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

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[1]*Physical Activity Sciences Laboratory, Laval University, Ste-Foy, Québec, Canada G1K 7P4;* [2]*Division of Biostatistics and* [6]*Department of Genetics and Psychiatry, Washington University School of Medicine, St. Louis, Missouri 63110;* [3]*Department of Kinesiology, Indiana University, Bloomington, Indiana 47405;* [4]*Department of Health and Kinesiology, Texas A&M University, College Station, Texas 77843; and* [5]*School of Kinesiology and Leisure Studies, University of Minnesota, Minneapolis, Minnesota 55455*

Bouchard, Claude, Ping An, Treva Rice, James S. Skinner, Jack H. Wilmore, Jacques Gagnon, Louis Pérusse, Arthur S. Leon, and D. C. Rao. Familial aggregation of $\dot{V}O_{2max}$ response to exercise training: results from the HERITAGE Family Study. *J. Appl. Physiol.* 87(3): 1003–1008, 1999.—The aim of this study was to test the hypothesis that individual differences in the response of maximal O_2 uptake ($\dot{V}O_{2max}$) to a standardized training program are characterized by familial aggregation. A total of 481 sedentary adult Caucasians from 98 two-generation families was exercise trained for 20 wk and was tested for $\dot{V}O_{2max}$ on a cycle ergometer twice before and twice after the training program. The mean increase in $\dot{V}O_{2max}$ reached ~400 ml/min, but there was considerable heterogeneity in responsiveness, with some individuals experiencing little or no gain, whereas others gained >1.0 l/min. An ANOVA revealed that there was 2.5 times more variance between families than within families in the $\dot{V}O_{2max}$ response variance. With the use of a model-fitting procedure, the most parsimonious models yielded a maximal heritability estimate of 47% for the $\dot{V}O_{2max}$ response, which was adjusted for age and sex with a maternal transmission of 28% in one of the models. We conclude that the trainability of $\dot{V}O_{2max}$ is highly familial and includes a significant genetic component.

trainability; heritability; individuality; family lines

MAXIMAL O_2 UPTAKE ($\dot{V}O_{2max}$) 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 $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ response to a standardized training program in previously sedentary people. There are reasons to believe that the trainability of $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ changes with training range from 0.65 to 0.77. The *F* ratios of the between-pair variance in $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ 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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offspring and ≤65 yr of age for parents). Second, all participants were required to be sedentary at baseline. Third, individuals with a body mass index >40 kg/m^2 were excluded, unless they were able to meet the demands of the exercise tests and exercise training program. Fourth, resting blood pressure levels could not exceed 159 mmHg for systolic and 99 mmHg for diastolic. Antihypertension drug therapy was also a cause for exclusion. Participants were required to be in good physical health and to complete the 20-wk exercise program. Further details about inclusion and exclusion criteria can be found in Bouchard et al. (6).

Exercise training program. The training program was conducted on cycle ergometers (Universal Aerobicycle, Cedar Rapids, IA) interfaced with a Mednet computer system (Universal Gym Mednet, Cedar Rapids, IA) to control the power output of the ergometers so that constant training heart rates could be maintained. Subjects started training at the heart rate associated with 55% of their initial $\dot{V}O_{2max}$ for 30 min/day and gradually progressed to the heart rate associated with 75% of their initial $\dot{V}O_{2max}$ for 50 min/day at the end of 14 wk. They maintained this intensity and duration throughout the remaining 6 wk. Frequency was maintained at three sessions per week throughout the 20-wk training program (14). The power output of the cycle ergometer was adjusted automatically to the heart rate response of the subject at all times during all training sessions. All training sessions were supervised on site. A detailed description of the training program can be found elsewhere (6, 12).

