

Inheritance patterns, consanguinity & risk for asthma

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Received January 22, 2009

Background & objectives: Family history is an important risk factor for the development of asthma, contingent upon genetic and environment interaction. Since there is paucity of data on asthma inheritance in Indian population, the present study was undertaken to investigate the inheritance patterns of asthma and the effect of family history and consanguineous marriage on asthma inheritance.

Methods: A total of 200 families, 100 index children and 100 index adults with clinically diagnosed asthma, along with 400 non-asthmatic children and adults as controls were selected for the present study. Information about the family history of each patients and controls was collected and analyzed pedigrees were also constructed.

Results: A history of asthma in any member of the family was observed in 44.5 per cent of cases and 5.3 per cent of controls ($P < 0.001$). A differential risk of developing asthma was noted in family history of asthma in different first and second degree relatives of children and adult patients. Consanguineous marriage was also noted in parents in 24.5 per cent of cases and 12.3 per cent of controls ($P < 0.001$). The most common mode of asthma inheritance was recessive.

Interpretation & conclusions: Our results showed that consanguineous marriage and family history of asthma are important determinants in the development of asthma in the offspring.

Key words Asthma - consanguineous marriage - family history - pedigree

Asthma has been regarded as a syndrome encompassing all the different phenotypes¹. Also, it is an episodic disease followed by acute exacerbations interspersed with symptom-free periods² and associated with significant respiratory morbidity and mortality. Around 300 million people worldwide are affected by asthma. Prevalence varies by country and has been estimated to be 2.5-5 per cent in India and 14 per cent in UK^{3,4}. The prevalence of

asthma in Mysore, south India, was reported to be 9 per cent for children and 5 per cent for adults and an increase of around 50 per cent over a period of 5 years has been observed in children⁵.

Family history, an important risk factor for asthma development, is most likely contingent upon genetic and environment interactions. Though several studies have been done on the hereditary of asthma, no idiosyncratic

conclusion has been drawn in relation to heredity mechanisms of this disease and it is not in congruence with classic Mendelian patterns⁶. Los *et al*⁶ reviewed different studies of asthma inheritance and classified them based on phenotypic considerations including symptom based diagnosis of asthma, serum IgE and bronchial hyperresponsiveness. Each phenotype has revealed different patterns of inheritance such as two-allele gene with co-dominant inheritance^{7,8}, oligogenic or polygenic model⁹⁻¹¹, recessive¹², two locus recessive¹³, mixed with recessive inheritance¹⁴, and single locus with contribution for polygenes¹⁵ although some studies have failed to demonstrate any autosomal patterns of inheritance⁷. Understandably, the inheritance studies have fallen short to draw a consensus and duplicate conclusions in other studies were probably attributable to the heterogeneous population studied and the heterogeneity of the disease syndrome as well. In future, if further studies are able to elucidate and define various phenotypes in asthma and studies are directed towards each of these phenotypes separately, a consensus may evolve regarding this matter. So far, two large studies have demonstrated a codominant model in segregation studies⁶.

Studies have shown differential effects of family history on asthma inheritance in different age groups. Litonjua *et al*¹⁶ concluded that maternal asthma was strongly associated with asthma in children over all ages in both univariate and multivariate models. Paternal asthma was found to be weakly associated in the univariate model but the association was strengthened in the multivariate model. An additive effect was noted on the risk of development of childhood asthma when both parents were asthmatic in comparison to those where only one of the parents was experiencing this disease. In addition, the parental phenotypic expression of allergy had shown a significant effect on this kind of allergy in the offspring¹⁶.

There is a lack of data concerning asthma inheritance in Indian population. Further, limited data are available on the effect of consanguineous marriage on asthma inheritance. The present study was therefore undertaken to investigate the inheritance patterns of asthma in children and adults, effects of family history of asthma, and consanguineous marriage on asthma inheritance.

