11.6)
T2	Qu *et al*,	2011	7 (1.7)	86 (20.9)	319 (77.4)	100 (12.1)	724 (87.9)	2 (0.5)	69 (17.4)	326 (82.1)	73 (9.2)	721 (90.8)
T2	Jie *et al*,	2011	127 (84.7)	22 (14.7)	1 (0.7)	276 (92.0)	24 (8.0)	72 (97.3)	2 (2.7)	0 (0.0)	146 (98.7)	2 (1.4)
T2	Su *et al*,	2008	4 (2.21)	49 (27.1)	128 (70.7)	57 (15.8)	305 (84.3)	0 (0.0)	12 (8.0)	139 (92.1)	12 (4.0)	290 (96.0)
T2	Hirota *et al*,	2006	382 (78.9)	97 (20.0)	5 (1.0)	861 (89.0)	107 (11.1)	442 (71.0)	168 (27.0)	12 (1.9)	1052 (84.6)	192 (15.4)
F+1	Awasthi	2011	39 (18.5)	94 (44.6)	78 (37.0)	172 (40.8)	250 (59.2)	40 (29.2)	73 (53.3)	24 (17.5)	153 (55.8)	121 (44.2)
F+1	Tripathi	2011	25 (14.3)	77 (44.0)	73 (41.7)	127 (36.3)	223 (63.7)	61 (24.1)	116 (45.9)	76 (30.0)	238 (47.0)	268 (53.0)

	Trial name	Publication year	Case LL	Case LM	Case MM	Case L allele	Case M allele	Control LL	Control LM	Control MM	Control L allele	Control M allele
id	name											
F+1	Qu *et al*,	2011	178 (43.2)	19 (48.1)	36 (8.7)	554 (67.2)	270 (32.8)	173 (43.6)	182 (45.8)	42 (10.6)	528 (66.5)	266 (33.5)
F+1	Jie *et al*,	2011	72 (48)	67 (44.7)	11 (7.3)	211 (70.3)	89 (29.7)	52 (70.3)	18 (24.3)	4 (5.4)	122 (82.7)	26 (17.6)
F+1	Chi *et al*,	2011	177 (53.8)	125 (38.0)	27 (8.2)	479 (72.8)	179 (27.2)	183 (57.9)	118 (37.3)	15 (4.8)	484 (76.6)	148 (23.4)
F+1	Hirota *et al*,	2006	214 (43)	224 (45.0)	60 (12.1)	652 (65.5)	344 (34.5)	272 (42.0)	291 (45.0)	84 (13.0)	835 (64.5)	459 (35.5)
Q-1	*Awasthi *et al*,	2012	0 (0)	60 (15.5)	326 (84.5)	60 (7.8)	712 (92.2)	0 (0.0)	60 (15.4)	330 (84.6)	60 (7.7)	720 (92.3)
Q-1	Qu *et al*,	2011	7 (1.7)	100 (24.3)	305 (74.0)	114 (13.8)	710 (86.2)	3 (0.8)	87 (21.9)	307 (77.3)	933 (14.7	701 (88.3)
Q-1	Su *et al*,	2008	0 (0)	44 (24.3)	137 (75.7)	44 (12.2)	318 (87.9)	0 (0.0)	11 (7.3)	140 (92.7)	11 (3.6)	291 (96.4)
T+1	Awasthi *et al*,	2012	0 (0)	80 (20.7)	306 (79.3)	80 (10.4)	692 (89.6)	0 (0.0)	60 (15.4)	330 (84.6)	60 (7.7)	720 (92.3)
T+1	Qu *et al*,	2011	14 (3.4)	97 (23.5)	301 (73.1)	125 (15.2)	699 (84.8)	3 (0.8)	39 (9.8)	355 (80.4)	45 (5.7)	749 (94.3)
T+1	Su *et al*,	2008	0 (0)	37 (20.4)	144 (79.6)	37 (10.2)	325 (89.8)	0 (0.0)	41 (27.2)	110 (72.9)	41 (13.6)	261 (86.4)
ST+5	Awasthi *et al*,	2011	26 (12.3)	94 (44.6)	91 (43.1)	146 (34.6)	276 (65.4)	33 (24.1)	67 (48.9)	37 (27)	133 (48.5)	141 (51)
ST+5	Tripathi *et al*,	2011	18 (10.3)	61 (34.9)	96 (54.9)	97 (27.71)	253 (72.3)	65 (25.7)	129 (51)	59 (23.3)	259 (51.2)	247 (49)
V-3	Awasthi *et al*,	2012	76 (19.7)	180 (46.6)	130 (33.7)	332 (43.0)	440 (57.0)	67 (17.2)	175 (44.9)	148 (38.0)	309 (39.6)	471 (60.4)
V-3	Hirota *et al*,	2006	185 (37)	245 (49.0)	70 (14.0)	615 (61.5)	385 (38.5)	273 (43.0)	279 (43.9)	83 (13.1)	825 (65.0)	445 (35.0)
S2	Jie *et al*,	2011	92 (61.3)	52 (34.7)	6 (4)	236 (78.7)	64 (54.3)	43 (58.1)	28 (37.8)	3 (4.1)	114 (77.0)	34 (22.9)
S2	Awasthi *et al*,	2011	18 (8.5)	85 (40.3)	108 (51.2)	121 (28.7)	301 (71.3)	72 (52.6)	51 (37.2)	14 (10.2)	195 (71.2)	79 (28.8)
S2	Tripathi *et al*,	2011	20 (11.4)	67 (38.3)	88 (50.3)	107 (30.6)	243 (69.4)	159 (62.9)	79 (31.2)	15 (5.9)	397 (78.5)	109 (21.5)
S2	Chi *et al*,	2011	152 (46.2)	135 (41.0)	42 (12.8)	439 (66.7)	219 (33.3)	178 (56.3)	110 (34.8)	28 (8.9)	466 (73.7)	166 (26.3)
S2	Thongngarm *et al*,	2008	114 (57)	77 (38.5)	9 (4.5)	305 (76.3)	95 (23.8)	72 (72.0)	21 (21.0)	7 (7.0)	165 (82.5)	35 (17.5)
S2	Hirota *et al*,	2006	299 (62.0)	159 (32.9)	24 (4.9)	757 (78.5)	207 (21.5)	354 (54.9)	251 (38.9)	39 (6.1)	959 (74.5)	329 (25.5)

