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Familial aggregation of $\dot{V}O_{2}\text{max}$ response to exercise training: results from the HERITAGE Family Study

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Maximal O$_2$ uptake ($\dot{V}O_{2}\text{max}$) varies considerably among sedentary adults. Age, sex, body mass, and body composition all contribute to this heterogeneity. In a recent report (4), our laboratory has also shown that there is significant familial aggregation for $\dot{V}O_{2}\text{max}$ in the sedentary state even when the data are adjusted for age, sex, body mass, and body composition. These observations were derived from the HERITAGE Family Study, and they indicate that the heritability of $\dot{V}O_{2}\text{max}$ among sedentary adults after adjustment for the above covariates could be as high as 50%, although this value is undoubtedly inflated by nongenetic familial factors.

However, no data have been reported as of yet on the familial resemblance of the $\dot{V}O_{2}\text{max}$ response to a standardized training program in previously sedentary people. There are reasons to believe that the trainability of $\dot{V}O_{2}\text{max}$ would be characterized by a significant level of familial aggregation. For instance, members of the same pair of identical twins are significantly more alike than are unrelated individuals in the $\dot{V}O_{2}\text{max}$ increase after exposure to a standardized training program. This statement was confirmed by the results of three different experimental studies. In the first, 10 pairs of monozygotic twins were trained for 20 wk with a standardized endurance training program (10). In the second, six pairs of identical twins were endurance trained for 15 wk to verify whether the results of the first study could be replicated (7). Finally, in the third study, 14 pairs of monozygotic twins were trained for 15 wk with a high-intensity intermittent program to examine whether the findings of a significant intrapair resemblance in the $\dot{V}O_{2}\text{max}$ gain could be found with a different training regimen (11). The findings of all three studies are remarkably concordant: the intraclass correlations for the intrapair resemblance in the $\dot{V}O_{2}\text{max}$ changes with training range from 0.65 to 0.77. The F ratios of the between-pair variance in $\dot{V}O_{2}\text{max}$ gain to the within-pair variance are quite similar with a range from 6 to 9 (5).

Based on these intervention studies with identical twins, we hypothesized that the $\dot{V}O_{2}\text{max}$ response to a standardized training regimen would exhibit familial aggregation with some families characterized by a high-trainability pattern and others by low responsiveness. The purpose of this study was to test this hypothesis by using the data on Caucasians from the HERITAGE Family Study that were obtained on subjects in the sedentary state and after 20 wk of standardized endurance training.

METHODS

Sample. The HERITAGE Family Study was designed to investigate the role of the genotype in cardiovascular, metabolic, and hormonal responses to aerobic exercise training and the contribution of regular exercise to changes in selected cardiovascular disease and diabetes risk factors. Five centers, located at Indiana University, Laval University, University of Minnesota, Texas A&M University, and Washington University, are involved in the HERITAGE Family Study consortium. The study design, sample, and protocol have been described earlier (6).

A total of 481 individuals from 98 two-generation families of Caucasian descent (236 men, 245 women) were available for this study. The following criteria were applied to screen subjects for participation. First, individuals were required to be between the ages of 17 and 65 yr (17–40 yr of age for

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Means and SD for unadjusted data

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Fathers (n = 95)</th>
<th>Mothers (n = 86)</th>
<th>Sons (n = 141)</th>
<th>Daughters (n = 159)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr</strong></td>
<td>53.4 5.4</td>
<td>52.0 4.9</td>
<td>25.4 6.1</td>
<td>25.5 6.4</td>
</tr>
<tr>
<td><strong>V\textsubscript{O2max}, ml O\textsubscript{2}/min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2,618.9 451.1</td>
<td>1,639.5 256.8</td>
<td>3,294.2 497.3</td>
<td>2,063.0 306.7</td>
</tr>
<tr>
<td>Postexercise</td>
<td>2,993.0 484.2</td>
<td>1,939.0 287.8</td>
<td>3,780.3 517.6</td>
<td>2,433.6 368.4</td>
</tr>
<tr>
<td>Response</td>
<td>374.1 204.8</td>
<td>299.5 159.7</td>
<td>486.1 246.7</td>
<td>370.7 194.0</td>
</tr>
</tbody>
</table>

