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Major Genetic Effects on Airway-Parenchymal Dysanapsis of the Lung: The Humboldt Family Study

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We examined familial resemblance and performed segregation analysis for the maximal expiratory flow rate at 50% of vital capacity ($Vmax_{50}$) and the ratio of $Vmax_{50}$ to forced vital capacity (FVC), based on data from 309 nuclear families with 1,045 individuals in the town of Humboldt, Saskatchewan, in 1993. $Vmax_{50}$ is considered as an index of airway function and $Vmax_{50}$/FVC is considered as an index of airway-parenchymal dysanapsis. Both $Vmax_{50}$ and $Vmax_{50}$/FVC were preadjusted for host characteristics (age, height, and weight), environmental factors, and history of respiratory symptoms and diseases in four separate groups (mothers, fathers, daughters, and sons). Both $Vmax_{50}$ and $Vmax_{50}$/FVC showed low father-mother correlations and significant parent-offspring and sibling-sibling correlations. Segregation analysis indicated that for residual $Vmax_{50,}$ the model of no-parent-offspring transmission with possible heterogeneity between two generations fitted the data as well as did the general model with arbitrary transmission probabilities. The Mendelian hypothesis for $Vmax_{50}$ was rejected, which was consistent with our previous findings for other indexes of airway function. For residual $Vmax_{50}$/FVC, however, a single locus explained all the familial resemblance and both no-parent-offspring-transmission hypotheses [$\tau(AA) = \tau(AB) = \tau(BB) = q_A$ and $\tau(AA) = \tau(AB) = \tau(BB)$] were rejected. The study provides evidence for a single locus influencing airway-parenchymal dysanapsis. Genet. Epidemiol. 16:95–110, 1999.

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INTRODUCTION

A number of studies have documented familial aggregation for pulmonary function testing variables [Cotch et al., 1990; Coultas et al., 1991; Devor and Crawford, 1984; Higgins and Keller, 1975; Kauffmann et al., 1989; Lewitter et al., 1984; Schilling et al., 1977; Tager et al., 1976]. However, it has not been clear whether the resemblances for various pulmonary function testing variables are related to common environmental exposures or inherited susceptibilities. Our earlier reports have illustrated that different pulmonary function indexes may share different mechanisms [Chen et al., 1996a, 1997]. Segregation analyses on the forced expiratory volume in 1 sec (FEV_1) and the maximal mid-expiratory flow rate (MMFR), commonly used as indicators of airway function, have suggested that their familial aggregations are most likely controlled by multiple loci with no major gene effects, and/or are due to common environmental factors [Chen et al., 1996a]. Other recent studies have also shown lack of major genetic effects on FEV_1 in general populations [Givelber et al., 1996; Holberg et al., 1996], although heterogeneity may exist between families with and without chronic obstructive pulmonary disease [Rybicki et al., 1990] or asthma [Holberg et al., 1996]. For forced vital capacity (FVC), an index of lung volume, our recent analysis provided evidence of major genetic effects on the trait [Chen et al., 1997]. Those findings support the idea that heredity may have different influences on parenchymal size of the lung as opposed to airway function.

Green et al. [1974] postulated that inter-individual difference in central airway size was a major determinant of the variability of normal maximal expiratory flow and that adjusting for lung size did not decrease the variability. The authors suggested that these differences have an embryological basis, reflecting disproportionate but physiologically normal growth of airway and parenchymal components called "dysanaptic" growth [Green et al., 1974]. Mead [1980] further examined the relationship between lung volume and airway area and advanced the concept of airway-parenchymal dysanapsis, reasoning that persons with large lungs do not necessarily have larger airways than do persons with small lungs. Martin et al. [1988] found that airway-parenchymal dysanapsis existed in early childhood. Since airway-parenchymal dysanapsis may influence the pathogenesis of airway disease [Green et al., 1974] and small airway size relative to lung size may increase the risk of airway obstructive disease, an understanding of its genetic mechanisms would potentially have an important impact on the comprehension of the development and progression of lung disease.

Mead [1980] used $Vmax_{50}/[VC \times Pst(L)_{50}]$ as an index of airway-parenchymal dysanapsis. $Vmax_{50}$ is the maximal expiratory flow rate at 50% of total volume. $Pst(L)_{50}$ is the maximal flow static recoil pressure characteristic at 50% of vital capacity (VC), which is not applicable for large-scale population-based studies, and therefore was not measured in our study. Green et al. [1974] have documented that lung static recoil contributes little to the variability between individuals and that the major variability in maximum flows is attributable to airway dimension. We used $Vmax_{50}/FVC$ as an estimate of Mead's $Vmax_{50}/[VC \times Pst(L)_{50}]$, and its justification has been discussed in detail by

Tager et al. [1986]. The correlation between $Vmax_{50}$/VC and $Vmax_{50}$/[VC x $Pst(L)_{50}$] is high, ranging from 0.78 to 0.84 [Tager et al., 1986].