Material & Methods

Population and study sample: The subjects including adults and children were part of an ongoing genetic

screening study (Mysore Asthma Genetics Group) in Mysore, south India. The study was conducted from May 2007 to August 2008 in two tertiary care university hospitals and a tertiary allergy center (Cheluvamba and JSS hospitals and Allergy, Asthma and Chest Center of Mysore) and consisted of 200 families selected consecutively with members having asthma comprising 100 index children and 100 index adults.

Selection of the controls: Two hundred children and two hundred adults were selected as controls. From each home, only one subject was considered. A total of 400 families were thus included. Hundred homes each in randomly selected 4 wards (Agrahara, Vidyanarya puram, Rajendra nagara and J.P. nagara) were included. These wards and homes were earlier selected randomly from the general population of Mysore as part of the ICMR multicenter study on prevalence of asthma in Mysore district. Control group was homogeneous for age, gender and religion.

Inclusion criteria: (i) Age: Children <18 yr and adults >19 yr; (ii) Confirmed diagnosis of asthma according to GINA (Global Initiative of Asthma) guidelines¹⁷ in adults and IAP (Indian Academy of Pediatrics) guidelines¹⁸ in children; and (iii) availability of data on the presence of physician diagnosed asthma in all the siblings of the probands, the parents, siblings of parents, and maternal and paternal grandparents.

Childhood asthma - More than 3 episodes of airflow obstruction with several qualifying features: afebrile episodes; personal atopy; atopy/asthma in parent/ sibling; nocturnal exacerbation; exercise/activity induced symptoms; trigger induced symptoms; seasonal exacerbations; relief with bronchodilators± short course oral steroid¹⁸.

Adult asthma - The index adult was diagnosed to have asthma according to Global Initiative on Asthma guidelines with reversible airway obstruction of 12 per cent and 200 ml improvement in FEV1 after inhalation of Salbutamol¹⁷. Spirometry was performed according to American Thoracic Society Guidelines¹⁹.

Consanguineous marriage - Consanguinity is defined as the marriage between close relatives²⁰. In our study, we considered the marriage as consanguineous if the marriage occurred between the relatives of the first or second degree.

Family history “any”: This term was used to indicate the presence of asthma in any one or more of the family members of the asthmatic proband.

Methodology: A genetic register was designed exclusively for the study. The structured questionnaire administered included data on patient demographics, respiratory symptoms, and detailed family history including data on the pedigree, triggers, medications used and emergency room visited. For families having an index asthmatic child, the eligible mother answered the questionnaire including these questions: Have you ever had a doctor's diagnosis of asthma? Is the biological father of this child resident with you in the same house? Are you related to the biological father? If so, can you please specify the relationship? Has the biological father of this child ever had a doctor's diagnosis of asthma? Can you list all the siblings of this child and the siblings of yourself and the biological father? Did any of them ever have a doctor's diagnosis of asthma? Did any of your parents or the parents of the biological father of this child have doctor's diagnosis of asthma? When was the last time you were in contact with each of them?

For eligible adults, the interview included similar questions about their children, siblings and parents regarding the presence of doctor's diagnosis of asthma ever and whether they were related to their spouse to identify consanguineous marriages.

In subjects, where there was no contact with any member of the family for the last three months, the interviewer was requested to telephonically contact all the family members in the pedigree to ascertain whether any of them had a doctor's diagnosis of asthma or not. In cases where some of them had been deceased, they were requested to ask the nearest relative residing with the subject; for example, they were asked to answer if the deceased ever had a doctor's diagnosis of asthma.

The study protocol was approved by the Institutional Human Ethical Committee (IHEC) of University of Mysore and informed consent was obtained from the parents and patients.

Statistical analysis: Statistical packages of software system (Epi Info, version 3.4.1 and SPSS, version 10) were used. Statistical significance was analyzed by Chi-square test and $P < 0.05$ was considered significant²¹. Also, a multivariate analysis was performed to assess independent association of variable recognized to be significant in univariate analysis. The statistical power was estimated utilizing the DSS research software²².

