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Stability of Genetic Influences on Pulmonary Function in a Longitudinal Study of Octogenarian Twins

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Abstract

Using data from the first four waves of the OCTO-Twin study (twins 80+ years), the present study investigated the stability and change of genetic and environmental contributions to pulmonary function. Using a genetic simplex model, variance in peak expiratory flow (PEF) at each wave was decomposed into additive genetic and non-shared (specific) environmental factors. Additionally, this analysis distinguished the source of these influences, either from previous waves (transmissions) or from novel influences at each wave (innovations). At each time point (except wave 1), the genetic variance was due to genetic transmissions from prior time points. Conversely, the specific environmental variance in PEF at each time point was mainly due to environmental innovations. These results imply that genetic factors contribute to the stability of pulmonary function over time while environmental factors contribute to its change.

Introduction

Pulmonary function is considered to be a significant biomarker of aging and is shown to be related to physical, cognitive, and psychological functioning in older cohorts (Anstey et al., 2004; Cook et al., 1995; Seeman et al., 1994). Numerous studies have found normal pulmonary function to be influenced by genetic factors. A meta-analysis performed by Chen (1999) identified approximately fifty studies that examined the genetic epidemiology of pulmonary function in family studies and twins. The heritability of lung function was between 17% – 75% across all studies (Chen, 1999). Moderate to high heritabilities have also been found in older populations (McClearn et al., 1994). Longitudinal studies of the heritability of pulmonary function have reported differential findings. Gottlieb et al. (2001) reported only modest genetic influences on the rate of change in lung function over several decades. Finkel et al. (2003), in a primarily older sample aged 50–90 years old, found that genetic factors significantly influenced mean values and rate of decline in lung function. There is also evidence for differential genetic effects among various pulmonary function phenotypes, including forced vital capacity (FVC), forced expiratory volume (FEV₁), and peak expiratory flow (PEF) (Chen, 1999).

The purpose of this study is to extend the accumulated evidence concerning longitudinal changes in the genetic variance of pulmonary function as indexed by peak expiratory volume (PEF), or the rate in which an individual can exhale. This study will specifically examine the stability and change of genetic and environmental contributions to pulmonary function in a sample of twins ages 80 and older.

Methods

The sample for this study was obtained from the first four waves of the longitudinal study, “Origins of Variance in the Old-Old: Octogenarian Twins” (OCTO-Twin Study; McClearn et al., 1997), which was drawn from the Swedish Twin Registry. Mean ages for each wave, respectively, were 83, 85, 87, and 89 years. In this study, there are more females than males at each wave (Wave 1–4, respectively, 159M/286F, 130M/220F, 86M/155F, 60M/131F). Lung function was evaluated by obtaining peak expiratory flow rate (PEF) readings, which measure how fast an individual can breathe out. Three separate attempts were measured with the maximum measure used for the present analyses.

Statistical analysis

Using a twin design allows for decomposition of the phenotypic variance of a trait into additive genetic (A), shared environmental (C) and non-shared environmental (E) factors (Neale et al., 2002). Additive genetic effects refer to the total effects of multiple alleles on a trait. Monozygotic twins (MZ) are assumed to share 100% of their segregating genes, while dizygotic twins, on average, shared 50%. Both MZ and DZ twins are assumed, by definition, to share 100% of their shared environment, or non-genetic effects that would make twins more similar. However, these influences tend to be very small in older populations and will not be included in the present study (Rowe, 1994). Non-shared environmental factors refer to non-genetic influences that make each twin unique and different from one another; this factor also includes measurement error. Quantitative genetic modeling programs, such as Mx (Neale et al., 2002), utilize maximum likelihood methods to estimate the magnitude of each of these variance components. In this study, a genetic simplex model (Boomsma and Molenaar 1987) was applied to the data. In this model, genetic and environmental influences both novel and specific to each wave (innovations) and shared with previous waves (transmissions) can be estimated.

Results

Male PEF mean values (in liters/minute) were substantially higher than female PEF values for all testing occasions (Wave 1: 387M/281F, Wave 2: 396M/297F, Wave 3: 391M/292F, Wave 368M/263F). However, only in waves 3 and 4 did this mean difference achieve statistical significance. To note, all means were adjusted for age, height, smoking status and lung disease status. Additionally, PEF at each wave was significantly correlated ($p < 0.05$) with PEF at the previous wave, with correlation estimates ranging from 0.60–0.69. Intraclass correlations between MZ and DZ pairs were also calculated. The correlations were as follows: Males Wave 1–4, respectively, 0.48*MZ/0.04DZ, 0.71*MZ/0.66*DZ, 0.52MZ/0.66*DZ, and 0.86*MZ/0.49DZ; Females Wave 1–4, respectively, 0.27*MZ/0.21DZ, 0.45*MZ/0.24*DZ, 0.72*MZ/0.35*DZ, and 0.61*MZ/0.23DZ. In general, monozygotic twin (MZ) PEF correlations were higher than those of dizygotic twins (DZ); however, except for Wave 1, these differences did not achieve statistical significance.