MATERIALS AND METHODS

The Humboldt Family Study is a population-based study and has been detailed in previous reports [Chen et al., 1996a, 1997]. In brief, young families were ascertained through parents who reported having at least one child between age 6 and 17 years living in the town of Humboldt, Saskatchewan, in 1993. Canvassers contacted all households within the town and left a questionnaire for all adults aged 18–74 years [Chen et al., 1995]. The questionnaire was completed in the home by adult subjects and returned during a prearranged clinic visit [Chen et al., 1995]. The questionnaire ascertained whether or not the respondent had children aged 6–17 years, as well as their names and ages. The children's portion of the study was conducted in each of four schools in the town (one high school and three primary schools). We identified 214 young families with both parents who participated in the study, and 95 families in which only one parent participated. In total, 1,045 individuals from 309 families were included in the analysis. The distribution of the participants by family size was presented in a previous report [Chen et al., 1997].

Pulmonary function testing was performed by using the MedGraphics CPF-S System (Medical Graphics Corporation, MedGraphics, St. Paul, MN), which followed the Standardization of Spirometry recommended by the American Thoracic Society [1987]. Each subject was tested until three acceptable forced expiratory maneuvers were obtained. The values of FVC and $Vmax_{50}$ were determined from the flow volume curves. The best FVC was used in the analysis and $Vmax_{50}$ came from the tracing with the best sum of FVC and FEV_1. Weight and height were also recorded.

We used class D regressive models [Bonney, 1984] for familial correlation and segregation analyses, and used REGC program of the Statistical Analysis for Genetic Epidemiology package [SAGE, 1994]. When examining the pattern of resemblance of the pulmonary function test outcomes, we adjusted for host characteristics (age, height, and weight), environmental factors (home environment, smoking, and passive smoking), and history of respiratory symptoms and diseases (cough, wheeze, asthma, bronchitis, and pneumonia). These variables could either be preadjusted by using regression analysis or be included as covariates in class D regressive models. However, most of the variables tended to have inconsistent effects on pulmonary function testing variables across the two generations and/or gender strata. Therefore, the second choice was not an ideal one for our case. We performed a prior adjustment for these variables on $Vmax_{50}$ and $Vmax_{50}$/FVC separately within four groups (mothers, fathers, daughters, and sons). $Vmax_{50}$ and $Vmax_{50}$/FVC were regressed on age, height, weight, their quadratic and cubic terms, and other variables with terms significant at the 0.10 level being retained. Residual phenotypes were calculated. They were the differences between observed and expected values.

The class D regressive model was first used to test various patterns of familial correlations (ρ_{fm} = father-mother correlation; ρ_{mo} = mother-offspring correlation; ρ_{fo} = father-offspring correlation; and ρ_{sib} = sibling-sibling correlation) for residual $Vmax_{50}$ and $Vmax_{50}$/FVC without major genes. Other parameters in the correlation models

included a population mean (μ) and a variance (σ^2). The data showed that the variance for both residual $Vmax_{50}$ and $Vmax_{50}$/FVC was not sex-dependent and a common variance was used in modelling. If there was no significant difference in correlations between first-degree relatives, a narrow-sense heritability was estimated. The heritability in the narrow sense is the proportion of phenotypic variation in a population that is due to the additive effects of alleles at one or more loci, and is twice the correlation between first-degree relatives [Khoury et al., 1993, p 271].

In segregation analysis, the class D regressive model was used to determine whether there were major gene effects on the phenotypes. A major gene effect on each phenotype is assumed to result from segregation at a single locus having two alleles, A and B. The parameters of a gene frequency (q_A), genotypic means [μ(AA), μ(AB), and μ(BB)], and a genotypic variance (σ^2) were estimated for each phenotype. An arbitrary major gene was first assumed. Before there was evidence of Mendelian transmission, a more general term called "ousiotypes" or types were used instead of genotypes as suggested by Cannings et al. [1978]. A common variance was used to minimize the number of parameters. Because the estimation of ousiotype dependent variances requires enormous sample size, we assumed a common variance across the ousiotypes. The parameters of transmission probabilities were estimated, which are the probabilities of a parent's transmitting the A allele to an offspring. Under Mendelian transmission, τ(AA) = 1, τ(AB) = ½, and τ(BB) = 0. The nontransmitted environmental effect was obtained both with the three transmission probabilities being equal to q_A [τ(AA) = τ(AB) = τ(BB) = q_A] (assuming complete homogeneity between generations) and with three equal transmission probabilities [τ(AA) = τ(AB) = τ(BB)] (allowing possible heterogeneity between generations) [SAGE, 1994].