Results

Of the 200 probands (100 children and 100 adults) with asthma, complete pedigree was available for 140 probands (62 children and 78 adults) for evaluating the inheritance patterns. Family history and data on consanguineous marriages were available for all the 600 families. Regarding demographic variables including age distribution, gender and religion (Table I) there were no significant differences between the cases and controls. Mean age of children was 5.49 ± 4.64 yr and that of adults was 44.64 ± 14.21 yr. The male-female ratio observed in children was 70 : 30 and in adults 42 : 58. Most of the patients in this study were Hindus.

Analysing data, 44.5 per cent of the case group and 5.3 per cent of the control group ($P < 0.001$) indicated family history of asthma. More than 95 per cent chance of detecting an 8.4 times increase in the risk of family history was observed. A history of asthma in any member of the family was found to have a significant relationship with the presence of asthma in the index case. The highest odd ratio was observed in relation to a family history of asthma in the parent siblings,

Table I. Demographic information and severity of asthmatic patients and non-asthmatic controls in Mysore, India

	Patients (%)	Controls (%)	χ^2 corrected (Yates)
<i>Children:</i> <10 yr	82 (41)	143 (35.8)	3.38
10-18 yr	18 (9)	57 (14.3)	
Gender: Male	69 (34.5)	119 (29.7)	2.18
Female	31 (15.5)	81 (20.2)	
Religion: Hindu	83 (41.5)	163 (40.7)	1.51
Muslim	17 (8.5)	34 (8.5)	
Christian	0 (0)	3 (0.7)	
Severity: Mild	22 (11)	-	-
Moderate	53 (26.5)	-	
Severe	25 (12.5)	-	
<i>Adults:</i> 19-39 yr	41 (20.5)	95 (25.8)	1.33
40-59 yr	44 (22)	75 (18.8)	
>60 yr	15 (7.5)	30 (7.5)	
Gender: Male	42 (21)	103 (25.7)	2.04
Female	58 (39)	97 (24.2)	
Religion: Hindu	91 (45.5)	177 (44.2)	0.61
Muslim	8 (4)	19 (4.7)	
Christian	1 (0.5)	4 (1)	
Severity: Mild	51 (25.5)	-	-
Moderate	32 (16)	-	
Severe	17 (8.5)	-	
Total	200 (100)	400 (100)	-

All comparisons were nonsignificant

followed by siblings and history of asthma in the maternal grandparents (Table II).

In addition, consanguineous marriage was noted in parents in 24.5 per cent of cases and 12.3 per cent of controls ($P < 0.001$). There was 93.5 per cent chance of detecting a two times increase in the risk of family history. Taking this variable into account, parental consanguinity had a significant relationship with the presence of asthma in the offspring (Table II). By analysing the subgroups of the children and adults separately, it was observed that the family history of asthma occurred in 34 per cent of asthmatic children and 55 per cent of asthmatic adults. The association of different family histories in children and adults are presented in Figs 1 and 2 respectively. Also, Family history “any” was found to be significantly associated with the presence of asthma in both children and adults while parental family history of asthma was significant in adults but not in children.

A total of 490 subjects, 111 asthmatic cases and 379 non asthmatic controls did not show any indication of family history of asthma. A total of 110 subjects had a family history of asthma. Presence of asthma was observed in one member of the family in 94 subjects (74 cases and 20 controls) and more than one family member in 16 subjects (15 cases and 1 control). As a result, an increasing risk of asthma was noted with increasing number of family members with asthma in this study population ($P < 0.0001$).

