

## Genetic epidemiology of pulmonary function

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Respiratory diseases are major threats to human health.<sup>1</sup> It is believed that chronic obstructive pulmonary disease (COPD) is both environmental and genetic<sup>2,3</sup>; however, specific genetic factors in the development of COPD have not been clearly identified, except for protease inhibitor types. Alpha<sub>1</sub>-antitrypsin deficiency is rare in the general population<sup>4,5</sup> and accounts for less than 2% of the cases of COPD.<sup>6,7</sup> The molecular genetics of COPD has recently been reviewed by Barnes.<sup>8</sup>

Pulmonary function measures are the most important phenotypes of COPD. The respiratory muscles, the thorax, and the lungs are the components of the ventilatory apparatus which can be evaluated by appropriate function tests.<sup>9</sup> The dynamic functional capacity of the ventilatory apparatus can be assessed by the volume-time or flow-volume manoeuvres. Airflow rates and volumes inhaled or exhaled over specific time intervals provide information on the flow resistive properties of the airways.<sup>10</sup> These pulmonary function measures predict the development of lung diseases<sup>11–13</sup> and overall mortality.<sup>14–18</sup> While the environmental determinants of pulmonary function have been extensively studied—for example, smoking and ambient air pollution—the genetic determinants have recently received increasing attention. Genetic epidemiological studies of pulmonary function are of potential importance in understanding normal pulmonary function and the aetiology and prevention of COPD and other respiratory diseases. This paper reviews

the familial aggregation and segregation of pulmonary function and presents evidence for different influences of heredity on airway function, lung volume, and airway-parenchymal dysanapsis (relative airway size to lung size). Some methodological issues related to segregation analysis are also discussed.

## Family aggregation

## FAMILY STUDIES

A number of family studies have provided evidence for familial resemblance of pulmonary function measures.<sup>19–30</sup> Studies have consistently shown significant parent-offspring and sibling-sibling correlations in lung volume and flow rate measures (table 1). Most studies found that spousal correlations in pulmonary function were trivial, although Higgins and Keller<sup>27</sup> reported a small but significant correlation in forced expiratory volume in one second (FEV<sub>1</sub>) between spouses, and Kauffmann *et al*<sup>21</sup> found significant spousal correlations in residual forced vital capacity (FVC), FEV<sub>1</sub>, and forced expiratory flow between 25% and 75% of the vital capacity (FEF<sub>25–75%</sub>).

One study found that familial correlations in pulmonary function were dependent on familial resemblance of body habitus and were no longer significant after the ponderal index (height/weight<sup>1/3</sup>) was taken into consideration.<sup>28</sup> Other studies found that the familial correlations remained significant after adjustment for both height and weight<sup>22–26</sup> or adjustment for height alone.<sup>21</sup> Over-adjustment could

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Table 1 Family studies in pulmonary function