A likelihood-ratio test (LRT) was used to select the most parsimonious model, which is minus twice the difference in the $\log_e$ likelihood (lnL) between models before and after constraining parameters. The LRT is distributed asymptotically as a chi-square with degrees of freedom (df) equal to the difference in the number of parameters between two models. However, if the value of a parameter under the null hypothesis is at the boundary of the parameter space, the LRT statistic follows a mixture of a chi-square distribution with 1 df and a degenerate chi-square distribution with 0 df when it is fixed equal to an unbounded parameter [Khoury et al., 1993, p 268]. When two parameters are at boundary values, the LRT follows a mixture of ¼ a chi-square with 2 df, ½ a chi-square with 1 df, and ¼ a chi-square with 0 df [Self and Liang, 1987]. A better-fitting model was also considered with a lower value of the Akaike's information criterion [AIC = –2lnL +2(number of parameters estimated [Akaike, 1974]. Because the subjects were not selected with respect to their lung function (random ascertainment), an ascertainment correlation was not necessary.

RESULTS

Table I shows the distributions of $Vmax_{50}$, $Vmax_{50}$/FVC, environmental factors and history of respiratory symptoms and diseases in the sample. Means and standard deviations of age, height, and weight have been presented previously [Chen et al., 1997]. $Vmax_{50}$ and $Vmax_{50}$/FVC were regressed on age, height, weight, their quadratic and cubic terms, environmental factors, and history of respiratory symptoms

TABLE I. Distribution of $Vmax_{50}$, $Vmax_{50}$/FVC, Environmental Factors, History of Respiratory Symptoms, and Diseases Among the Participants*

	Mothers (n = 287)	Fathers (n = 232)	Daughters (n = 261)	Sons (n = 265)
Age	37.0 ± 6.3	39.5 ± 7.4	10.8 ± 3.3	10.6 ± 3.1
Lung function testing variables				
$Vmax_{50}$ (l/s)	4.02 ± 1.05	5.24 ± 1.60	3.25 ± 1.20	3.26 ± 1.32
$Vmax_{50}$ (l/s)/FVC (1)	1.06 ± 0.28	1.01 ± 0.30	1.23 ± 0.34	1.12 ± 0.32
Environmental factors (%)[a]				
Active smoker	19.5	22.0	4.2	2.3
Passive smoker	18.8	16.8	31.8	25.3
Single family unit	87.1	89.7	88.1	90.6
<4 bedrooms	48.1	42.7	41.4	38.1
≥4 household members	43.6	48.3	48.7	54.0
Gas heating	87.1	89.2	86.6	89.4
Pet(s) at home	38.3	40.1	50.2	42.3
History of respiratory symptoms/diseases (%)[a]				
Cough	8.0	9.1	11.5	9.1
Wheeze	26.5	34.5	27.2	32.1
Wheeze at night	2.8	4.7	4.6	4.2
Asthma	5.6	4.7	10.3	11.3
Pneumonia	12.5	10.8	10.7	7.5
Bronchitis	25.1	12.9	13.8	19.2
Respiratory allergy	34.5	25.4	22.2	28.3

*Values represent mean ± SD.
[a]Details of definitions are available either in a previous report [Chen et al., 1996b] or upon request.

and diseases in mothers, fathers, daughters, and sons, respectively. Terms significant at the 0.10 level were retained in the regression models. Table II presents the variabilities of $Vmax_{50}$ and $Vmax_{50}$/FVC explained by the variable terms included in the regression models.

Familial Correlations and Segregation Analysis of $Vmax_{50}$

Table III shows the comparison of different patterns of familial correlation for residual $Vmax_{50}$ estimated under the class D model. The arbitrary correlations are

TABLE II. Variables Terms in Prediction of $Vmax_{50}$ and $Vmax_{50}$/FVC by Gender and Generation Strata

	Variables included	Variance explained (%)
$Vmax_{50}$		
Mothers	Age, age^2, height, weight, wheeze, bronchitis	12.4
Fathers	Age, height, gas heating, asthma, wheeze at night	19.9
Daughters	Age, age^2, age^3, height, $height^2$, gas heating, cough	59.0
Sons	Age, height, $height^2$, $height^3$, wheeze	67.1
$Vmax_{50}$/FVC		
Mothers	Height, weight, wheeze, bronchitis	10.4
Fathers	Height, $height^2$, gas heating, asthma, wheeze at night	9.5
Daughters	Age, age^2, age^3, gas heating, cough, wheeze	18.1
Sons	Age, height, $height^2$, $height^3$, wheeze	23.6

TABLE III. Familial Correlations (± Standard Deviations) for Residual $Vmax_{50}$ Estimated Under Class D Regressive (No Major Gene) Models[†]

Model	ρ_{fm}	ρ_{mo}	ρ_{fo}	ρ_{sib}	–2lnL	Models compared	LRT	df
(1) General	0.077 ± 0.050	0.222 ± 0.073	0.183 ± 0.048	0.401 ± 0.090	2,899.42			
(2) No father-mother	[0][a]	0.203 ± 0.074	0.163 ± 0.047	0.398 ± 0.091	2,901.81	2 vs. 1	2.39 (NS)	1
(3) Equal parent-offspring	[0][a]	0.175 ± 0.037	$=\rho_{mo}$	0.395 ± 0.091	2,901.99	3 vs. 2	0.18 (NS)	1
(4) Equal parent-offspring and sibling-sibling	[0][a]	0.179 ± 0.033	$=\rho_{mo}$	$=\rho_{mo}$	2,905.80	4 vs. 2	3.99*	1–2
(5) No parent-offspring	[0][a]	[0][a]	[0][a]	0.429 ± 0.079	2,921.25	5 vs. 2	19.44**	2
(6) No correlation	[0][a]	[0][a]	[0][a]	[0][a]	2,935.87	6 vs. 2	34.06**	3

