Genetic influence on the age at onset of asthma: A twin study

Simon Francis Thomsen, MD, PhD,[a] David Lorenzo Duffy, MD, PhD,[b] Kirsten Ohm Kyvik, MD, PhD, MPM,[c] and Vibeke Backer, MD, DMSc[a] *Copenhagen and Odense, Denmark, and Brisbane, Australia*

Background: Although the genetics of asthma susceptibility have been frequently explored, little is known about genetic factors that influence the age at onset of asthma.
Objective: To study the variation in the age at onset of asthma attributable to genetic and environmental factors.
Methods: Data on the age at onset and predictors of asthma were collected in 2002 via a multidisciplinary questionnaire study of 34,782 Danish twins 20 to 71 years of age. Survival analytic methods were applied to partition variation in the age at onset of asthma into genetic and environmental components.
Results: Sex, hay fever, atopic dermatitis, smoking, and exposure to passive smoking in childhood were significant risk factors, whereas BCG vaccination was protective for asthma. The risk of asthma in the co-twin of an affected twin was higher in monozygotic than in dizygotic twins (hazard ratio, 2.59; 95% CI, 1.83-3.68; $P < .001$). The risk of asthma in the co-twin decreased with increasing age at onset of asthma in the index twin (hazard ratio per ten years, 0.86; 95% CI, 0.76-0.98; $P = .019$). The effect was attenuated in dizygotic twins relative to monozygotic twins ($P = .005$). Genetic factors explained 34% of the variation in the age at onset of asthma, and environmental factors accounted for 66%.
Conclusion: Host-related differences in genetic makeup cause different individuals to develop asthma at different ages. Better understanding of the causes for variation in the age at onset of disease may ultimately lead the way to targeted treatments.
(J Allergy Clin Immunol 2010;126:626-30.)

Key words: *Asthma, genetics, twin study, age at onset, heritability, epidemiology*

Although asthma can occur at any age, most cases develop in childhood with a gradual decrease in incidence after adolescence. Boys have a greater risk of asthma in the first years of life, whereas girls are more frequently affected during adolescence and in adulthood.[1] Allergy plays a pivotal role in childhood-onset asthma, whereas adult-onset asthma seems less related to allergic mechanisms.[2] Accordingly, individuals with early-onset asthma more often have atopic dermatitis and hay fever than subjects whose asthma develops in adulthood. Moreover, subjects with early-onset asthma more frequently have a family history of atopic disease than subjects with later-onset asthma.[3] Individuals with adult-onset asthma also tend to have lower lung function, to be smokers, and to have a poorer prognosis than individuals with childhood-onset asthma.[4] On the contrary, parental smoking during pregnancy or in early life of the child seems to be a stronger predictor of early-onset persistent asthma than later-onset asthma, particularly in children with atopic heredity.[3] Subjects with childhood asthma who relapse in adulthood appear to have a more severe form of disease than subjects whose asthma occurs in adulthood,[5] consistent with a lower lung function according to a longer duration of disease.[6]

Genetic studies of asthma have so far mainly identified asthma susceptibility loci,[7] whereas studies of genetic variation underlying the age at onset of disease are sparse. Bouzigon et al[8] found evidence of 2 regions (5q13 and 1p31) with suggestive linkage to time to onset of asthma in French families. Interestingly, the 5q13 region was also linked to asthma severity. Furthermore, a region on 7q showed suggestive linkage to asthma in the same population but with different genotype relative risks according to the age at onset of disease.[9] Hizawa et al[10] found that the -28G allele of the RANTES promoter region at chromosome 17q increased the risk of late-onset asthma (>40 years of age) compared with early-onset and middle age–onset asthma in Japanese. In German children, age at onset of wheezing was strongly linked to chromosome 6q24-q25.[11] Although these markers have been identified, the overall contribution of genetic factors to the age at onset of asthma has not been estimated. We consequently analyzed questionnaire data on a large sample of adult Danish twins with the aim to study the overall contribution of the genetic makeup to the variation in the age at onset of asthma.