Reference	Location and year	Study subjects	Lung function indices	Correlations				Comments
				$\rho_{sp}$	$\rho_{mo}$	$\rho_{fo}$	$\rho_{sb}$	
Tager <i>et al</i> <sup>19</sup>	USA, 1976	148 households, 469 subjects	FEV <sub>1</sub> , % FEV <sub>1</sub> score	0.04 0.05	0.18* 0.11	0.25* 0.16*	0.26* 0.19*	FEV <sub>1</sub> (%) less correlated than FEV <sub>1</sub> score
Schilling <i>et al</i> <sup>20</sup>	USA, 1977	376 families, 816 children and their parents	rFVC rFEV <sub>1</sub> rVmax <sub>50</sub>	0.07 0.07 0.07	0.19* 0.17* 0.15*	0.12* 0.11* 0.12*	0.27* 0.21* 0.16*	Separate parent-offspring correlations; smaller ones are selected
Kauffmann <i>et al</i> <sup>21</sup>	France, 1989	945 families, 1160 children and their parents	rFVC rFEV <sub>1</sub> rFEF <sub>25–75%</sub>	0.18* 0.20* 0.23*	0.26* 0.26* 0.21*	0.19* 0.15* 0.16*	0.30* 0.34* 0.27*	Significant spousal correlations
Coultas <i>et al</i> <sup>22</sup>	USA, 1991	733 households, 336 spouse pairs, 1059 parent-child pairs, 412 sib pairs	rFVC rFEV <sub>1</sub>	0.11 0.10	0.26* 0.22*	$=\rho_{mo}$ $=\rho_{mo}$	0.37* 0.24*	Parent-offspring correlations: 6–17 year group
Chen <i>et al</i> <sup>23–25</sup>	Canada, 1996, 1997, 1998	309 families, 1045 subjects	rFVC rFEV <sub>1</sub> rFEF <sub>25–75%</sub> rVmax <sub>50</sub> /FVC	0.08 0.04 0.11 0.11	0.17* 0.11* 0.15* 0.16*	0.18* 0.18* 0.22* 0.25*	0.35* 0.11* 0.19* 0.27*	First degree relative correlations were not significantly different for rFEV <sub>1</sub> , rFEF <sub>25–75%</sub> , and rVmax <sub>50</sub> /FVC
Givelber <i>et al</i> <sup>26</sup>	USA, 1998	1408 families, 5003 adult subjects	rFEV <sub>1</sub>	0.05	0.19*	0.12*	0.22*	Sib-sib correlation was greater than parent-offspring correlation

FEV<sub>1</sub> = forced expiratory volume in one second; FVC = forced vital capacity; FEF<sub>25–75%</sub> = forced expiratory flow between 25% and 75% of the vital capacity; Vmax<sub>50</sub> = maximal expiratory flow rate at 50% of vital capacity;  $\rho_{sp}$  = spousal correlation;  $\rho_{mo}$  = mother-offspring correlation;  $\rho_{fo}$  = father-offspring correlation;  $\rho_{sb}$  = sibling-sibling correlation; r = residual.

\*p<0.05.

Table 2 Twin studies in pulmonary function

Reference	Location and year	Pairs of twins		Lung function indices	Intrapair correlation (difference)		Comments
		MZ	DZ		MZ	DZ	
Man and Zamel <sup>34</sup>	Canada, 1976	10	6	VC (l)	(0.30)	(0.55)*	Difference seems larger for the geometry of larger airways than for smaller ones
				Vmax <sub>60</sub> (l/s)	(0.37)	(1.23)*	
				Vmax <sub>40</sub> (l/s)	(0.30)	(0.63)	
Hubert <i>et al</i> <sup>32</sup>	USA, 1982	127	141	FVC	0.66†	0.08	Correlation in FVC between DZ twins was not significantly different from zero
				FEV <sub>1</sub>	0.62†	0.25†	
Redline <i>et al</i> <sup>33</sup>	USA, 1987	256	158	FVC	0.76†	0.39†	Adjusted for body size and smoking
				FEV <sub>1</sub>	0.71†	0.16	
				FEF <sub>25-75%</sub>	0.52†	0.21	
				FEV <sub>1</sub> /FVC	0.55†	0.18	
				FEF <sub>25-75%</sub> /FVC	0.53†	0.21	
Ghio <i>et al</i> <sup>36</sup>	USA, 1989	47	27	FVC (l)	(0.28)	(0.36)	Differences between MZ and DZ were not significant after adjusting for height
				FEV <sub>1</sub> (l)	(0.26)	(0.34)	
				FEF <sub>25-75%</sub> (l/s)	(0.58)	(0.77)	

MZ = monozygotic twins; DZ = dizygotic twins; VC = vital capacity; FEV<sub>1</sub> = forced expiratory volume in one second; FVC = forced vital capacity; FEF<sub>25-75%</sub> = forced expiratory flow between 25% and 75% of the vital capacity; Vmax<sub>40</sub>, Vmax<sub>60</sub> = maximal expiratory flow rate at 40% and 60% of vital capacity.

\*p<0.05, difference between MZ and DZ.

†p<0.05, difference from zero.

be one reason for the disappearance of familial aggregation of pulmonary function,<sup>22</sup> and different analytical methodology could be another.