V\textsubscript{O2max}, maximal \textsubscript{O2} uptake. Significant mean differences between father and son or between mother and daughter (within-sex comparisons) for all values (P < 0.01); significant mean differences between father and mother or between son and daughter (within-generation comparisons) for all values (P < 0.01).
the log likelihood (−2 ln L) obtained under the two models. The likelihood ratio is approximately distributed as a \( \chi^2 \), with the degrees of freedom being equal to the difference in the number of parameters estimated in the two models. In addition to the likelihood ratio test, Akaike's information criterion (AIC), which is \(-2 \ln L \) plus twice the number of estimated parameters, was used to compare nonnested models. The "best" model is the one with the smallest AIC (1).

The general model (model 1) and several null hypotheses were fitted to the data. Sex differences were evaluated in models 2–4; i.e., model 2 tests for no sex differences in the offspring, model 3 tests for no sex differences in the parents or offspring, and model 4 tests for no sex and no generation differences. In model 5, all eight correlations are equated, testing a single correlation hypothesis. Several models were also included to test for maternal inheritance, where mother-offspring and sibling correlations are expected to be equal. In particular, model 6 tests for a maternal mode of inheritance without any assumptions regarding the father's contribution. Maternal inheritance was further tested under the assumptions that the father-offspring correlations are independent of sex in model 7, that the father's contribution is entirely environmental in model 8, and that the father-offspring and spouse correlations are zero in model 9. Finally, additional hypotheses testing the strength of the familial resemblance were conducted by familial class, including no sibling resemblance in model 10, no parent-offspring resemblance in model 11, and no spouse resemblance in model 12. A parsimonious model was derived by combining nonrejected null hypotheses. Maximal heritability was computed by using the familial correlations from the most parsimonious model. This estimate includes both genetic and familial environmental sources of variance and is adjusted for the degree of spouse resemblance.

**RESULTS**

Means and SDs for the baseline, posttraining, and \( \dot{V}O_2 \max \) response are presented in Table 1. In each of the models testing the response \( \dot{V}O_2 \max \) adjusted by age and sex, the log likelihood and degrees of freedom (df) are reported, followed by the likelihood ratio test (\( \chi^2 \)), its associated probability (P), and Akaike's information criterion (AIC).

![Graphs showing differences in \( \dot{V}O_2 \max \) response](image1.png)

![Graph showing distribution of subjects](image2.png)

Table 2. Model-fitting summary for the response \( \dot{V}O_2 \max \)-adjusted phenotypes

<table>
<thead>
<tr>
<th>Model</th>
<th>Response ( \dot{V}O_2 \max ) Adjusted by Age and Sex</th>
<th>df</th>
<th>( \chi^2 )</th>
<th>P</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>General model</td>
<td></td>
<td>16.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>( fs = fd ), ( ms = md ), ( ss = dd = sd )</td>
<td>4</td>
<td>4.91</td>
<td>0.297</td>
<td>12.91</td>
</tr>
<tr>
<td>3</td>
<td>( fs = fd ), ( ms = md ), ( ss = dd = sd )</td>
<td>5</td>
<td>6.35</td>
<td>0.274</td>
<td>12.35</td>
</tr>
<tr>
<td>4</td>
<td>( fs = fd ), ( ms = md = ss = dd = sd )</td>
<td>6</td>
<td>11.53</td>
<td>0.073</td>
<td>15.53</td>
</tr>
<tr>
<td>5</td>
<td>( fm = fs = fd = ms = md = ss = dd = sd )</td>
<td>7</td>
<td>13.89</td>
<td>0.053</td>
<td>15.89</td>
</tr>
<tr>
<td>6</td>
<td>( ms = md = ss = dd = sd )</td>
<td>4</td>
<td>5.14</td>
<td>0.273</td>
<td>13.14</td>
</tr>
<tr>
<td>7</td>
<td>( fs = fd ), ( ms = md = ss = dd = sd )</td>
<td>5</td>
<td>6.74</td>
<td>0.241</td>
<td>12.74</td>
</tr>
<tr>
<td>8</td>
<td>( fm = fs = fd ), ( ms = md = ss = dd = sd )</td>
<td>6</td>
<td>11.19</td>
<td>0.083</td>
<td>15.19</td>
</tr>
<tr>
<td>9</td>
<td>( fm = fs = fd = 0 ), ( ms = md = ss = dd = sd )</td>
<td>7</td>
<td>16.75</td>
<td>0.019</td>
<td>18.75</td>
</tr>
<tr>
<td>10</td>
<td>( ss = dd = sd = 0 )</td>
<td>3</td>
<td>30.96</td>
<td>&lt;0.001</td>
<td>40.96</td>
</tr>
<tr>
<td>11</td>
<td>( fs = ms = md = 0 )</td>
<td>4</td>
<td>10.17</td>
<td>0.038</td>
<td>18.17</td>
</tr>
<tr>
<td>12</td>
<td>( fm = 0 )</td>
<td>1</td>
<td>9.77</td>
<td>0.002</td>
<td>23.77</td>
</tr>
</tbody>
</table>