Mutant allele= M, wild type allele= L, homozygous normal genotype= LL, heterozygous genotype=LM, homozygous mutant genotype=MM; *= personal communication;

vs LL association of SNPs S2 and ST+5 were observed with maximum OR of 3.30 [95% CI (2.58, 4.22)] and 4.34 [95% CI (2.82, 6.69)], respectively. After calculating (LM+MM) *vs* LL, none of the SNPs showed maximum OR with disease asthma, except ST+5 with the OR of 2.61 [95% CI (1.77, 3.85)]. However meta-analysis for this SNP was done only on 2 studies. And lastly when we analyzed combination of genotype MM *vs* (LL+LM) three of eleven SNPs namely, T1, S2 and ST+5 were found as risk with [OR= 1.95; 95% CI (1.58, 2.39)], 2.92 [95% CI (2.30, 3.70)] and 2.88 [95% CI (2.12, 3.90)], respectively.

Publication bias

We applied Begg-Mazumdar test, Kendall's tau and Egger's test to analyze publication Bias. All the tests showed no significant publication bias, P>0.05.

Discussion

This is the first report evaluating the role of ADAM33 gene polymorphisms in the predisposition of asthma in Asian population and we observed association of SNPs Q-1, S2, ST+5 and T1 with asthma, however we found only two studies showing association of ST+5 with susceptibility to asthma and both was from India[4,15], therefore more studies are needed from Asian countries to get clear picture of association of SNP ST+5 with

asthma in Asian population. Previously Blakey *et al[24]* conducted meta-analysis on Caucasian populations of all existing data demonstrated either positive or negative association results with asthma, study included total 13 SNPs named as, F+1, M+1, Q-1, S1, S2, ST+4, ST+5, ST+7, T1, T2, T+1, V-1 and V4 and found SNPs F+1 and ST+7 to be statistically significantly associated with asthma with a maximum OR of 1.46 (95% CI 1.21 to 1.76) for ST+7 (p=0.0001). However, study was done on Caucasian populations only. ST+7 SNP had not been included in our study as we did not find much study on Asian population for performing the analysis.

Our study, in the context of the Asian populations, presented an overview of the studies of the ADAM33 gene polymorphisms that have been examined for their association with asthma.