[†]$Vmax_{50}$ = maximal expiratory flow rate at 50% of total volume; ρ_{fm} = father-mother correlation; ρ_{mo} = mother-offspring correlation; ρ_{fo} = father-offspring correlation; ρ_{sib} = sibling-sibling correlation; lnL = log likelihood; LRT = Likelihood-ratio test; NS = not significant. The mean and variance of the residual phenotype are omitted.

[a]Correlation is fixed at zero.

*$0.046 < P < 0.136$.

**$P < 0.001$.

presented in model 1. When the father-mother correlation was set to zero, model 2 was not statistically different from model 1 ($P = 0.122$). Mother-offspring and father-offspring correlations were not significantly different from each other (model 3 vs. model 2: $P = 0.671$). Sibling-sibling correlation seemed to be greater than parent-offspring correlation, but the difference was not statistically significant (model 4 vs. model 2: $0.046 < P < 0.136$). Parent-offspring correlations were statistically significant (model 5 vs. model 2: $P < 0.001$). Therefore, models with no father-mother correlation and common parent-offspring correlation (models 3 and 4) were more parsimonious than others.

Table IV presents the results of segregation analysis for residual $Vmax_{50}$. In the general model (model 1), we estimated 12 arbitrary parameters and their standard deviations by using the maximum likelihood method. The model with ousiotypes plus polygenes (model 2) fit the data as well as model 1 ($P = 0.497$). The ousiotypes only model, polygenes only model, or sporadic model had significant worse fit as compared to the general model.

Table V presents the transmission parameter estimates and their standard deviations for residual $Vmax_{50}$. Model 1 in Table V is the same as model 2 in Table IV. A comparison of the Mendelian model (model 2) with the general transmission model indicated that the hypothesis of Mendelian transmission was rejected ($P < 0.001$). The no-parent-offspring-transmission hypothesis (complete homogeneity between two generations assumed) was also rejected ($P < 0.001$). The hypothesis of no-parent-

TABLE IV. Parameter Estimates (± Standard Deviations) From Segregation Analysis of Residual $Vmax_{50}$ Under Class D Regressive Models[†]

	General (1)	Ousiotypes plus polygenes (2)	Ousiotypes only (3)	Polygenes only (4)	Sporadic (5)
q_A	0.45 ± 0.06	0.44 ± 0.06	0.75 ± 0.10	[1.0][a]	[1.0][a]
τ (AA)	0.92 ± 0.09	0.92 ± 0.09	(1.00)[b]		
τ (AB)	(1.00)[b]	(1.00)[b]	0.79 ± 0.11		
τ (BB)	(1.00)[b]	(1.00)[b]	(0.00)[b]		
μ (AA)	0.03 ± 0.05	0.03 ± 0.05	–0.34 ± 0.10	–0.00 ± 0.04	0.00 ± 0.03
μ (AB)	–0.78 ± 0.07	–0.79 ± 0.07	0.47 ± 0.34		
μ (BB)	1.17 ± 0.16	1.15 ± 0.16	1.80 ± 1.42		
σ^2	0.64 ± 0.04	0.64 ± 0.04	0.73 ± 0.06	1.01 ± 0.05	1.01 ± 0.04
ρ_{fm}	0.15 ± 0.11	[0][a]	[0][a]	[0][a]	[0][a]
ρ_{fo}	0.26 ± 0.09	0.23 ± 0.04	[0][a]	0.18 ± 0.03	[0][a]
ρ_{mo}	0.27 ± 0.06	$=\rho_{fo}$	[0][a]	$=\rho_{fo}$	[0][a]
ρ_{sib}	0.19 ± 0.07	$=\rho_{fo}$	[0][a]	$=\rho_{fo}$	[0][a]
–2lnL	2808.46	2810.84	2896.01	2905.80	2935.87
Models compared		2 vs. 1	3 vs. 1	4 vs. 1	5 vs. 1
LRT		2.38 (NS)	87.55*	97.34*	127.41*
df		3	4	—[c]	—[c]

[†]q_A = gene frequency; τ(A), τ(AB); and τ (BB) = transmission probabilities; μ(AA), μ(AB), and μ(BB) = genotypic means; σ^2 = genotypic variance. For other definitions, see Table III.
[a]The parameter is fixed and not estimated in the model.
[b]The parameter is maximized at its boundary value.
[c]Two parameters in model 1 are maximized at boundary values, and the LRT follows a mixture of ¼ a chi-square with 2 df, ½ a chi-square with 1 df, and ¼ a chi-square with 0 df [Self and Liang, 1987].
*$P < 0.001$.