$\dot{V}O_{2max}$ measures. Each individual was examined for a battery of measurements before and after the 20-wk standardized exercise program. Two maximal exercise tests designed to lead to $\dot{V}O_{2max}$ on a cycle ergometer were performed on 2 separate days at baseline and again on 2 separate days after training on a SensorMedics 800S (Yorba Linda, CA) cycle ergometer connected to a SensorMedics 2900 metabolic measurement cart. The tests were conducted at about the same time of day, with at least 48 h between the two tests. The electrocardiogram was used to monitor heart rate. Gas-exchange variables (O_2 uptake, CO_2 production, minute ventilation) were recorded as a rolling average of three 20-s intervals. The criteria for $\dot{V}O_{2max}$ were respiratory exchange ratio >1.1, plateau in O_2 uptake (change of <100 ml/min in the last three 20-s intervals), and a heart rate within 10 beats/min of the maximal heart rate predicted for age. All subjects achieved a $\dot{V}O_{2max}$ by at least one of these criteria in at least one of the two tests, both pre- and posttraining. In the first test, subjects exercised at a power output of 50 W for 3 min, followed by increases of 25 W each 2 min until volitional exhaustion. For older, smaller, or less fit individuals, who were generally the older mothers among the family members, the test was started at 40 W, with increases of 10–20 W each 2 min thereafter. In the second test, subjects exercised for ~10 min at an absolute (50 W) and at a relative power output equivalent to 60% $\dot{V}O_{2max}$. They then exercised for 3 min at a relative power output that was 80% of their $\dot{V}O_{2max}$, after which resistance was increased to the highest power output attained in the first maximal test. If the subjects were able to pedal after 2 min, power output was increased each 2 min thereafter until they reached volitional fatigue. The average $\dot{V}O_{2max}$ from these two sets was taken as the $\dot{V}O_{2max}$ for that subject and used in this analysis if both values were within 5% of each other. If they differed by >5%, the higher $\dot{V}O_{2max}$ value was used. Reproducibility of $\dot{V}O_{2max}$ in these subjects was examined and was characterized by an intraclass correlation coefficient of 0.97 for repeated tests, with a coefficient of variation of 5% and no difference among clinical centers (4, 12). The $\dot{V}O_{2max}$ response was defined as the absolute difference (ml O_2/min) between posttraining $\dot{V}O_{2max}$ and baseline $\dot{V}O_{2max}$ (i.e., $\dot{V}O_{2max}$ response = posttraining $\dot{V}O_{2max}$ − baseline $\dot{V}O_{2max}$) and is the phenotype used in the present study.

Data adjustment. The response of $\dot{V}O_{2max}$ to training was adjusted for age by using a stepwise multiple-regression procedure. Briefly, the response variable was regressed on up to a cubic polynomial in age within four sex-generation groups (fathers, mothers, sons, and daughters). Only terms significant at the 5% level were retained. The resulting squared residuals were similarly adjusted for age effects on the variance; the final adjusted phenotype was standardized to a mean of 0 and a SD of 1. Significant terms and percentages of variance accounted for by age in each of the sex-by-generation groups for the $\dot{V}O_{2max}$ response phenotype were seen only in sons (9.2%) and daughters (5.0%). A separate set of adjustments allowing for the effects of age, sex, and baseline $\dot{V}O_{2max}$ was also conducted. However, baseline $\dot{V}O_{2max}$ was not a significant predictor of the $\dot{V}O_{2max}$ response at the 0.05 level.

Familial correlation model. An ANOVA comparing the between-family to the within-family variances was first used to verify the hypothesis that the response of $\dot{V}O_{2max}$ aggregates in families. A sex-specific familial correlation model was then used to investigate whether there was evidence of familial factors underlying the variation in the age-adjusted response $\dot{V}O_{2max}$. The computer program SEGPATH (9) was used to fit the model directly to the family data by using the method of maximum likelihood under the assumption that the phenotype within a family jointly follows a multivariate normal distribution. The general model was based on four groups of individuals [i.e., fathers (f), mothers (m), sons (s), and daughters (d)], giving rise to eight correlations in three familial classes [i.e., 1 spouse (fm), 4 parent-offspring (fs, fd, ms, md), and 3 sibling (ss, dd, sd)]. The general model and several null hypotheses were evaluated. Each null hypothesis was tested by a comparison to the general model by using the likelihood ratio test, which is the difference in minus twice

Table 1. *Means and SD for unadjusted data*

	Fathers (n = 95)		Mothers (n = 86)		Sons (n = 141)		Daughters (n = 159)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age, yr	53.4	5.4	52.0	4.9	25.4	6.1	25.5	6.4
$\dot{V}O_{2max}$, ml O_2/min								
Baseline	2,618.9	451.1	1,639.5	256.8	3,294.2	497.3	2,063.0	306.7
Postexercise	2,993.0	484.2	1,939.0	287.8	3,780.3	517.6	2,433.6	368.4
Response	374.1	204.8	299.5	159.7	486.1	246.7	370.7	194.0

$\dot{V}O_{2max}$, maximal O_2 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 ($P < 0.01$).