Chen *et al*<sup>23-25</sup> compared the mother-offspring, father-offspring, and sibling-sibling correlations in various pulmonary function measures. No significant differences were found in the correlations of airway function measures including the FEV<sub>1</sub>, FEF<sub>25-75%</sub>, and maximal expiratory flow rate at 50% of vital capacity (Vmax<sub>50</sub>). For FVC, however, the sibling-sibling correlation was greater than the parent-sibling correlation, which was consistent with the results from other studies.<sup>20 22 29</sup> This additional resemblance between siblings may be due to shared sibling environment and environmental factors may have different impacts on the lung volume measure than on the flow rate measures.<sup>29</sup> Givelber *et al*<sup>26</sup> found that the sibling-sibling correlation in FEV<sub>1</sub> was greater than parent-offspring correlations. Since the FEV<sub>1</sub> was measured much earlier for the parents (1948-52) than for the offspring (1971-74), measurement error could be larger for data from the parents than those from the offspring due to outmoded spirometric techniques.<sup>26</sup> The results are not consistent in terms of differences between mother-offspring and father-offspring correlations for various pulmonary function measures. Givelber *et al*<sup>26</sup> suggested a greater mother-offspring correlation in FEV<sub>1</sub> compared with the father-offspring correlation. Coultas *et al*<sup>22</sup> and Chen *et al*<sup>23-25</sup> found that there was no significant difference between mother-offspring and father-offspring correlations.

#### TWIN STUDIES

Comparisons of monozygotic (MZ) and dizygotic (DZ) twins can be used to assess the relative importance of genetic and environmental effects, since MZ twins share 100% of genes while DZ twins share only 50%.<sup>31</sup> A higher degree of similarities in MZ twins than in DZ twins suggests a genetic influence on pulmonary function phenotypes. Studies have shown that the intrapair correlation of pulmonary function measures was greater<sup>32 33</sup> and the intrapair difference was smaller in MZ twins

than in DZ twins.<sup>34 35</sup> Only one study<sup>36</sup> showed that the intrapair difference in pulmonary function between DZ twins was not significantly larger than that between MZ twins (table 2).

Two studies of MZ twins have suggested that genetic factors are important in determining susceptibility to airway dysfunction from cigarette smoke.<sup>37 38</sup> Webster *et al*<sup>37</sup> studied 45 pairs of MZ twins and found that the intrapair difference in values of maximal expiratory flow rate at 60% of the vital capacity was small and was similar for smoking pairs and non-smoking pairs. There was a large difference between twins discordant for smoking. In a study of MZ twins raised apart Hankins *et al*<sup>38</sup> examined the FEV<sub>1</sub>, FEF<sub>25-75%</sub>, and maximal expiratory flow rate at 70% of vital capacity and found similar results. However, the absence of DZ twins as a comparison group limits the ability to make strong inferences from these studies.

#### Genetic heritability

Both family and twin studies have clearly shown that pulmonary function including flow rate and lung volume measures are familial. The reason for the familial aggregation can be environmental, genetic, or both. Genetic heritability, which is the proportion of the genetic variance to the total phenotypic variance in a defined population, can be used to quantify the degree of genetic contributions. The genetic variance can be further divided into additive genetic variance, dominance variance, and epistatic variance (interlocus interaction). Heritability in the narrow sense, which is the proportion of additive genetic variance to the total phenotypic variance, is used to measure possible genetic effects not due to major gene segregation.

A number of family studies have examined the degree to which the observed familial aggregation of pulmonary function is attributable to genetic factors and have shown a moderate degree of heritability for various pulmonary function measures (table 3). Based on the data of 439 subjects from 108 families of patients without pulmonary disease, Astemborski *et al*<sup>39</sup> found that additive genetic variation accounted for 28% of the variation in

Table 3 Additive genetic heritability of lung function based on data from family studies