After analysing the available pedigree in both children and adults, it was observed that the most common mode of asthma inheritance was recessive (Table III). Recessive inheritance was observed more commonly in children (88.70%) as compared with adults (61.53%). Sample pedigrees of autosomal

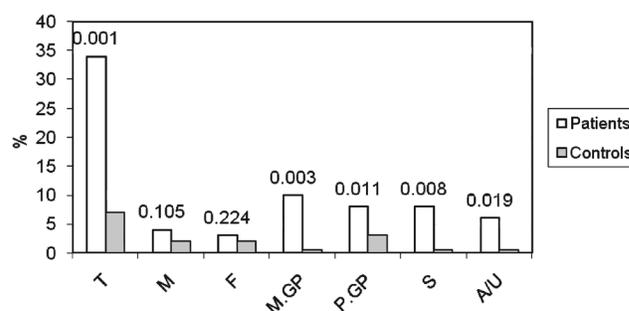


Fig. 1. Family history of children with asthma in Mysore city. T, total; M, mother; F, father; M.GP, maternal grandparent; P.GP, paternal grandparent; S, sibling; A/U, aunt/uncle. Numbers on bars show *P* value.

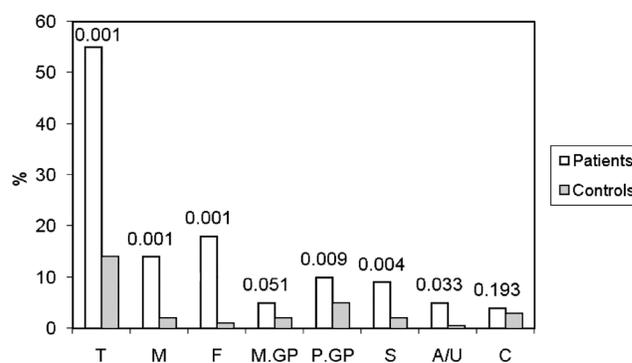


Fig. 2. Family history of adults with asthma in Mysore city. T, total; M, mother; F, father; M.GP, maternal grandparent; P.GP, paternal grandparent; S, sibling; A/U, aunt/uncle; C, children. Numbers on bars show *P* value.

recessive and dominant in both consanguineous and non consanguineous families with asthmatic probands are depicted in Fig. 3. High proportion of offspring’s from non consanguineous marriages was found to have recessive pattern of asthma inheritance in both children 45 out of 48 (93.75%) and adults 39 out of 61 (63.93%) as compared to consanguineous marriages including

Table II. Family history and consanguineous marriages in asthmatic patients and non-asthmatic controls in Mysore, India

	Patients N= 200		Controls N= 400		Odd ratio (95% Confidence Interval)	<i>P</i>
	#	%	#	%		
Maternal FH	18	9	4	1	9.79 (3.26-29.33)	0.001
Paternal FH	21	10.5	3	0.8	15.50 (4.56-52.61)	0.001
Maternal GP. FH	15	7.5	2	0.5	16.10 (3.64-71.06)	0.001
Paternal GP. FH	18	9	8	2	4.84 (2.06-11.35)	0.001
Sibling FH	17	8.5	2	0.5	18.42 (4.22-80.39)	0.001
Aunt/Uncle FH	11	5.5	1	0.25	22.97 (2.97-177.62)	0.003
Son/Daughter FH	4	2	3	0.8	2.70 (0.59-12.18)	0.196
Parental Consanguinity	49	24.5	49	12.3	2.32 (1.49-3.60)	0.001

FH, family history; GP, grandparents

Table III. Inheritance pattern of asthma in 140 families from Mysore, India

Pattern	Children			Adults			Children and adults		
	Cons	Noncons	Total	Cons	Noncons	Total	Cons	Noncons	Total
Dominant (%)	4 (6.46)	3 (4.83)	7 (11.29)	8 (10.26)	22 (28.20)	30 (38.46)	12 (8.57)	25 (17.85)	37 (26.42)
Recessive (%)	10 (16.12)	45 (72.58)	55 (88.70)	9 (11.53)	39 (50.00)	48 (61.53)	19 (13.57)	84 (60.00)	103 (73.57)
Total (%)	14 (22.58)	48 (77.41)	62 (100)	17 (21.79)	61 (78.20)	78 (100)	31 (22.14)	109 (77.85)	140 (100)