TABLE V. Transmission Parameter Estimates (± Standard Deviations) From Segregation Analysis of Residual $Vmax_{50}$ Under Class D Regressive Models[†]

			No parent-offspring transmission	
	General (1)	Mendelian (2)	τ (AA) = τ (AB) = τ (BB) (3)	τ (AA) = τ (AB) = τ (BB) = q_A (4)
q_A	0.44 ± 0.06	0.93 ± 0.06	0.57 ± 0.06	0.93 ± 0.06
τ (AA)	0.92 ± 0.09	[1.0][a]	0.01 ± 0.02	$=q_A$
τ (AB)	(1.00)[b]	[0.5][a]	$=\tau$ (AA)	$=q_A$
τ (BB)	(1.00)[b]	[0.0][a]	$=\tau$ (AA)	$=q_A$
μ (AA)	0.03 ± 0.05	–0.07 ± 0.09	1.11 ± 0.15	0.12 ± 0.09
μ (AB)	–0.79 ± 0.07	0.33 ± 0.54	–0.78 ± 0.08	–0.90 ± 0.28
μ (BB)	1.15 ± 0.16	3.07 ± 1.65	0.01 ± 0.06	2.80 ± 1.23
σ^2	0.64 ± 0.04	0.96 ± 0.07	0.65 ± 0.04	0.84 ± 0.12
ρ	0.23 ± 0.04	0.17 ± 0.04	0.23 ± 0.04	0.22 ± 0.05
–2lnL	2810.84	2898.93	2811.74	2897.88
Models compared		2 vs. 1	3 vs. 1	4 vs. 1
LRT		88.09*	0.90 (NS)	887.04*
df		—[c]	—[c]	—[c]

[†]ρ = correlation among all first-degree relatives. For other definitions, see Tables III and IV.
[a]The parameter is fixed and not estimated in the model.
[b]The parameter is maximized at its boundary value.
[c]Two parameters in model 1 are maximized at boundary values, and the LRT follows a mixture of ¼ a chi-square with 2 df, ½ a chi-square with 1 df, and ¼ a chi-square with 0 df [Self and Liang, 1987].
*$P < 0.001$.

offspring-transmission with possible heterogeneity between two generations, however, could not be rejected, indicating that environmental factors and/or polygenes explain the mixture of distributions for $Vmax_{50}$.

Familial Correlations and Segregation Analysis of $Vmax_{50}$/FVC

Table VI presents the results of the familial correlations for residual $Vmax_{50}$/FVC. The pattern was similar to that for residual $Vmax_{50}$ except that parent-offspring and sibling-sibling correlations were similar. Based on the polygenic model (model 4), the narrow-sense heritability, which is the proportion of phenotype variation in a population that is due to the additive effects of alleles at one or more loci [Khoury et al., 1993, p 271], was estimated to be 0.40.

Table VII presents the results of segregation analysis for residual $Vmax_{50}$/FVC. The model with ousiotypes plus polygenes and the ousiotypes only model (model 3) fit the data with no significant difference as compared to the general model in which all parameters were estimated (model 1) ($P = 0.075$ and $P = 0.168$, respectively). The polygenic and sporadic models (models 4 and 5) had significantly worse fits than the general model ($0.001 < P < 0.002$ and $P < 0.001$, respectively). When further examining the transmission parameters under the class D model (Table VIII), we found that the Mendelian hypothesis could not be rejected (model 2 vs. model 1: $0.746 < P < 0.873$) while both no-parent-offspring-transmission hypotheses were rejected (model 5 vs. model 1: $P < 0.001$, and model 6 vs. model 1: $P < 0.001$, respectively). The data suggest that a single locus influences the level of $Vmax_{50}$/FVC. For the mode of inheritance, the data showed that both dominant model (AIC = 261.76) and recessive model (AIC = 266.54) had a worse fit than the unrestricted or codominant model (AIC = 253.76) (Table VIII). The maximum likelihood param-

TABLE VI. Familial Correlations (± Standard Deviations) for Residual $Vmax_{50}$/FVC Estimated Under Class D Regressive (No Major Gene) Models[†]

Model	ρ_{fm}	ρ_{mo}	ρ_{fo}	ρ_{sib}	–2lnL	Models compared	LRT	df
(1) General	0.110 ± 0.072	0.156 ± 0.051	0.247 ± 0.051	0.269 ± 0.060	258.38			
(2) No father-mother	[0][a]	0.138 ± 0.050	0.237 ± 0.051	0.266 ± 0.060	260.64	2 vs. 1	2.26 (NS)	1
(3) Equal parent-offspring	[0][a]	0.186 ± 0.034	$=\rho_{mo}$	0.267 ± 0.061	262.39	3 vs. 2	1.75 (NS)	1
(4) Equal parent-offspring and sibling-sibling	[0][a]	0.199 ± 0.031	$=\rho_{mo}$	$=\rho_{mo}$	264.04	4 vs. 2	3.40 (NS)	1–2
(5) No parent-offspring	[0][a]	[0][a]	[0][a]	0.278 ± 0.061	288.17	5 vs. 2	27.53*	2
(6) No correlation	[0][a]	[0][a]	[0][a]	[0][a]	308.50	6 vs. 4	44.46*	2

[†]FVC = forced vital capacity. For other definitions, see Tables III and IV. The mean and variance of the residual phenotype are omitted.
[a]Correlation is fixed at zero.
*$P < 0.001$.