Summary of association of studied polymorphisms in their studies are mentioned in Table 3. A study conducted on Chinese population by Wang *et al* did not find any association of SNPs, namely S+1, T1 and F+1, with asthma. [16] In another study by Su *et al* on Chinese Han population analyzing six SNPs of ADAM33 gene, namely V4, T+1, T2, T1, S1 and Q-1, for association with asthma, found that V4, T2, T1 and Q-1, increase risk of susceptibility.[13]

Thongngarm *et al* in their study on Thai population found a positive association between ADAM33 polymorphisms S2 and ST+4 with asthma susceptibility.[14] Bijanzadeh *et al* failed to find an association between asthma and the T1 SNP of ADAM33 gene in a southern Indian population.[5] However, another case control study, conducted in Northern India to assess association of ADAM33 gene polymorphisms namely, F+1, S2, ST+4, ST+5 and V4, with asthma in children and in adults , showed significant association of all of them with the disease.[4,15] Chi *et al* conducted study on Chinese population found association of S2 with asthma, while SNPs F+1, T2 and V4 were not associated with risk of disease asthma.[6] Jie *et al* done study on East China Han population and observed association of T1, T2 and F+1 with asthma, however S1, ST+4 and S2 were not observed to be associated with asthma.[8] Similarly, Qu *et al*, found association of 3 SNPs namely, T+1, T1, T2, S1 and V4 with asthma, whereas F+1, T2 and Q-1 were not associated with asthma.[11,38,39]

This study has some limitations that need to be acknowledged. Haplotype analysis may have provided more information and would have been more powerful than single polymorphism analysis. Haplotypes are considered to carry information about possible unobserved causal variants in the region[10], butan analysis of haplotypes was not possible because of inadequate haplotype data. Second, this study could not address gene–gene and gene-environment interactions.

In conclusion, to our knowledge, this is the first and most comprehensive genetic meta-analysis to date to find out association of ADAM33 gene polymorphisms with asthma. We found allelic association of S2 and Q-1 SNPs with asthma. The evidence from the meta-analyses supports the notion of a role for the polymorphisms S2, Q-1, and T1 of ADAM33 in susceptibility to Asthma in Asian population.

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Conflict of interest

The authors declare no conflict of interest.

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Edward Syndrome

Sunil Mhaske*, Ramesh B. Kothari, Sandeep Deokate***, Ram Sethi***, Nishad Patil***, Pavan Suryawanshi***, Rahul Maski***, Neha Sharma******

Abstract

Edward syndrome is a genetic disorder caused by presence of all or part of an extra 18 chromosome. It is the 2nd most common autosomal trisomy after Down syndrome.

Keywords: Edward's syndrome; Trisomy18; TrisomyE.

Introduction

Edward syndrome occurs in around 1 in 6000 live births & around 80% of those affected are females. The majority of fetuses with the syndrome die before birth. The incidence increases as the mother's age increases. The syndrome has a very low rate of survival, resulting from heart abnormalities, kidney malformations & other internal organ disorders.

Case summary

20 years old rural habitat primi with 34 weeks gestation was admitted to our labour room with pain in abdomen since 1 day. Pain was intermittent in nature, radiating to back and medial aspect of thigh. She had history of threatened abortion for which she took treatment details of which are not available. She was referred to our hospital by a private practitioner.

According to her last menstrual cycle, her gestational age was 34 weeks. She was a registered case at PHC with 3 antenatal visits. She had taken iron and folic acid tablets with 2 doses of TT injection. She had a family history of 3rd degree consangious marriage. There was no any history of previous abortions.

On examination, she was an averagely built female with mild pallor. Pulse was 92/minute & Blood pressure being 130/80 mmHg. Per abdominal examination showed uterus of 34 weeks with fetus of breech presentation. Per vaginal examination showed 6 cm dilated, 60% effaced cervix with intact membranes without any PV bleeding.

Antenatal USG showed fetus with 34 weeks gestational age with breech presentation, massive polyhydramnios, IUGR with fetal oesophageal atresia. Mother's investigations revealed Hb - 9gm%, TLC - 15800/cumm, Platelet count - 2.24 lacs/cumm. Liver function tests and renal function tests were within normal limits. VDRL, HbsAg and Tridot were negative. Urine showed traces of albumin.