Reference	Location and year	Study subjects	Lung function indices	Additive genetic heritability	Comments
Lewitter and Tager <sup>41</sup>	USA, 1984	404 families, 602 parents, 756 children	FEV <sub>1</sub> score	42–47%	Path analysis; consistent over time
Devor and Crawford <sup>29</sup>	USA, 1984	96 families, 307 subjects	FEF <sub>25–75%</sub> score	42–47%	Path analysis
			rFVC	20%	
Astemborski <i>et al</i> <sup>39</sup>	USA, 1985	108 families, 439 adults	rFEV <sub>1</sub>	17%	Variance components analysis; adult study population
			rFEV <sub>1</sub> /FVC	28%	
Beatty <i>et al</i> <sup>40</sup>	USA, 1987	158 families, 781 subjects	rFEV <sub>1</sub> /FVC	24%	Variance components analysis; ascertained through a proband with obstructive lung disease
			rFEV <sub>1</sub>	9%	
			rFEV <sub>1</sub> /FVC	25%	Path analysis; no inter-generational differences
Cotch <i>et al</i> <sup>42</sup>	USA, 1990	384 families, 978 subjects	rFEV <sub>1</sub> (cross sectional)	36%	
			rFEV <sub>1</sub> (longitudinal)	40%	Path analysis; no substantial changes based on age and smoking status
Coultas <i>et al</i> <sup>22</sup>	USA, 1991	733 households, 336 spouse pairs, 1059 parent-child group pairs, 412 sib pairs	rFVC (non-smoking parents)	43%	
			rFVC (smoking parents)	42%	Class D regressive model
			rFEV <sub>1</sub> (non-smoking parents)	65%	
			rFEV <sub>1</sub> (smoking parents)	44%	
Chen <i>et al</i> <sup>23–25</sup>	Canada 1996, 1997, 1998	309 families, 1045 subjects	rFEV <sub>1</sub>	26%	
			rFEV <sub>50</sub>	36%	
			rFEF <sub>25–75%</sub>	34%	
			rVmax <sub>50</sub> /FVC	40%	

FEV<sub>1</sub> = forced expiratory volume in one second; FVC = forced vital capacity; FEF<sub>25–75%</sub> = forced expiratory flow between 25% and 75% of the vital capacity; Vmax<sub>50</sub> = maximal expiratory flow rate at 50% of vital capacity; r = residual.

residual FEV<sub>1</sub> and 24% of the variation in residual FEV<sub>1</sub>/FVC. The estimators were smaller among families of patients with airway obstruction disease.<sup>40</sup> Four studies used the path analysis approach to identify hereditary and environmental sources of familial aggregation for pulmonary function traits. Lewitter *et al*<sup>41</sup> studied 404 nuclear families including 602 parents and 756 children and found that 42–47% of the variability in FEV<sub>1</sub> and FEF<sub>25–75%</sub> could be explained by underlying genetic differences among the individuals. Another analysis by Cotch *et al*<sup>42</sup> showed a similar estimate of heritability of 36–40% for FEV<sub>1</sub> and no significant difference between white and black individuals. Coultas *et al*<sup>22</sup> found an increased genetic variance in smokers. The genetic variances for FVC and FEV<sub>1</sub> were 10% and 25% greater for smokers than for non-smokers, respectively.<sup>22</sup> The heritability estimates of pulmonary function measures were lower in another study. Based on the data from 305 men and 339 women Devor and Crawford<sup>29</sup> estimated that approximately 20% and 17% of the variation in FVC and FEV<sub>1</sub>, respectively, was due to the transmission from parents to offspring. Smoking and age could alter the familial aggregation of pulmonary function, and different study designs may be the reason for the discrepancy.<sup>22</sup> Shared heritable factors might not only influence the lung growth and development, but also the decline in pulmonary function in adults.<sup>22</sup> In the recent Humboldt Family Study of 309 nuclear families Chen *et al*<sup>23–25</sup> used a class D regressive model and estimated the additive genetic heritability as 26–40% for FEV<sub>1</sub>, Vmax<sub>50</sub>, FEF<sub>25–75%</sub>, and Vmax<sub>50</sub>/FVC.