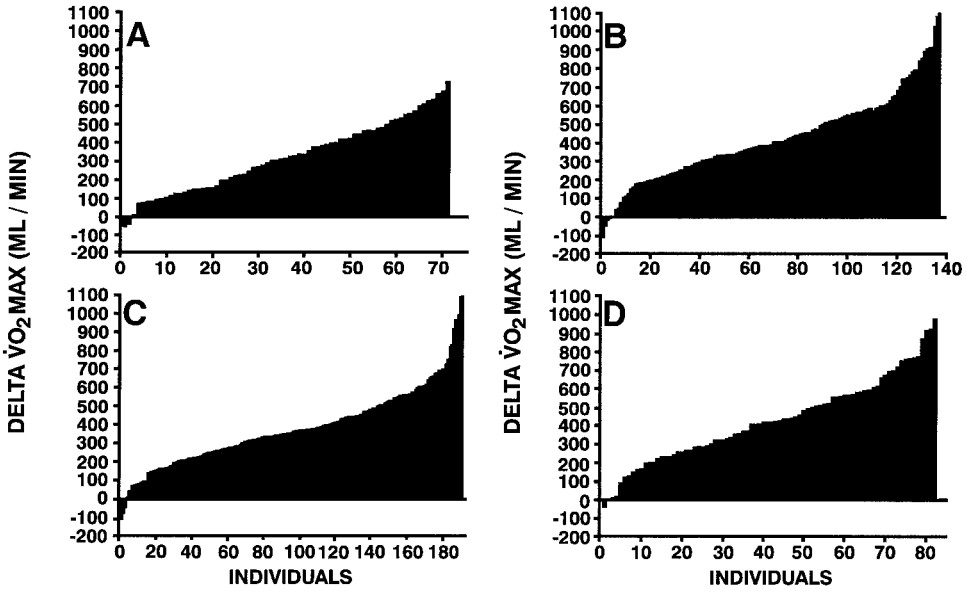

Fig. 1. Individual differences (delta) in increase in maximal O_2 uptake ($\dot{V}O_{2max}$) with training for 481 individuals of the study distributed across the four Clinical Centers: Indiana (*A*), Minnesota (*B*), Quebec (*C*), and Texas (*D*).

the log likelihood (−2 ln L) obtained under the two models. The likelihood ratio is approximately distributed as a χ^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.

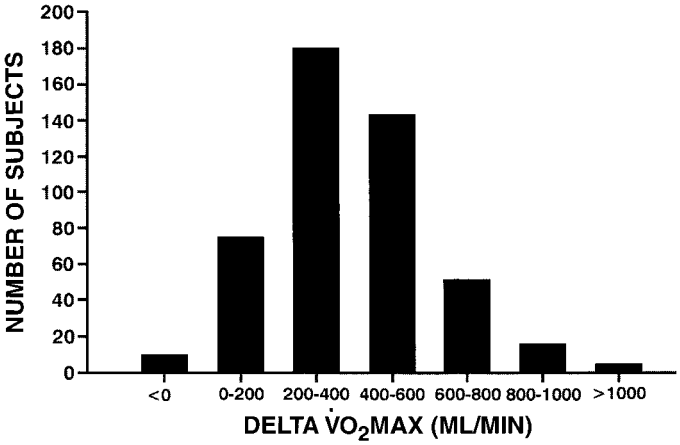

Fig. 2. Distribution of the 481 subjects by classes of increase (delta) in $\dot{V}O_{2max}$ from baseline levels.

RESULTS

Means and SDs for the baseline, posttraining, and $\dot{V}O_{2max}$ response are presented in Table 1. In each of the

Table 2. *Model-fitting summary for the response $\dot{V}O_{2max}$-adjusted phenotypes*

Model	Response $\dot{V}O_{2max}$ Adjusted by Age and Sex			
	df	χ^2	*P*	AIC
1 General model				16.00
2 fs = fd, ms = md, ss = dd = sd	4	4.91	0.297	12.91
3 fs = fd = ms = md, ss = dd = sd	5	6.35	0.274	12.35
4 fs = fd = ms = md = ss = dd = sd	6	11.53	0.073	15.53
5 fm = fs = fd = ms = md = ss = dd = sd	7	13.89	0.053	15.89
6 ms = md = ss = dd = sd	4	5.14	0.273	13.14
7 fs = fd, ms = md − ss = dd = sd	5	6.74	0.241	12.74
8 fm = fs = fd, ms = md = ss = dd = sd	6	11.19	0.083	15.19
9 fm = fs = fd = 0, ms = md = ss = dd = sd	7	16.75	0.019	18.75
10 ss = dd = sd = 0	3	30.96	<0.001	40.96
11 fs = fd = ms = md = 0	4	10.17	0.038	18.17
12 fm = 0	1	9.77	0.002	23.77
Parsimonious model				
3	5	6.35	0.274	12.35
7	5	6.74	0.241	12.74

AIC, Akaike's information criterion; f, father; m, mother; s, son; d, daughter.