Model fitting

Model fit was judged by the estimated -2 log likelihood ($-2LL$), which follows a χ^2 distribution. First, a full model that included all parameters and that also calculated separate

(unequal) parameters between males and females was estimated ($-2LL = 2912$, $df = 1189$). All sub models were then compared to this full model; a significant $-2LL$ change from the full model indicates a worse fit of the sub model, while a non-significant change indicates a better fit of the sub model. The first sub model examined if all male and female parameters could be equated ($\Delta-2LL = 42$, $\Delta df = 14$, $p < 0.0005$). This sub model had a significantly worse fit, meaning all sex specific parameters could not be equated. Further analysis revealed that sex differences were specifically occurring in genetic innovation parameters at Wave 1. Sub models that eliminated both genetic transmission ($\Delta-2LL = 187$, $\Delta df = 6$, $p < 0.0005$) and environmental transmission ($\Delta-2LL = 67$, $\Delta df = 6$, $p < 0.0005$) parameters also had significantly worse fits. This indicates that genetic and environmental influences from the previous waves are contributing to the genetic and environmental variance of subsequent waves. A sub model eliminating specific, innovation genetic parameters at each wave, except Wave 1, ($\Delta-2LL = 2$, $\Delta df = 6$, $p > 0.05$) did not significantly worsen the model fit; this suggests that for each wave of PEF, the genetic variance is completely accounted for by the genetic influences at Wave 1. A model eliminating environmental specific parameters was not possible because this parameter also includes error variance and therefore must always be retained in the model. The final and best fitting genetic simplex model ($\Delta-2LL = 21$, $df = 16$, $p > 0.05$) is shown in Figure 1. Figure 2 illustrates the proportions of lung function variance accounted for by genetic and environmental factors. The total genetic variance for PEF at each occasion was higher for males than females.

Discussion

This study quantified genetic and environmental sources of variance in repeated measures for lung function assessed by peak expiratory flow rate (PEF) in an octogenarian Swedish twin sample. Results demonstrated both genetic factors stable over an 8-year time span and wave specific environmental factors contributed to the total phenotypic variance at each wave for PEF.

This study also revealed possible sex differences in pulmonary function in old age and in its genetic influences. First, mean values of pulmonary function were higher in males and females. Additionally, the genetic variance of pulmonary function in men was higher than that in women. This suggests the variance in pulmonary function in women is more sensitive to environmental influences. Further research is necessary to uncover what environmental influences may more greatly affect lung function in women than in men. Another interesting finding was that the proportion of variance accounted for by environmental transmission factors increased from Wave 2 to Wave 3 but markedly decreased in Wave 4. Statistically, this could be due to low sample sizes at this final wave. However, another potential explanation could be a survivor effect. The average age at this wave was 89 years old; there may be something essentially different about individuals who have survived to this wave of measurement.

In conclusion, this study demonstrated that genetic effects from previous waves accounted for the majority of the genetic variance in PEF, while the total environmental variance was mainly composed of specific environmental influences occurring at each testing interval. In other words, while genetic influences on pulmonary function were stable over time, the change pulmonary function is primarily dictated by non-genetic, environmental factors. This impact of environmental influences suggests that modifications can be made through prevention and intervention programs in order delay or lessen the decline of pulmonary function in the elderly, which could result in increased health and lifespan.

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Figure 1.

Genetic simplex model for peak expiratory flow (PEF) for one twin over four waves.

$A_1, E_1, \dots$ refer to the latent genetic and environmental influences on the variance in PEF at each wave.

$a_1, e_1, \dots$ refer to parameters estimates of the total genetic and environmental influences for PEF at each wave.

$a_{1s}, e_{1s}, \dots$ refer to genetic and environmental parameters estimates specific to each wave.

$a_{1tr}, e_{1tr}, \dots$ refer to parameters estimates of the genetic and environmental variance transmitted from the prior wave.

All parameter estimates are unstandardized.

Figure 2.
Proportion of total variance in peak expiratory flow accounted for by additive genetic and non-shared environmental innovations and transmissions, by gender.