A male baby weighing 2 kgs was delivered by vaginal route with right medio lateral episiotomy. Baby did not cry immediately after birth. His heart rate was 134/minute. Respiration was non-spontaneous. Cyanosis was present. He was intubated with endotracheal tube of internal

diameter 3 mm & put on AMBU bag ventilation. Baby turned to pink color after 10 minutes of AMBU. Reflexes were absent. His

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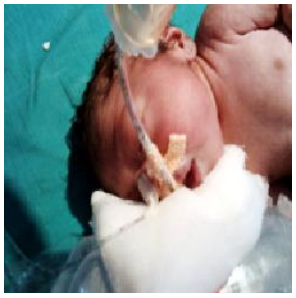
length was 36 cm, head circumference – 28 cm (< 3rd percentile), chest circumference – 26 cm. Placenta and cord were normal. The baby was shifted to NICU & was kept on artificial respiration with IPPV mode of ventilation & FiO_2 being 100 %. Baby was treated with antibiotics, IV fluids and adrenaline as required. The baby died after 3 days being on ventilatory support despite of best resuscitative efforts.

Microcephaly

Simian crease

Mongoloid slant



Following investigations were done:

Hb – 14 gm/dl, TLC - 15600/cmm, DLC – P: 42, L: 54, E: 02, M: 02, B: 00.

Platelets – 2.5 lacs/cmm Blood group: B – Rh+ve.

USG Cranium: Choroid plexus cyst with underdeveloped brain.

USG Abdomen and Pelvis: Bilateral inguinal hernia undescended testis.

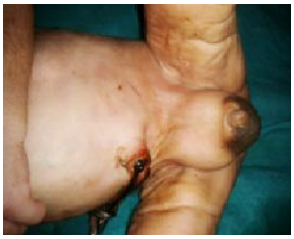
2D-ECHO revealed moderate VSD with left to right shunt.

Clinical features are listed as follows:

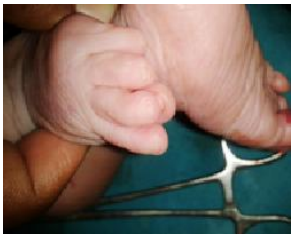
Clinical features	Edward Syndrome	Down Syndrome	Our patient
- Microcephaly	+	+	+
- Hypertelorism	+	-	+
- Mongoloid slant	-	+	+
- Low set ears	+	+	+
- Microphthalmia	-	-	+
- Depressed nasal bridge	-	-	-
- Simian crease	+	+	+
- Clenched hands with index finger overlapping 3rd finger & 5th finger overlapping 4th finger	+	+	+
- Short dorsiflexed 1st toe	+	-	-
- Short sternum	+	-	+
- Rocker bottom feet	+	+	+
- Inguinal hernia	+	+	+
- Oesophageal atresia	+	+	+
- Congenital heart defect (VSD, PDA, ASD)	+	+	+
- Cleft lip, cleft palate	+	-	-
- Hypotonia or Hyperflexibility	-	-	+
- Micropenis	-	+	+
- Mental subnormality	+	+	-
- Open mouth with protruding tongue	-	+	-
- IUGR	+	+	+

Micropenis

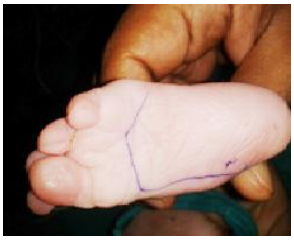
Hypotonia or Hyperflexibility



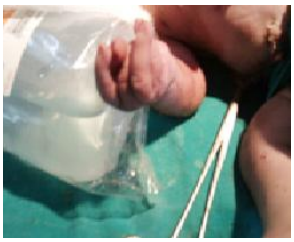
Overlapping of toes



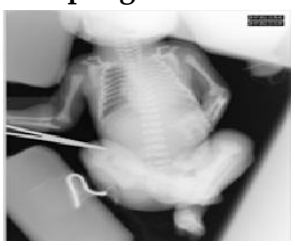
Short 1st toe



Clenched hands with index finger overlapping 3rd finger & 5th finger overlapping 4th finger



Esophageal atresia



Discussion

It is named after Dr. John H. Edward who 1st described the syndrome in 1960. Edwards served as professor of human genetics at Birmingham University from 1969 to 1979 and at Oxford University from 1979 to 1995. He was the author of *Human Genetics* (1978) as well as numerous papers on a variety of topics in the field.