Cons, consanguineous; Noncons, non-consanguineous

Table IV. Logistic regression analysis of asthmatic patients (n=200) and non-asthmatic controls (n=400) in Mysore

	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
FH "any"	14.47 (8.59-24.34)	0.001**	9.10 (1.58-52.17)	0.013**
Maternal FH	9.79 (3.26-29.33)	0.001*	1.69 (0.23-12.30)	0.601
Paternal FH	15.50 (4.56-52.61)	0.001*	2.18 (0.36-12.96)	0.390
MGP. FH	16.10 (3.64-71.06)	0.001*	2.85 (0.32-24.83)	0.341
PGP. FH	4.84 (2.06-11.35)	0.001*	0.65 (0.10-4.03)	0.649
Sibling FH	18.42 (4.22-80.39)	0.001*	2.41 (0.35-16.31)	0.365
PS FH	22.97 (2.97-177.62)	0.003*	5.07 (0.42-60.10)	0.198
Cons. parents	2.32 (1.49-3.60)	0.001**	6.88 (2.19-21.62)	0.001**

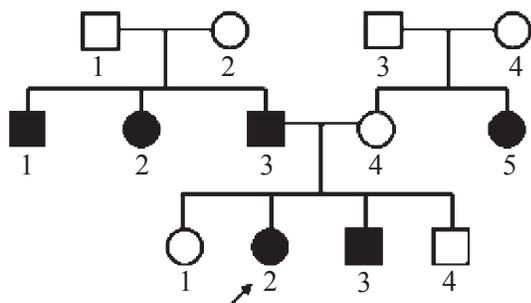
OR, odd ratio; CI, confidence interval; FH, family history; MGP, maternal grandparent; PGP, paternal grandparent; PS, parents' sibling; Cons, consanguineous marriage; **Significant association in univariate and multivariate analysis, *Significant association in univariate analysis only

Table V. Children and adult subgroup logistic regression analysis of asthmatic patients (n=200) and non-asthmatic controls (n=400) in Mysore

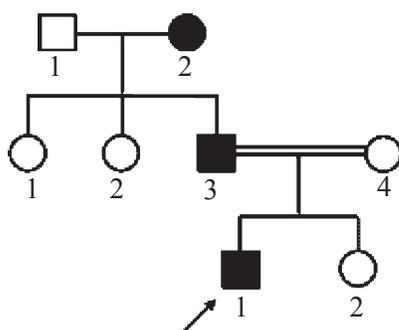
	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
<i>Children:</i>				
FH "any"	14.20 (6.00-33.56)	0.001**	17.39 (1.31-230.00)	0.030**
MGP. FH	21.94 (2.78-172.98)	0.003*	4.57 (0.21-97.90)	0.330
PGP. FH	5.71 (1.48-22.02)	0.011*	0.50 (0.03-6.90)	0.610
Sibling FH	17.25 (2.13-139.71)	0.008*	3.26 (0.20-51.25)	0.399
PS FH	12.69 (1.50-106.90)	0.019*	4.51 (0.10-194.58)	0.433
Cons. parents	1.92 (1.09-3.38)	0.023**	4.38 (1.06-18.07)	0.041**
<i>Adults:</i>				
FH "any"	16.23 (8.30-31.76)	0.001**	9.47 (1.02-88.00)	0.048**
Maternal FH	16.09 (3.58-72.29)	0.001*	7.38 (0.35-152.08)	0.195
Paternal FH	43.63 (5.73-331.88)	0.001*	6.24 (0.46-84.83)	0.169
PGP. FH	4.33 (1.43-13.04)	0.009*	0.66 (0.05-7.59)	0.745
Sibling FH	9.79 (2.07-46.22)	0.004*	1.14 (0.11-11.70)	0.910
PS FH	10.47 (1.20-90.87)	0.033*	18.17 (0.28-1167.57)	0.172
Cons. parents	3.32 (1.59-6.90)	0.001**	56.55 (3.04-1048)	0.005**