Parsimonious model

<table>
<thead>
<tr>
<th>Model</th>
<th>Response ( \dot{V}O_2 \max ) Adjusted by Age and Sex</th>
<th>df</th>
<th>( \chi^2 )</th>
<th>P</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>( fs = fd ), ( ms = md ), ( ss = dd = sd )</td>
<td>5</td>
<td>6.35</td>
<td>0.274</td>
<td>12.35</td>
</tr>
<tr>
<td>7</td>
<td>( ms = md = ss = dd = sd )</td>
<td>5</td>
<td>6.74</td>
<td>0.241</td>
<td>12.74</td>
</tr>
</tbody>
</table>

AIC, Akaike's information criterion; f, father; m, mother; s, son; d, daughter.
generations, there is no age difference between the genders. However, each of the baseline, postexercise, and VO\textsubscript{2max} response means is significantly higher in men than in women, and higher in offspring than in parents. The mean VO\textsubscript{2max} response ranges from 293 ml/min in mothers to 486 ml/min in sons, and the mean increase in VO\textsubscript{2max} was significant in each of the four sex and generation groups.

The extensive heterogeneity in the VO\textsubscript{2max} changes brought about by regular exercise is illustrated by Clinical Center in Fig. 1. A similar pattern of variation in trainability, expressed as gains in milliliters of O\textsubscript{2} per minute, across all four centers was observed. Indeed, each center had nonresponders and low responders as well as others who increased their VO\textsubscript{2max} by as much as 700 ml/min and up to 1.0 l/min. The distribution of the increases in VO\textsubscript{2max} for all 481 individuals is depicted in Fig. 2 for seven classes of changes with training.

The correlations between baseline VO\textsubscript{2max} and the VO\textsubscript{2max} response to training were computed separately for fathers, mothers, daughters, and sons. The correlations ranged from 0.03 to –0.16. Despite these low correlation levels, the VO\textsubscript{2max} response phenotype was further adjusted for baseline VO\textsubscript{2max} (age and baseline value within sex and generation groups), and all the analyses were repeated. No differences were found between the age-adjusted and the age- and baseline VO\textsubscript{2max}-adjusted VO\textsubscript{2max} response phenotypes. We have, therefore, elected to present only the age-adjusted phenotype data from here on.

An ANOVA was implemented to test for aggregation in families, with the age-adjusted VO\textsubscript{2max} response as the dependent variable and family identification as the independent variable. The F value from the ANOVA indicates that there are 2.5 times more variance (P = 0.0001) between than within families, with 39% of the variance being accounted for by family membership. This clearly shows that the VO\textsubscript{2max} response aggregates in families (results not shown).