TABLE VII. Parameter Estimates (± Standard Deviations) From Segregation Analysis of Residual $Vmax_{50}$/FVC Under Class D Regressive Models[†]

	General (1)	Ousiotypes plus polygenes (2)	Ousiotypes only (3)	Polygenes only (4)	Sporadic (5)
q_A	0.64 ± 0.04	0.93 ± 0.02	0.72 ± 0.05	[1.0][a]	[1.0][a]
τ (AA)	0.28 ± 0.15	0.98 ± 0.02	(1.00)[b]		
τ (AB)	(1.00)[b]	0.59 ± 0.15	0.42 ± 0.08		
τ (BB)	0.29 ± 0.27	(0.00)[b]	0.14 ± 0.22		
μ (AA)	–0.01 ± 0.04	–0.06 ± 0.02	–0.15 ± 0.02	–0.00 ± 0.01	–0.00 ± 0.01
μ (AB)	–0.11 ± 0.03	0.39 ± 0.05	0.08 ± 0.04		
μ (BB)	0.38 ± 0.04	0.23 ± 0.34	0.47 ± 0.06		
σ^2	0.05 ± 0.00	0.06 ± 0.00	0.05 ± 0.00	0.08 ± 0.00	0.08 ± 0.00
ρ_{fm}	0.15 ± 0.10	[0][a]	[0][a]	[0][a]	[0][a]
ρ_{fo}	0.12 ± 0.08	0.14 ± 0.05	[0][a]	0.20 ± 0.03	[0][a]
ρ_{mo}	0.28 ± 0.08	$=\rho_{fo}$	[0][a]	$=\rho_{fo}$	[0][a]
ρ_{sib}	0.23 ± 0.09	$=\rho_{fo}$	[0][a]	$=\rho_{fo}$	[0][a]
–2lnL	236.08	243.00	242.53	264.04	308.50
Models compared		2. vs. 1	3 vs. 1	4 vs. 1	5 vs. 1
LRT		6.92 (NS)	6.45 (NS)	27.96*	72.42**
df		3	4	9–10	10–11

[†]For definitions, see Tables III, IV, and VI.
[a]The parameter is fixed and not estimated in the model.
[b]The parameter is maximized at its boundary value.
*$P < 0.01$.
**$P < 0.001$.

eter estimates under the codominant model predict that the single major locus explains 40.0% of the residual variance and individual-specific environmental effects explain the remaining 60.0% of the residual variance.

DISCUSSION

There is strong evidence of familial aggregation for airway function. However, it has not been clear whether major genes are involved in airway growth. This analysis showed no major gene control of $Vmax_{50}$, which is consistent with our previous findings for FEV_1 and MMFR [Chen et al., 1996a]. MMFR is the average rate of flow during the middle half of a forced expiratory volume maneuver and $Vmax_{50}$ is the instantaneous rate of flow at 50% of total lung volume. Our data indicate that multiple loci and/or common environmental factors are responsible for the familial resemblance of airway function, which is supported by other recent studies. Based on the data from 7,200 subjects from 2,126 families participating in the Framingham Study, Givelber et al. [1996] also found no major gene effect on FEV_1. In a study of 1,163 subjects from 309 nuclear families, Holberg et al. [1996] showed no major gene control for FEV_1 in non-asthmatic families. However, heterogeneity might exist between asthma and non-asthmatic families [Holberg et al., 1996]. When we performed segregation analyses separately in families with and without physician-diagnosed asthma, both showed lack of major genetic effects on FEV_1, MMFR, and $Vmax_{50}$.

The determinants of expiratory flow rate are complicated [Chen et al., 1996a], and involve the interaction of airway size, elastic recoil of the lung, and dynamic

TABLE VIII. Transmission Parameter and Genotype Estimates (± Standard Deviations) From Segregation Analysis of Residual $Vmax_{50}$/FVC Under Class D Regressive Models[†]