METHODS

Sample

The study population was composed of the twin cohorts born between 1931 and 1982 who were enrolled in the Danish Twin Registry.[12] In 2002, when the study subjects were between 20 and 71 years of age, they were mailed a multidisciplinary questionnaire on health and lifestyle. Asthma was identified on the basis of an affirmative response to the question, "Do you have or have your ever had asthma?" whereas the age at onset of asthma was determined by the question, "How old were you (in years) when you got asthma?" Additional questions used herein were on history of hay fever, atopic dermatitis, smoking, vaccination with BCG, exposure to passive smoking in childhood, and symptoms of chronic bronchitis ("having experienced at least 3 months per year of coughing with production of phlegm during the past 2 years"). Four questions on physical similarity and mistaken identity determined twin zygosity. This method has a misclassification rate of less than 5%.[13] In total, 34,782 subjects participated in the study (response rate, 75%). Of these, 11,671 were intact pairs, 3408 monozygotic pairs, 4273 dizygotic pairs of same sex, and 3691 dizygotic pairs of opposite sex, leaving 299 pairs of unknown zygosity. Asthma was present in 1714 of the intact twin pairs. Of these, 1614 pairs had complete information on age at onset.

From [a]the Department of Respiratory Medicine, Bispebjerg Hospital, Copenhagen; [b]the Queensland Institute of Medical Research, Brisbane; and [c]the Danish Twin Registry and Institute of Regional Health Services Research, University of Southern Denmark, Odense.

S.F.T. is sponsored by the Danish Medical Research Council grant.
Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.
Received for publication January 14, 2010; revised April 30, 2010; accepted for publication June 4, 2010.
Available online August 5, 2010.

Reprint requests: Simon Francis Thomsen, MD, PhD, Department of Respiratory Medicine, Bispebjerg Hospital, DK-2400 Copenhagen NV, Denmark. E-mail: sft@city.dk.

0091-6749/$36.00

doi:10.1016/j.jaci.2010.06.017

TABLE I. Characteristics of 34,782 twin subjects, 20 to 71 years of age, who participated in a nationwide questionnaire study

Age group	20-30 (n = 6,690)	31-40 (n = 7,933)	41-50 (n = 7,281)	51-60 (n = 7,855)	61-71 (n = 5,023)	Total (n = 34,782)
Men	2,907 (43.5)	3,402 (42.9)	3,463 (47.6)	3,677 (46.8)	2,397 (47.7)	15,846 (45.6)
Women	3,783 (56.5)	4,531 (57.1)	3,818 (52.4)	4,178 (53.2)	2,626 (52.3)	18,936 (54.4)
Ever asthma	676 (10.2)	722 (9.2)	600 (8.3)	549 (7.1)	457 (9.3)	3004 (8.7)
Men	260 (9.0)	293 (8.7)	240 (7.0)	195 (5.4)	204 (8.7)	1192 (7.6)
Women	416 (11.1)	429 (9.6)	360 (9.5)	354 (8.6)	253 (9.9)	1812 (9.7)
Current asthma	356 (5.4)	421 (5.4)	379 (5.3)	367 (4.7)	343 (7.0)	1866 (5.4)
Men	131 (4.5)	167 (4.9)	141 (4.1)	125 (3.4)	147 (6.2)	711 (4.5)
Women	225 (6.0)	254 (5.7)	238 (6.3)	242 (5.9)	196 (7.7)	1155 (6.2)
Ever smoking	2,762 (42.1)	4,056 (52.0)	4,361 (61.3)	4,861 (64.2)	3,184 (67.9)	19224 (57.0)
Men	1,173 (41.1)	1,656 (49.5)	2,058 (60.7)	2,513 (70.5)	1,738 (76.2)	9,138 (59.2)
Women	1,589 (42.8)	2,400 (54.0)	2,303 (61.9)	2,348 (58.7)	1,446 (60.1)	10,086 (55.2)
Current smoking	2,077 (31.6)	2,627 (33.7)	2,676 (37.6)	2,748 (36.3)	1,526 (32.6)	11654 (34.6)
Men	932 (32.6)	1,150 (34.4)	1,263 (37.2)	1,374 (38.5)	790 (34.6)	5509 (35.7)
Women	1,145 (30.9)	1,477 (33.2)	1,413 (38.0)	1,374 (34.3)	736 (30.6)	6,145 (33.6)
Chronic bronchitis						
With asthma						
Men	22 (9.5)	40 (14.8)	51 (23.0)	54 (30.0)	65 (33.5)	232 (21.1)
Women	55 (15.9)	79 (21.5)	91 (28.6)	91 (28.5)	98 (41.7)	414 (26.1)
Without asthma						
Men	69 (2.7)	125 (4.2)	188 (6.1)	250 (7.4)	171 (8.2)	803 (5.7)
Women	80 (2.5)	166 (4.3)	230 (7.0)	225 (6.2)	118 (5.3)	819 (5.1)

Data presented as n (%).