The familial correlation model-fitting results are given in Table 2. The hypotheses of no sibling resemblance (model 10), no parent-offspring resemblance (model 11), and no spouse resemblance (model 12) are rejected, supporting significant familial resemblance. The maternal hypotheses (models 6–8) are not rejected, although dropping father-offspring and spouse resemblance (model 9) produces a worse fit. None of the models testing for sex differences (models 2–4) and a single correlation (model 5) is rejected. Based on the likelihood ratio tests and the AIC, model 3 (no sex differences in offspring or parents; AIC = 1,371.57) and model 7 (maternal inheritance with no restrictions on father-offspring and spouse resemblance independent of sex; AIC = 1,371.96) are the most parsimonious.

Parameter estimates (correlations ± SE) under the general and parsimonious models are summarized in Table 3. The maximal general heritability, defined as the most comprehensive estimator of the familial transmission, was estimated as twice the average of the seven correlations for related individuals (i.e., all except spouse correlation) and is also shown in Table 3.
Under the parsimonious model, the maximum general heritability was estimated as 47% for the maternal model, the maximum heritability reached 28%

Figure 3 depicts the distribution of the age- and sex-adjusted VO_{2max} response within and between families and illustrates the extent of the familial resemblance in the trainability of VO_{2max}. The figure shows that there are families with a predominantly low-response phenotype and others with large concentrations of high responders.

**DISCUSSION**

The maximal heritability estimate of the VO_{2max} response to training adjusted for age and sex reaches 47% in this study, with maternal heritability reaching 28%. Adjusting the response data for baseline VO_{2max} did not modify these estimates. Spouse resemblance in the response phenotype is noticeable and may indicate effects of shared environments as well as assortative mating. In the same population, our laboratory has earlier reported a maximal heritability of 59% (and maternal heritability of 36%) for the baseline VO_{2max} data (4). Thus the familial factors underlying VO_{2max} in sedentary families are quantitatively similar to those underlying its response to exercise training. However, even though they are quantitatively about the same, the familial and genetic factors underlying the two phenotypes appear to be different, as indicated by the lack of a relationship between baseline VO_{2max} and VO_{2max} response.

Maximal aerobic power is characterized by limited trainability in children under 10 yr of age, but VO_{2max} is clearly a trainable phenotype, on the average, in older children, adolescents, young adults, and older adults of both sexes (3, 8, 13). However, no children were involved in the present study, and age of subjects was only a minor correlate of the VO_{2max} response (see Data adjustment). Nonetheless, there were considerable individual differences in the response of these phenotypes to exercise training. Among adults, some individuals exhibit a pattern of high response, whereas others present a pattern of no or minimal response, with a broad range of response phenotypes between the extremes.

What is the main cause of the heterogeneity in the response to training? We believe that it has to do with as yet undetermined genetic characteristics (2). To test this hypothesis, we have in the past performed training studies with pairs of monozygotic twins, the rationale being that the response pattern should vary for individuals having differing genetic characteristics (between pairs) compared with brothers or sisters having the same genotype (within pairs). There was about six to nine times more variance between genotypes (pairs of twins) than within genotypes (within pairs of twins) in the response of VO_{2max} to standardized training protocols (3). A related measure of aerobic performance is total work output during a prolonged exercise bout. In one of these experiments performed with six pairs of identical twins, total power output during a 90-min maximal cycle ergometer test was monitored before and after 15 wk of training (7). Resemblance in total power output within twin pairs was significant (intraclass r = 0.83), and the ratio of between-pairs to within-pairs variances was ~11.

The most convincing evidence for the presence of family lines in the trainability of VO_{2max} comes, however, from the present study. There was 2.5 times more variance between families than within families for the adjusted VO_{2max} response, and the model-fitting analytic procedure yielded a maximal heritability of 47%. A significant maternal effect on the response pattern was also observed. This raises the possibility that mitochondrial DNA is involved to a significant extent in the training-response heterogeneity. From the earlier observations in identical twins and the present report, we conclude that the individuality in trainability of VO_{2max} is highly familial with a significant genetic component. It should, therefore, be possible to identify the genes and mutations responsible for the heterogeneity in the training response of VO_{2max}.

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**REFERENCES**