		Mendelian transmission			No parent-offspring transmission	
	General (1)	Codominant (2)	Dominant (3)	Recessive (4)	τ (AA) = τ (AB) = τ (BB) (5)	τ (AA) = τ (AB) = τ (BB) = q_A (6)
q_A	0.72 ± 0.05	0.70 ± 0.05	0.09 ± 0.03	0.44 ± 0.06	0.31 ± 0.08	0.06 ± 0.03
τ (AA)	(1.00)[b]	[1.0][a]	[1.0][a]	[1.0][a]	0.35 ± 0.09	$=q_A$
τ (AB)	0.42 ± 0.08	[0.5][a]	[0.5][a]	[0.5][a]	$=\tau$ (AA)	$=q_A$
τ (BB)	0.14 ± 0.22	[0.0][a]	[0.0][a]	[0.0][a]	$=\tau$ (AA)	$=q^A$
μ (AA)	–0.15 ± 0.02	–0.15 ± 0.02	0.33 ± 0.05	0.32 ± 0.05	0.42 ± 0.09	0.01 ± 3.64
μ (AB)	0.08 ± 0.04	0.07 ± 0.04	0.33 ± 0.05	–0.08 ± 0.02	–0.12 ± 0.09	0.40 ± 0.06
μ (BB)	0.47 ± 0.06	0.45 ± 0.06	–0.07 ± 0.02	–0.08 ± 0.02	0.02 ± 0.09	–0.05 ± 0.02
σ^2	0.05 ± 0.00	0.05 ± 0.00	0.05 ± 0.00	0.05 ± 0.00	0.05 ± 0.01	0.06 ± 0.00
–2lnL	242.53	243.76	253.17	258.54	287.03	287.82
Models compared		2 vs. 1	3 vs. 2	4 vs. 2	5 vs. 1	6 vs. 1
LRT		1.23 (NS)	9.41*	14.78**	44.50**	45.29**
df		3–4	1	1	3–4	2–3

[†]For definitions, see Tables III, IV, and VI.
[a]The parameter is fixed and not estimated in the model.
[b]The parameter is maximized at its boundary value.
*$P < 0.01$.
**$P < 0.001$.

airway pressure-area behavior. The considerable variability in maximal expiratory flow rates in normal humans [Black et al., 1974] has been a matter of some interest. Green et al. [1974] found a low correlation between lung volume and maximal expiratory flow, and no obvious relationship between static lung recoil and $Vmax_{50}$, suggesting that there are substantial between-individual differences in airway size and function, independent of lung size. Green et al. [1974] coined the term "dysanapsis" to describe the apparently unequal growth patterns of the tracheobronchial tree and lung parenchyma. Mead [1980] indicated that the airway size/lung volume ratio would be constant and independent of lung volume if there was a perfectly proportional growth of airways and lung parenchyma, and would vary reciprocally with lung volume if airway size and lung volume were independent. Mead [1980] found that the ratio decreased approximately as $(VC)^{-4/3}$, suggesting independence of airway diameter but dependence of airway length on lung size. The dysanapsis was suggested to be a general phenomenon [Knudson et al., 1983].

Airway-parenchymal dysanapsis has been observed not only in adults [Brooks et al., 1988; Castile et al., 1980; Collins et al., 1986; Dolyniuk and Fahey, 1986; Hoffstein, 1986; Knudson et al., 1983; Martin et al., 1987] but also in children [Martin et al., 1988; Pagtakhan et al., 1984]. Martin et al. [1988] found that substantial interindividual variability of maximal expiratory flow rates relative to lung volumes was present in early childhood and remained constant during growth, suggesting that the dysanapsis originates in early childhood. However, whether the airway-parenchymal dysanapsis is inherited and what the form of inheritance is, have not been known.

In this report, we examined the airway vs. parenchyma, reflected by the ratio of $Vmax_{50}$ to FVC, to determine the familial resemblance. There was no significant father-mother correlation for $Vmax_{50}$/FVC, similar to the results for FEV_1, MMFR [Chen et al., 1996a], FVC [Chen et al., 1997], and $Vmax_{50}$. Correlations between first-degree relatives were significant. No significant differences, however, were observed in parent-offspring and sibling-sibling correlations. The narrow heritability was estimated to be 0.40, compared to 0.26 for FEV_1 and 0.34 for MMFR [Chen et al., 1996a].

Segregation analysis was performed by using class D regressive model, to determine whether there were major gene effects on residual $Vmax_{50}$/FVC. The data indicated that ousiotypes explained all the familial resemblance of $Vmax_{50}$/FVC with no residual familial correlations left. Compared to the general model, the polygenic and sporadic models didn't fit the data well. When further examining the transmission probabilities of the ousiotypes based on the ousiotypes only model, we found that the transmission of ousiotypes controlling $Vmax_{50}$/FVC was not different from the Mendelian expectation, while both no-parent-offspring-transmission hypotheses [$\tau(AA) = \tau(AB) = \tau(BB) = q_A$ and $\tau(AA) = \tau(AB) = \tau(BB)$] were rejected. All those results suggest that there is a single locus gene or a cluster of genes working in unison in determination of $Vmax_{50}$/FVC. In addition, a codominant model had a better fit than did dominant and recessive models. The common allele in all these models was associated with low values of $Vmax_{50}$/FVC.