Table 3. *Final correlations and heritability estimates*

Parameters	Response $\dot{V}O_{2max}$ Adjusted by Age and Gender		
	General	Most parsimonious (*model 3*)	Most parsimonious (*model 7*)
fm	0.33 ± 0.09	0.33 ± 0.10	0.33 ± 0.09
fs	0.03 ± 0.10	0.16 ± 0.06	0.13 ± 0.07
fd	0.18 ± 0.09	[0.16]	[0.13]
ms	0.22 ± 0.10	[0.16]	0.28 ± 0.05
md	0.23 ± 0.09	[0.16]	[0.28]
ss	0.45 ± 0.10	0.33 ± 0.07	[0.28]
dd	0.34 ± 0.10	[0.33]	[0.28]
sd	0.22 ± 0.10	[0.33]	[0.28]
Maximal general heritability, %		47	47
Maximal maternal heritability, %			28

Parameters in square brackets were equated to a preceding parameter.

generations, there is no age difference between the genders. However, each of the baseline, postexercise, and $\dot{V}O_{2max}$ response means is significantly higher in men than in women and higher in offspring than in parents. The mean $\dot{V}O_{2max}$ response ranges from 293 ml/min in mothers to 486 ml/min in sons, and the mean increase in $\dot{V}O_{2max}$ was significant in each of the four sex and generation groups.

The extensive heterogeneity in the $\dot{V}O_{2max}$ 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_2 per minute, across all four centers was observed. Indeed, each center had nonresponders and low responders as well as others who increased their $\dot{V}O_{2max}$ by as much as 700 ml/min and up to >1.0 l/min. The distribution of the increases in $\dot{V}O_{2max}$ for all 481 individuals is depicted in Fig. 2 for seven classes of changes with training.

The correlations between baseline $\dot{V}O_{2max}$ and the $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ response phenotype was further adjusted for baseline $\dot{V}O_{2max}$ (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 $\dot{V}O_{2max}$-adjusted $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ 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.

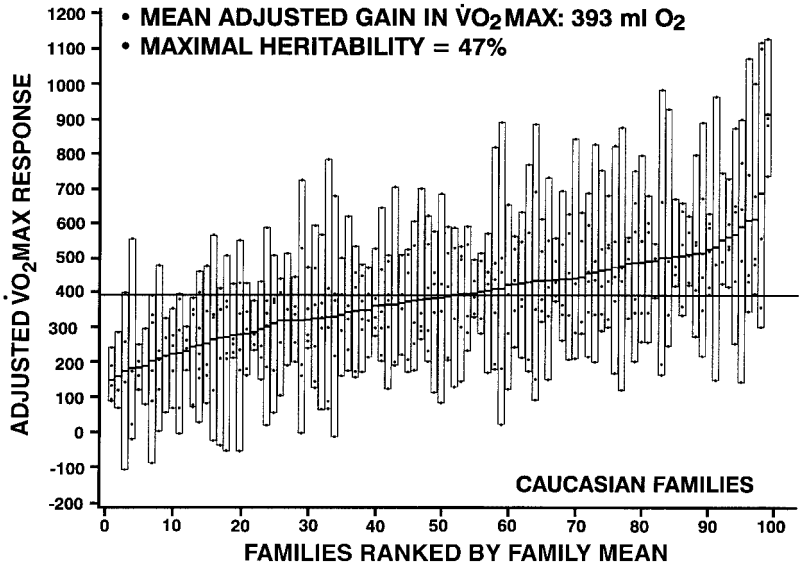

Fig. 3. Age- and sex-adjusted response in $\dot{V}O_{2max}$ phenotype plotted against family rank (i.e., families ranked by family mean). Adjusted $\dot{V}O_{2max}$ response value for each individual was calculated as the residual from regression model plus group mean. Each family is enclosed within a bar: ●, individual data points; solid horizontal dash, family mean. Horizontal reference line is group mean. Maximal heritability is taken from 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 $\dot{V}O_{2max}$ response within and between families and illustrates the extent of the familial resemblance in the trainability of $\dot{V}O_{2max}$. 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 $\dot{V}O_{2max}$ response to training adjusted for age and sex reaches 47% in this study, with maternal heritability reaching 28%. Adjusting the response data for baseline $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ data (4). Thus the familial factors underlying $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ and $\dot{V}O_{2max}$ response.

Maximal aerobic power is characterized by limited trainability in children under 10 yr of age, but $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ comes, however, from the present study. There was 2.5 times more variance between families than within families for the adjusted $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$.

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