The heritability estimates for different measures of pulmonary function in twin studies have been inconsistent. Hubert *et al*<sup>29</sup> studied 127 MZ and 141 DZ male twin pairs aged 42–56 years and estimated the heritability to be as high as 77% for FEV<sub>1</sub>. In a study of 256 MZ and 158 DZ adult twins Redline *et al*<sup>33</sup> found that 40–75% of the measured variability in pulmonary function was accounted for by genetic influences. In another study, however, Ghio *et al*<sup>36</sup> found that the heritability was not

significant after adjustment for height in 74 university student pairs of twins with an average age of 20 years. Twin studies usually provide an inflated estimate of heritability<sup>43</sup> because twins share very similar, if not the same, exposures in utero, and share a more homogeneous living environment than other individuals. Since heritability is the ratio of the genetic variance to the total variance, heritability increases with decreasing variance due to environment. The heritability estimates can be more biased if the effects of environmental factors are more similar in MZ twins than in DZ twins. Some studies have shown that MZ twins have a greater concordance in smoking habits than DZ twins.<sup>32–44</sup> Correlational analysis of the distribution of given traits within family members is one way to increase the robustness of the twin data analysis.<sup>45</sup>

Heritability is a population-specific parameter and is affected by the environment in which the population developed. In addition, if there is an interaction between genotype and environment—for example, smoking may alter the genetic effects on pulmonary function—it is almost impossible to separate the genetic variance and environmental variance completely. Because of these limitations, heritability estimation should be explained with caution.

### Major genetic effects on pulmonary function

#### SEGREGATION ANALYSIS

Genetic effects may be the consequence of a single gene (a major gene), a small number of genes (oligogenes), or a large number of genes each with a small effect (polygenes). In segregating families the relatively large effects of major genes should be detectable using the tools of segregation analysis, while the more general predictions of polygenes predict the overall patterns of correlation among relatives. The classical segregation analysis is used to identify Mendelian ratios when a phenotype is controlled by a major gene, which is traditionally assumed to result from segregation at a single locus having two alleles, A and B. The likelihood method is frequently used in

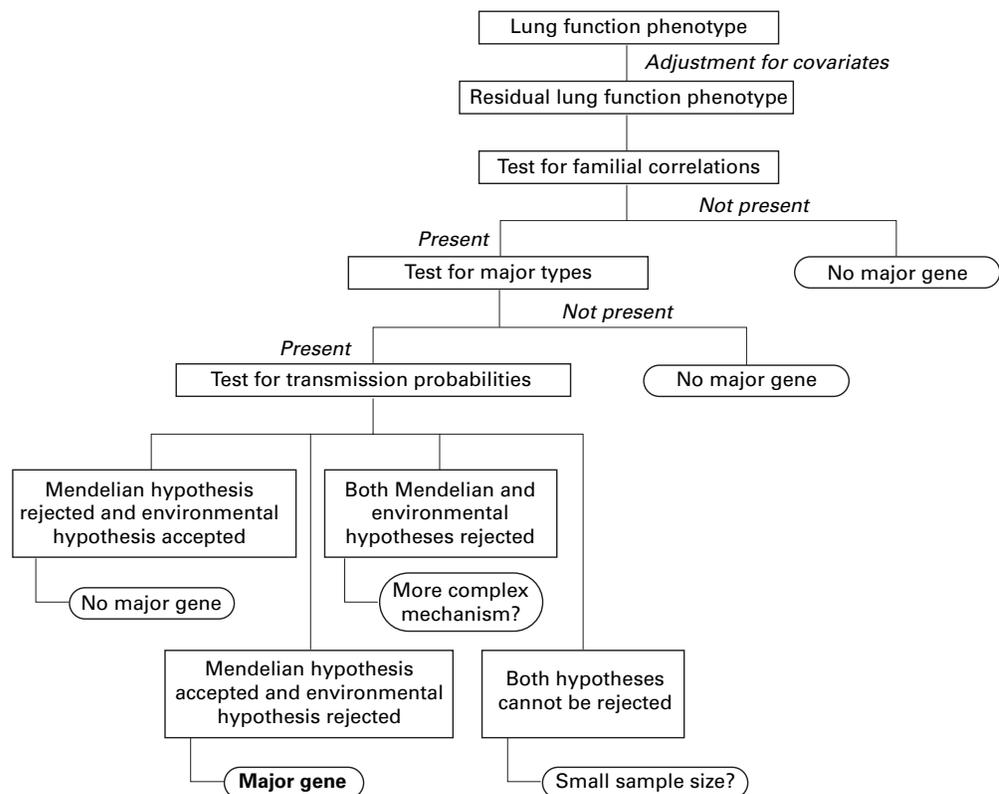


Figure 1 Analytical strategy of segregation analysis for pulmonary function phenotypes.