OR, odd ratio; CI, confidence interval; FH, family history; MGP, maternal grandparent; PGP, paternal grandparent; PS, parents' sibling; Cons, consanguineous marriage; **Significant association in univariate and multivariate analysis; *Significant association in univariate analysis only

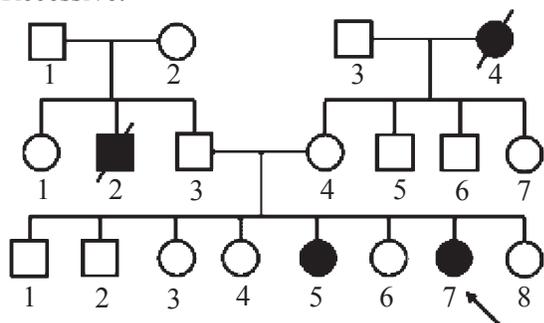
(A) Dominant:



(B) Consanguineous Dominant:



(C) Recessive:



(D) Consanguineous Recessive:

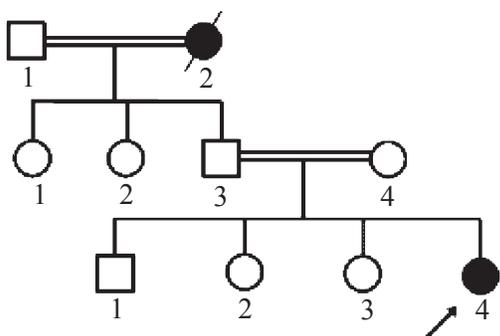


Fig. 3. Some of the selected pedigrees out of 140 asthmatic families in Mysore city. The inheritance patterns of the asthma patients were dominant (A), Consanguineous dominant (B), Recessive (C) and Consanguineous recessive (D). The Roman number in the left side of the figure indicates the number of generation. The Arabic number below the symbol denotes the number of individual in the generation. The arrow directed to the filled symbol represents the proband.

children, 10 out of 14 (71.42%) and adults 9 out of 17 (52.94%).

Table IV shows the combined results for both children and adults regarding univariate and logistic regression of case-control study of asthma patients. The analyses were done to establish specific relationship of various family history and consanguinity. For the whole group, on logistic regression analysis, family history “any” and parental consanguineous marriage were found to be independently associated with development of asthma in the offspring. A subgroup analysis including univariate and logistic regression was conducted separately for children and adults (Table V). It was observed that the results were similar and family history “any” and parental consanguineous marriage were independently associated with the development of asthma in both children and adults.

Discussion

As early as 1909, Drinkwater²³, using the example of a three-generation pedigree, suggested that asthma is a dominant Mendelian trait, whereas a subsequent large study on the genetic transmission of asthma by Cooke and van-der-Veer²⁴ was not able to show such a simple mode of inheritance. Tips’ theory on a polygenetic mode of inheritance of asthma was further developed and suggested that asthma is a multifactorial trait in which multiple gene loci interact with one or more external factors²⁵. We currently are familiar with the fact that asthma is, first, a complex genetic disease and second, a heterogeneous condition of asthma may predominate in different geographic locations and finally, the risk of developing asthma is greatest when both genetic and environmental risk factors are present simultaneously²⁶.

Although a strong familial aggregation of asthma and allergic diseases has been established¹⁷, all of the studies on family history of asthma were limited to first degree relatives²⁷. On one hand, the present study revealed that 44.5 per cent of patients had one or two asthmatic patients in their family and family history, on the other hand, was found to be an important risk factor for asthma. In previous studies, a family history of atopy was found in 48.4 to 58.4 per cent of asthmatics⁶ while in the present study, on univariate analysis of all the subjects including adults and children, family history of asthma in all the first and second degree relatives was found to be significantly associated with asthma. In addition, on multivariate analysis, it was observed that only

parents' consanguineous marriage and family history "any" were found to be significant; individual family history, though significantly associated with asthma in univariate analysis, was not significantly associated in multivariate analysis.