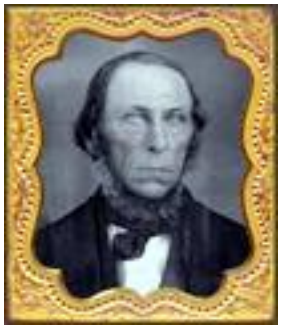
Signs and symptoms

Children born with Edward syndrome may have some or all of the following characteristics:

Kidney malformations, Structural heart defects at birth (i.e., ventricular septal defect, atrial septal defect, patent ductus arteriosus), Intestines protruding outside the body (omphalocele), Esophageal atresia, Mental retardation, developmental delays, growth deficiency, feeding difficulties, breathing difficulties, and arthrogryposis (a muscle disorder that causes multiple joint contractures at birth).

Some physical malformations associated with Edwards syndrome include small head (microcephaly) accompanied by a prominent back portion of the head (occiput); low-set, malformed ears; abnormally small jaw (micrognathia); cleft lip/cleft palate; upturned nose; narrow eyelid folds (palpebral fissures); widely spaced eyes (ocular hypertelorism); drooping of the upper eyelids (ptosis); a short breast bone; clenched hands; choroid plexus cysts; underdeveloped thumbs and or nails, absent radius, webbing of the second and third toes; clubfoot or Rocker bottom feet; and in males, undescended testicles.

Dr. John H. Edward



In utero, the most common characteristic is cardiac anomalies, followed by central nervous system anomalies such as head shape abnormalities. The most common intracranial anomaly is the presence of choroid plexus cysts, which are pockets of fluid on the brain. These are not problematic in themselves, but their presence may be a marker for trisomy18. Sometimes excess amniotic fluid or polyhydramnios is exhibited.

Genetics

Edward syndrome is a chromosomal abnormality characterized by the presence of an extra copy of genetic material on the 18th chromosome, either in whole (trisomy 18) or in part (such as due to translocations). The additional chromosome usually occurs before conception. The effects of the extra copy vary greatly, depending on the extent of the extra copy, genetic history, and chance. Edward syndrome occurs in all human populations but is more prevalent in female offspring.

Trisomy 18 (47, XX, +18) is caused by a meiotic nondisjunction event. With nondisjunction, a gamete is produced with an extra copy of chromosome 18; the gamete thus has 24 chromosomes. When combined with a normal gamete from the other parent, the embryo has 47 chromosomes, with three copies of chromosome 18.

A small percentage of cases occur when only some of the body's cells have an extra copy of chromosome 18, resulting in a mixed population of cells with a differing number of chromosomes. Such cases are sometimes called mosaic Edward syndrome. Very rarely, a piece of chromosome 18 becomes attached to another chromosome (translocated) before or after conception. Affected individuals have two copies of chromosome 18 plus extra material from chromosome 18 attached to another chromosome. With a translocation, a person has a partial trisomy for chromosome 18, and the abnormalities are often less severe than for the typical Edwards syndrome.

Diagnosis

Edward syndrome may be diagnosed at birth by the physical abnormalities characteristic to the syndrome. In addition, physical examination of the infant may show arched fingerprint patterns, while x-rays may show a short sternum. Definitive diagnosis is achieved through karyotyping. Using special stains and microscopy, individual chromosomes are identified, and the presence of an extra chromosome 18 is revealed.

Edward syndrome can be detected before birth. If a pregnant woman is older than 35, has a family history of genetic abnormalities, has previously conceived a child with a genetic abnormality, or has suffered earlier miscarriages, she may undergo tests to determine whether her child carries genetic abnormalities. Tests include maternal serum alpha-fetal protein analysis or screening, ultrasonography, amniocentesis, and chorionic villus sampling.

In addition, a pregnant woman carrying a child with Edward syndrome may have an unusually large uterus during pregnancy, due to the presence of extra amniotic fluid. In addition, an unusually small placenta may be noted during birth.

Treatment

There is no cure for Edward syndrome. 90 to 95 % of all babies born with it die within a year of birth. The few infants that do survive need special treatment ranging from muscular

therapy to nervous system and skeletal corrections for their various handicaps.