segregation analyses, and other approaches are also proposed including generalised estimating equations.<sup>46</sup>

There are various strategies of model evaluation. Figure 1 gives an example of the analytical strategy for a segregation analysis. If a pulmonary function phenotype is familial, the next step is to determine mixtures of phenotypic distribution. Before there is evidence of Mendelian transmission, a more general term called “ousiotypes” or “types” has been suggested to describe the mixtures of distribution.<sup>47</sup> A key assumption is that individuals represent different ousiotypes or essential types that may reflect different genotypes for Mendelian models. The parameters of transmission probabilities can therefore be estimated, which are the probabilities of a parent transmitting the A allele to an offspring. Under Mendelian transmission,  $\tau(AA) = 1$ ,  $\tau(AB) = 0.5$ , and  $\tau(BB) = 0$ . A non-transmitted environmental effect was obtained with the three transmission probabilities being equal ( $\tau(AA) = \tau(AB) = \tau(BB)$ ). The process of segregation analysis involves testing a series of models of inheritance, including Mendelian models such as dominant and recessive models plus non-genetic models, to identify the best fitting and most parsimonious model for a given set of family data.

#### AIRWAY FUNCTION

Based on data from 85 families with COPD and 56 families without pulmonary disease, Rybicki *et al*<sup>48</sup> used the class A regressive model and found that there were major genetic effects on FEV<sub>1</sub>, and the major gene effects could explain all of the familial correlations for FEV<sub>1</sub>

in families ascertained through a COPD proband. In families of patients without pulmonary disease, however, there were no familial correlations for FEV<sub>1</sub> and therefore no evidence of genetic control of FEV<sub>1</sub>.<sup>48</sup> These results suggested substantial aetiological heterogeneity in the control of FEV<sub>1</sub> between the families with COPD and those without the disease. The reasons for the lack of familial correlations in the families of those without COPD and its discrepancy with other studies were not discussed in the report.<sup>48</sup>

The class A regressive model makes an assumption that siblings are correlated only through common parentage. This restriction, in the absence of a major gene, may lead to false inference of a major gene.<sup>49</sup> Chen *et al*<sup>23 25</sup> studied 309 young families and used the class D regressive model in the segregation analysis, which allows additional correlation among siblings and is characterised by equal sibling-sibling correlations. The data have suggested that FEV<sub>1</sub>, FEV<sub>25-75%</sub> and Vmax<sub>50</sub> are more likely to be controlled mainly by multiple loci—namely, many independent genes—each contributing in an additive fashion and/or common environmental factors are responsible for the familial resemblance of airway function. In a recent report of 5003 subjects from 1408 families in the Framingham study Givelber *et al*<sup>26</sup> provided consistent results. The most parsimonious model for FEV<sub>1</sub> included non-transmitted major types and residual familial correlations, and the Mendelian hypothesis was rejected.<sup>23</sup> Based on the data from 309 families (1163 individuals) in the Tucson children’s respiratory study Holberg *et al*<sup>50</sup> also suggested

polygenic control of FEV<sub>1</sub> or common environmental factors resulting in the familial aggregation of the trait; however, genetic heterogeneity might exist between families with and without asthmatic members.<sup>50</sup>

Silverman *et al*<sup>51</sup> studied  $\alpha_1$ -antitrypsin deficient individuals in 44 nuclear families and found that there was an additional major gene other than the Pi locus influencing FEV<sub>1</sub>. However, the major gene effect diminished after adjustment for pack-years of smoking.