Statistical analysis

We performed 2 different regression analyses to identify predictors for the age at onset of asthma. Initially, predictors of the age at onset of asthma were determined with a Cox proportional hazards regression model with age as the underlying time ignoring the familial relationships between the twins. Covariates were age group (birth cohort) in 10-year bands, sex, atopic dermatitis, hay fever, BCG vaccination, smoking (pack-years), and exposure to passive smoking in childhood. We subsequently fitted a Cox proportional hazards regression model to asthma-free survival of co-twins of a proband (index twin) who was the first member of that sibship to develop asthma.[14] The survival time for the co-twin started at the age the proband was affected and continued until the co-twin developed asthma or was censored at the age of last follow-up. In this analysis, an increased hazard ratio for monozygotic co-twins relative to dizygotic co-twins signals genetic influences on the age at onset of asthma. As covariates, we included the age at onset of asthma in the proband and age group (birth cohort) in 10-year bands, sex, BCG vaccination, and smoking (pack-years) in the co-twin.

We then explored the correlation between the age at onset of asthma within twin pairs and partitioned the variation in the age at onset of asthma into genetic and environmental components. Because of the correlation between members of a twin pair, nonparametric estimation of the bivariate survival function for the twins was estimated by the Dabrowska approach. To carry out variance components analysis of age at onset, we tested 2 different approaches. One was the Cox proportional hazards frailty model implemented in the R kinship package (www.r-project.org),[15] and the other involved fitting the Gaussian mixed model to martingale residuals calculated from the marginal cumulative hazard curve for the twins.[16]

RESULTS

The mean age of the participants was 44.5 years, and 54.4% were women. A total of 9.7% of the women and 7.6% of the men had a history of asthma ($P < .001$). The prevalence of asthma decreased with increasing age until age 60 years, after which a small increase was observed. In total, 50% of the men with asthma reported an age at onset below 15 years, whereas 50% of the women reported an age at onset below 24 years. Symptoms of chronic bronchitis were significantly associated with asthma both in men and in women. However, among subjects with asthma, the frequency of chronic bronchitis was higher in women than men (26.1% vs 21.1%; $P = .003$), whereas among subjects without asthma the frequency of chronic bronchitis was higher among men than women (5.7% vs 5.1%; $P = .012$; Table I).

According to the Cox proportional hazards model applied to the entire population of twins, sex, hay fever, atopic dermatitis, smoking, and exposure to passive smoking in childhood were significant risk factors, whereas BCG vaccination was protective for asthma (Table II). The effect of sex disappeared when restricting the analysis to subjects without symptoms of chronic bronchitis.

Fig 1 shows the risk of asthma in a co-twin of an affected twin. According to the Cox proportional hazards model restricted to affected sibships, the risk of asthma was increased about 3 times in a monozygotic co-twin relative to a dizygotic co-twin, indicating that variation in the age at onset of asthma was influenced by genetic factors (Table III). Conversely, the risk of asthma in dizygotic co-twins of the opposite sex was about half that of dizygotic co-twins of the same sex, suggesting that the genetic factors, which regulate the age at onset of asthma, may act differentially in men and women. The risk of asthma in the co-twin decreased with increasing age at onset of asthma in the index twin, indicating that familial aggregation was more substantial around early-onset asthma than late-onset asthma. The effect was attenuated in dizygotic twins relative to monozygotic twins ($P = .005$), consistent with early-onset asthma being under tighter genetic control compared with late-onset asthma.

Fig 2 shows the correlation between the age at onset of asthma within monozygotic and dizygotic twin pairs. The correlation was higher in monozygotic than in dizygotic twins, particularly among males (Table IV). According to the frailty model approach, the proportion of variation in the age at onset of asthma explained by (dominance) genetic variance was 34%, whereas the proportion explained by environmental variance was 66%. Variance components analysis with the Gaussian mixed model approach revealed a heritability of 12%.