Parental asthma has been shown in several studies to be a strong predictor of asthma in the child¹⁷. On subgroup univariate analysis of children and adults separately, we observed that family history "any" was a significant risk factor in both children and adults while parental family history, both paternal and maternal history of asthma was significant only in adults, and not in children. Supporting this, some studies have shown differential effect of parental family history of asthma in adults and children. For example, in adults, parental history of asthma, both paternal and maternal was significantly associated with asthma in the offspring⁷ and some other studies on children demonstrate preferential association with one of the parents, predominantly paternal or predominantly maternal^{7,16,27}.

Ramegowda & Ramachandra²⁸ reported that parental consanguinity increased congenital heart diseases in south India. The deleterious effects associated with consanguinity may be caused by the expression of rare recessive genes inherited from common ancestors²⁰ although some studies showed no statistically significant risk from parental consanguinity for the development of asthma²⁹. In the present study, the logistic regression analysis using all the family history and consanguineous marriage covariates have shown that when these covariates were considered together the effects of each member's family history of asthma were diluted but still of clinical relevance, albeit not statistically significant. However, the effect of family history "any" and parents' consanguineous marriage were not diluted indicating that these are the risk factors for asthma.

Autosomal recessive inheritance of asthma was more common than dominant inheritance in our study population. In the present study, about 24.5 per cent of the families had consanguineous marriages, which was associated with significantly higher risk of asthma inheritance as compared to non consanguineous families. In addition, taking multivariate analysis into account, parental consanguineous marriage was significantly associated with asthma of the whole group, children and adults in subgroups. Surprisingly, offsprings from consanguineous marriages had less

proportion of recessive pattern of asthma as compared to non consanguineous marriages. This is probably due to the polygenic nature of the disease which warrants further population based studies in a larger sample with the familial and genomics data and tools to map, identifying the specific gene/s and phenotype specific SNPs.

Studies have shown that although a single major gene effect could not be excluded, a "liability/threshold" model is supported by several facts. For example, the risk of asthma increases with regard to the number of relatives affected, and the number of affected relatives also increases with the disease severity of affected index individuals¹⁶. Studies have also displayed that the odds of having a child with asthma are three times greater in families with one asthmatic parent and six times greater in families with two asthmatic parents¹⁶. Our findings also supported this finding (22.7% no family history, 78% for one member of family and 93.7% for two members and above).

Inclusion of both children and adults and controls from the general population can be considered as strengths of our study. There were also some limitations in this study including inability to interview all the members in the family tree, and spirometry not being performed in the relatives of index case and controls. Another important limitation in the study was that the selection of the cases was from the hospital and selection of controls was from the general population. Future studies are required with both cases and controls selected from the general population to confirm the reproducibility of these findings.

In conclusion, our study demonstrated that family history of asthma is an important risk factor for developing asthma in the offspring and a differential risk of developing asthma was also noted in family history of asthma in different first and second degree relatives and consanguineous marriages. These factors raise important questions about the mode of inheritance and genetic transmission of asthma in our population, which needs to be investigated further.

Acknowledgment

The authors thank doctors, patients and patients' families in Cheluvamba and JSS hospitals and Allergy, Asthma and Chest Center of Mysore; Dr A.K. Prabhakar, JSS Hospital, Mysore; Sathish Chandran M. and Kareem Khan M. for helping in controls data collection. The first author (MB) acknowledge the University of Mysore, Chairman, DOS in Zoology and Ahwaz University of Medical Sciences, Iran for providing opportunity to carry out this work.

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