#### LUNG VOLUME

Based on the data from 309 nuclear families Chen *et al*<sup>24</sup> performed a segregation analysis for FVC, a measure of lung volume. Models with both major types and familial correlations gave the best fit for the data. However, neither Mendelian nor no parent-offspring transmission hypotheses were rejected. Heterogeneity may exist between families. The authors calculated the likelihood under the Mendelian model ( $L_{\text{Mendelian}}$ ) and the environmental model ( $L_{\text{environmental}}$ ) and used the ln-likelihood values to sort families into groups that support one model of inheritance over another. In a subset of 196 families with a  $\ln(L_{\text{Mendelian}}/L_{\text{environmental}})$  value greater than zero, the families suggested a Mendelian gene leading to lower values of FVC, and the single locus explained all the familial aggregation of residual FVC. In the other 113 families in whom the  $\ln(L_{\text{Mendelian}}/L_{\text{environmental}})$  value was less than zero the Mendelian hypothesis could not be rejected and the Mendelian model showed that a single locus accounted for all familial correlations except for the sibling-sibling correlation. However, the environmental hypothesis could not be rejected for this subgroup of families although the Mendelian model had a better fit than the environmental model based on the values of the Akaike's information criterion (AIC, see later).<sup>24</sup> The approach of dividing the families into two groups based on an individual likelihood ratio might remove certain confounding effects and increase the statistical power of detecting a major gene effect.<sup>24</sup>

#### AIRWAY-PARENCHYMAL DYSPANAPSIS

Green *et al*<sup>11</sup> found a low correlation between lung volume and maximal expiratory flow, and no obvious relationship between static lung recoil and Vmax<sub>50</sub>, suggesting that there are substantial differences between individuals in airway size and function that are independent of lung size. Disproportionate but physiologically normal growth of airway and parenchymal components suggests a "dysanaptic" growth which may have an embryological basis.<sup>11</sup> The concept of airway-parenchymal dysanapsis was advanced by Mead<sup>52</sup> who reasoned that subjects with large lungs do not necessarily have larger airways than those with small lungs. He used Vmax<sub>50</sub>/(VC × Pst(L)<sub>50</sub>) as an index of airway-parenchymal dysanapsis in which Vmax<sub>50</sub> is the maximal expiratory flow rate at 50% of total volume and Pst(L)<sub>50</sub> is the maximal flow static recoil pressure characteristic at 50% of vital capacity (VC). Green *et al*<sup>11</sup> have shown that lung static recoil contributes

little to the variability between individuals and that the major variability in maximum flows is attributable to airway dimensions. The correlation between Vmax<sub>50</sub>/VC and Vmax<sub>50</sub>/(VC × Pst(L)<sub>50</sub>) is high, ranging from 0.78 to 0.84.<sup>53</sup>

The dysanapsis is a general phenomenon. Airway-parenchymal dysanapsis has been observed both in adults<sup>12 54-59</sup> and children.<sup>60 61</sup> Martin *et al*<sup>60</sup> found substantial interindividual variability of maximal expiratory flow rates relative to lung volumes during early childhood which remained constant during growth, suggesting that the dysanapsis originates in early childhood.

Chen *et al*<sup>25</sup> examined the major gene effects on the ratio of Vmax<sub>50</sub> to FVC. There was evidence for mixtures of distribution while the polygenic and sporadic model did not give a good fit to these data. The transmission of ousiotypes for Vmax<sub>50</sub>/FVC was not different from the Mendelian expectation, and the no parent-offspring transmission hypothesis was rejected, suggesting that there is a single locus gene or a cluster of genes working in unison to determine Vmax<sub>50</sub>/FVC.

It has been suggested that airway-parenchymal dysanapsis might have relevance for the pathogenesis of obstructive airway disease.<sup>11 12</sup> A study by Litonjua *et al*<sup>3</sup> indicated that airway-parenchymal dysanapsis, as measured by MMFR/FVC, was a significant predictor for the degree of bronchial hyperresponsiveness.