Prognosis

In case of Edward syndrome, major causes of death include apnea and heart abnormalities. It is impossible to predict an exact prognosis during pregnancy or the neonatal period. Half of infants with this condition do not survive beyond the first week of life. The median lifespan is 5–15 days. About 8% of infants survive longer than 1 year, One percent of children live to age 10, typically in less severe cases of the mosaic Edward syndrome.

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The Role of Complement Factors in Neurodegeneration, Neuroinflammation and Neuroprotection: Friend or Foe?

Kumar Senthil P.*, Adhikari Prabha, Jaganathan*****

Abstract

Complement is a major component of innate immune system involved in defending against all the foreign pathogens through complement fragments that participate in opsonization, chemotaxis, and activation of leukocytes and through cytolysis by C5b-9 membrane attack complex. The complement (C) system has been implicated as a factor in the causation or propagation of tissue injury in central and peripheral nervous system disorders. Complement factors play a predominant role in nerve injury, inflammation and repair, thus playing part in neurodegeneration, neuroinflammation and neuroprotection.

Keywords: Immunology; Neuroimmunology; Immunogenetics; Genetic neurology; Complement system.

Complement is a major component of innate immune system involved in defending against all the foreign pathogens through complement fragments that participate in opsonization, chemotaxis, and activation of leukocytes and through cytolysis by C5b-9 membrane attack complex.[1] The complement (C) system has been implicated as a factor in the causation or propagation of tissue injury in central and peripheral nervous system disorders.[2]

Complement opsonins (C1q, C3b, and iC3b) interact with surface complement receptors to promote phagocytosis, whereas complement anaphylatoxins C3a and C5a initiate local inflammatory responses by taking part in humoral and cellular immunity mechanisms of neurodegeneration and neuroprotection involved in cytolysis and immune/ inflammatory responses.[3]

Many studies had reported their role in central nervous system disorders like encephalomyelitis, multiple sclerosis, Alzheimer's disease.[4,5] Rus and Nicolescu described the role of complement factors as; "Myelin and oligodendrocyte (OLG) activate the classical pathway of complement in vitro in the absence of antibodies.[6] Sublytic C5b-9 in the absence of cell death induces proto-oncogenes, activates cell cycle, and enhances cell survival in OLG. In addition, C5b-9 reverses the differentiation phenotype in OLG and enhances cell survival. beta amyloid protein is an activator of the complement system and neurons are susceptible to bystander complement mediated damage."

Astrocytes, ependymal cells, endothelial cells, microglia, and neurons synthesize various complement proteins or express complement receptors on their cell surfaces, and binding of proteolytic fragments derived from activation of complement by specific receptors leads to responses towards inflammation, opsonization, and B-cell activation.[7] A fine balance of C activation and regulation mediated the elimination of invading pathogens and the protection of the host from excessive C deposition on healthy

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tissues, and upon disruption of this delicate balance, the C system may cause injury and contribute to the pathogenesis of various diseases, including peripheral neuropathies.[8]

Complement cascade factors of classical (C1qa, C1qb, C1qc, C2 and C4) and alternative (C3, B and adipsin) pathways were known to play a critical role in myelin clearance after peripheral nerve injury.[9] The receptors located within the nerve fascicles are probably of glycoprotein nature and the receptors for C3b in peripheral nerve tissues may be of significance in the deposition of immune complexes, thus playing a role in acute polyradiculoneuritis.[10]

Furthermore, activation of complement by peripheral nerve myelin (PNM) *via* the alternative pathway was shown by cleavage of C3 in normal human serum (NHS) and of B in C2-deficient serum (C2d-HS). Increasing consumption of hemolytic activity of C3 in Mg-EGTA-treated NHS was also noted with increasing amounts of PNM as a consequence of a variety of pathologic conditions affecting the peripheral nervous system.[11]

RNA (RT-PCR and northern blot hybridization) and protein (western blot analysis and immunohistochemistry) studies confirmed high expression of classical pathway components, alternative pathway components and inhibitory components in sciatic nerve (first components of complement in axons, inhibitory components in perineurium) to protect the nerve from a complement attack.[12]

Complement factors play a predominant role in nerve injury, inflammation and repair.[13] Expression of complement and clusterin were prominent features of neural degeneration and regeneration and they provide useful insights into potentially new therapeutic approaches in neurodegenerative disorders.[14]Most of the studies were on experimental rodent models, and future clinical trials are needed to establish a bedside evidence to relate it into clinical practice.

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