The ratio of $Vmax_{50}$ (a measurement sensitive to airway size) to FVC (a measurement sensitive to lung size) provides information on relative size of airway and parenchyma [Mead, 1980]. Therefore, the results of the segregation analysis that we

conducted for $Vmax_{50}$/FVC suggest that the growth of airway relative to parenchyma, or airway-parenchymal dysanapsis, is under a major genetic control. Our data also suggest that the major gene segregation accounts for all the familial resemblance of the "dysanaptic" growth, which Green et al. [1974] suggested has an embryological basis. Our data consistently show lack of major genetic effects on FEV_1, MMFR, and $Vmax_{50.}$ The putative gene for $Vmax_{50}$/FVC seems not responsible for the interindividual differences in airway size and function other than its disproportionate growth relative to parenchymal size of the lung.

Airway-parenchymal dysanapsis has been suggested to have relevance for the pathogenesis of obstructive airway disease [Brooks et al., 1988; Green et al., 1974; Nishimura et al., 1991]. Airway size, relative to lung size, is one reason for the variability in the response to nonspecific bronchoconstrictors in individuals with respiratory symptoms [Tager et al., 1986]. A recent study also indicated that airway-parenchymal dysanapsis, as measured by MMFR/FVC, was a significant predictor of the degree of bronchial hyperresponsiveness [Litonjua et al., 1996]. Airway hyperresponsiveness is closely related to development of asthma, and may be genetically determined [Lockhart, 1993]. However, no major gene was found to account for the familial component of the transmission of bronchial response to methacholine in humans [Townley et al., 1986], although major genetic control of bronchial hyperresponsiveness was observed in animals [Levitt and Mitzner, 1989]. The linkage of the major genetic mechanism of airway-parenchymal dysanapsis with the genetic determination of airway hyperresponsiveness needs to be investigated in future studies.

A potential predisposition to pulmonary disease related to airway-parenchymal dysanapsis may explain gender-related differences in susceptibility in response to tobacco smoke. Mead [1980] found that there was a marked difference between $Vmax_{50}$ of men and women even when lung size and recoil were taken into consideration. Relatively larger airway size after adjustment for lung size in men than in women has been confirmed by other studies [Brooks et al., 1988; Martin et al., 1987]. Several studies have shown greater effects of smoking in women than in men on lung dysfunction [Buist et al. 1979; Chen et al., 1991; Detels et al., 1981; Glindmeyer et al., 1996; Manfreda et al., 1978] and on morbidity and mortality for chronic obstructive pulmonary disease [Bone et al., 1992; Mannino et al., 1996; Prescott et al., 1996]. Because of intricate relationships between host factors and pulmonary function test variables, the variables of age, height, weight, and other factors were adjusted prior to segregation analysis within gender and generation strata in this analysis. Residuals were calculated within each stratum. It has been suggested that the pattern of airway growth is different between males and females [Brooks et al., 1988]. As children, females have larger central airways than do males, and the airways of adolescent males may undergo a growth spurt, resulting in the adult pattern where the airways of men are larger than those of women [Brooks et al., 1988]. These gender-related issues require further investigation.

Some methodological considerations in this analysis are worth attention. We adjusted a number of host characteristics and environmental factors for each generation and sex group for lung function test variables and used the residuals for segregation analysis. The variance explained by relatively important covariates ranged from 12.4 to 67.1% for $Vmax_{50}$, and from 9.5 to 23.6% for $Vmax_{50}$/FVC. The marked variation and different explanatory variables across the generation and sex groups reflect the

complex nature of determination for lung function. Variables may have different effects between generations, e.g., age positively predicts lung function in children and young adults and negatively predicts lung function in middle-aged and older adults, or may have different effects between sexes, e.g., smoking has a greater effect on lung function in females than in males [Chen et al., 1991; Gold et al., 1996]. Therefore, it is appropriate to preadjust for these variables in each generation and sex group instead of including them in regressive models as covariates. In addition, we also preadjusted for respiratory symptoms and diseases before we conducted the segregation analyses. They can be outcomes of airway-parenchymal dysanapsis, but may also disproportionally affect $Vmax_{50}$ and FVC. When navigating between the Scylla of eliminating part of variance in dysanapsis and the Charybdis of potential confounding effects, we believe that the preadjustment for respiratory symptoms and diseases is a conservative approach. The respiratory symptoms and diseases could also be the surrogate measures for effects of smoking, passive smoking, and other environmental factors on the respiratory system, but the variables representing these effects would not matter in terms of residual calculations.

In this study, the prevalence of wheeze was higher in fathers than in mothers. The opposite was observed for bronchitis and respiratory allergy. If it were true that mothers tended to overreport bronchitis and respiratory allergy, they might overreport other respiratory conditions as well. This did not appear to be the case. Self-reporting of respiratory conditions should be validated in future studies.

Our study provides evidence of a major gene control in determination of airway-parenchymal dysanapsis. Because of its potential importance in the development of obstructive pulmonary disease, further study of genetic mechanisms of airway-parenchymal dysanapsis is well warranted.

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