#### METHODOLOGICAL ISSUES

##### *Adjustment for covariates*

Pulmonary function phenotypes are most likely to be multifactorial, controlled by both genetic and environmental factors. Various factors including host characteristics, environmental factors, and history of respiratory symptoms and disease influence these pulmonary function measures. Adjustment for these variables is always a challenge. One approach is to include these variable covariates in regressive models; however, most of the variables tend to have inconsistent effects on pulmonary function measures in different age and sex groups. For example, body weight shows both "muscularity effect" (increase in pulmonary function with increasing weight) and "obesity effect" (decrease in pulmonary function with increasing weight). There is more "muscularity effect" than "obesity effect" in children and young adults but more "obesity effect" than "muscularity effect" in older adults, which is sex related.<sup>62</sup> Cigarette smoking has a sex related effect on pulmonary function measures.<sup>63 64</sup> Age itself positively predicts pulmonary function in children and young adults and negatively predicts pulmonary function in middle aged and older adults. Clearly, these variables cannot be appropriately adjusted by including them in the same regressive models in a segregation analysis. Preadjustment for the variables in different age and sex groups is therefore preferred. The adjusted values are used to fit models of inheritance. The relative importance of the covariates in relation to pulmonary function phenotype varies across age and sex

groups, and this is reflected by the proportion of variation explained by these factors. Most studies of pulmonary function preadjusted these covariates including smoking, one of the most important determinants, in the segregation analyses.<sup>23-26 48 50</sup>

It is debatable whether or not to adjust for history of respiratory symptoms and disease. A history of respiratory symptoms and disease may reduce pulmonary function but it can also be a surrogate measure for the effects of smoking and other environmental factors on the respiratory system. Adjustment for these variables may eliminate some confounding effects but may also reduce the variance of pulmonary function phenotypes unnecessarily. Comparisons of adjusted and unadjusted results are always helpful.

#### Selection of parsimonious models

The likelihood ratio test is usually used to select the most parsimonious model, which is minus twice the difference in the log<sub>e</sub> likelihood (ln L) between models before and after reducing parameters. The test is based on a comparison of strictly hierarchical models. For several alternative non-hierarchical models the better fitting model is considered with a lower value of the Akaike's information criterion (AIC =  $-2 \times \ln L + 2 \times$  number of parameters estimated).<sup>65</sup> Although the AIC is not a statistical test and therefore provides no statistical inference, it is useful in identifying the most parsimonious model.

#### Statistical power

In segregation analysis a series of models of inheritance are fitted and the most parsimonious is chosen to explain the familial aggregation of a pulmonary function phenotype. Tests are typically based on "goodness of fit" measures and a type II error occurs when the genetic model is incorrect, but statistical testing fails to reject it because of small sample size.<sup>28</sup> Statistical power for segregation analysis is related to the size of gene effect and sample size.<sup>66</sup> Nuclear families with larger sibships are generally more informative<sup>31</sup>; however, the total number of subjects rather than sibship size per se may have more influence on the power.<sup>67</sup> Large sample size increases the power in discriminating the completing model.

#### Gene-environmental interaction

A previous study has documented gene-environment interactions in COPD.<sup>68</sup> Another study has suggested that a gene-environment interaction may influence pulmonary function.<sup>47</sup> The pulmonary function phenotype expression of a gene may therefore depend on environmental variables such as smoking. Ignoring gene-environment interactions may result in underestimating the genetic effects on quantitative traits.<sup>69</sup>

#### Conclusions and future directions

Both family studies and twin studies have shown familial aggregation of various measures of pulmonary function. There is a moderate degree of genetic heritability for these pulmo-

nary function measures. However, genetic factors may have different influences on phenotypes of airway function, lung volume, and airway-parenchymal dysanapsis. Airway function phenotypes are more likely to be controlled by many loci with no major gene effects and/or are due to common environmental factors in "normal" families. Aetiological heterogeneity may exist in families with COPD or asthma and heredity may have different effects on normal airway function and airway dysfunction. There is evidence of major gene control of phenotypes of airway-parenchymal dysanapsis and lung volume. It would be interesting to investigate further the different effects of heredity on various pulmonary function phenotypes and their potential linkage to diseases of the lung. In particular, researchers should seek biological evidence for major gene controls of lung volume and airway-parenchymal dysanapsis of the lung.

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