Familial resemblance for $\dot{V}O_{2max}$ in the sedentary state: the HERITAGE family study

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ABSTRACT

BOUCHARD, C., E. WARWICK DAW, T. RICE, L. PÉRUSSE, J. GAGNON, M. A. PROVINCE, A. S. LEON, D. C. RAO, J. S. SKINNER, and J. H. WILMORE. Familial resemblance for $\dot{V}O_{2max}$ in the sedentary state: the HERITAGE family study. *Med. Sci. Sports Exerc.*, Vol. 30, No. 2, pp. 252–258, 1998. This study investigates the familial resemblance of maximal oxygen uptake ($\dot{V}O_{2max}$) based on data from 86 nuclear families of Caucasian descent participating in the HERITAGE Family Study. In the current study, $\dot{V}O_{2max}$ was measured twice on a cycle ergometer in 429 sedentary individuals (170 parents and 259 of their offspring), aged between 16 and 65 yr. The $\dot{V}O_{2max}$ was adjusted by regression procedures for the effects of 1) age and sex; 2) age, sex, and body mass; and 3) age, sex, body mass, fat mass, and fat-free mass, as determined by underwater weighing. Evidence for significant familial resemblance was observed for each of the three $\dot{V}O_{2max}$ phenotypes. Spouse, sibling, and parent-offspring correlations were significant, suggesting that both genetic and environmental factors contribute to the familial resemblance for $\dot{V}O_{2max}$. Maximal heritability estimates were at least 50%, a value inflated to an undetermined degree by nongenetic factors. The hypothesis of maternal inheritance, with the father's contribution being environmental, was also found to fit the data with estimates of maternal heritability, potentially associated in part with mitochondrial inheritance, reaching about 30%. These results suggest that genetic and nongenetic factors as well as maternal influences contribute to the familial aggregation of $\dot{V}O_{2max}$ in sedentary individuals. **Key Words:** MAXIMAL OXYGEN UPTAKE, HERITABILITY, FAMILY STUDY, MITOCHONDRIAL INHERITANCE, MATERNAL EFFECT

The topic of the role of genetic and environmental or lifestyle factors on maximal oxygen uptake ($\dot{V}O_{2max}$) has been of interest to exercise scientists since the paper published by Klissouras (7) in 1971. In his study based on a small sample of monozygotic (MZ) and dizygotic (DZ) male twins, he showed that MZ twins were more alike than DZ brothers for $\dot{V}O_{2max}$ per kg of body mass and concluded that its heritability level was above 90% of the total phenotype variance. Over the last 25 yr or so, a few investigators have addressed the same issue using the classical twin study design or nuclear family data. Despite the growing number of studies on this issue, there are still widely divergent views on the role of the genotype on $\dot{V}O_{2max}$, and a high degree of confusion still persists concerning the validity and credibility of these studies.

To the best of our knowledge, six twin studies and three family studies have been published in the peer-reviewed literature on this topic. The twin studies are based on very small sample sizes (6–8), moderate sample sizes (3,12) or very large sample sizes (21). Unfortunately, $\dot{V}O_{2max}$ was only predicted in the study with the largest data base, i.e., 436 pairs of MZ twins and 622 pairs of DZ twins (21). The studies with the smallest sample size gave the highest heritability estimates for $\dot{V}O_{2max}$. The situation is made even more complex because of several methodological and analytical differences among studies that impact the outcome. In a study conducted with 53 pairs of MZ twins, 33 pairs of DZ twins, and 27 pairs of nontwin brothers, it was concluded that the heritability of $\dot{V}O_{2max}$ per kg of body mass adjusted for age and sex differences attained about 40% but that it decreased to 10% when the phenotype was further adjusted for fat-free mass (3). The most recent twin study

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incorporating $\dot{V}O_{2max}$ as a phenotype was that reported by Maes et al. (12). It was based on a sample of 10-yr-old twins from Belgium and their parents. The heritability estimates were quite high ($\geq$ 67%), but $\dot{V}O_{2max}$ values were apparently not adjusted for body mass and body composition in the same analysis.

In addition, three family studies have been published. In one of these studies (11), $\dot{V}O_{2max}$ was predicted for the nuclear family members of a relatively large sample from the Quebec Family Study. In the paper by Montoye and Gayle (14), $\dot{V}O_{2max}$ was measured in some subjects of the Tecumseh Community Health Study but predicted in others. Finally, in the third family study, also from Quebec, $\dot{V}O_{2max}$ was measured, but the sample size was rather small (9). In all these studies, the spouse correlation for $\dot{V}O_{2max}$ per kg of body mass or adjusted for body mass and body composition was about 0.2 and above. As evidenced by parent-offspring and sibling correlations, the familial aggregation was generally considered as significant in these studies, but the data were generally supportive of a genetic effect reaching only about 25–40% of the $\dot{V}O_{2max}$ adjusted for age, sex, and body mass and/or body composition (4).

In the present study, familial resemblance of $\dot{V}O_{2max}$ is investigated using the baseline data of the HERITAGE Family Study (5). The study incorporates several new analytical features and is based on 429 Caucasian subjects from 86 nuclear families who were sedentary before enrolling in the study.

METHODS

Sample. The HERITAGE multicenter 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 several cardiovascular disease and diabetes risk factors. The centers are presently located at the following institutions: Indiana University, Laval University, University of Minnesota, Texas A & M University, and Washington University. The HERITAGE sample and study protocol are more thoroughly described by Bouchard et al. (5). The current study includes data on 86 nuclear families of Caucasian descent. Exact sample sizes for fathers, mothers, sons, and daughters are given in Table 1. Recruitment of families was based on extensive publicity and advertisements at four clinical centers.

TABLE 1. Basic descriptive data for the HERITAGE Family Study sample.

Variable	*N*	Mean	SD	*N*	Mean	SD
	Fathers			Mothers		
Age	85	52.9	5.2	85	51.7	5.2
$\dot{V}O_{2max}$	85	2614.2	434.6	85	1630.2	276.4
$\dot{V}O_{2max}$/ weight	85	30.0	5.0	85	23.0	4.9
$\dot{V}O_{2max}$/ fat-free mass	83	41.6	5.2	81	36.9	5.0
	Sons			Daughters		
Age	125	24.8	5.9	134	24.5	5.9
$\dot{V}O_{2max}$	125	3320.7	503.8	134	2029.7	303.6
$\dot{V}O_{2max}$/ weight	124	41.8	8.4	134	32.7	5.3
$\dot{V}O_{2max}$/ fat-free mass	119	51.5	6.3	134	44.2	4.9

Unadjusted data are presented as conventional ratios.

Several criteria were used to screen subjects for participation. First, individuals were required to be between the ages of 16 and 65 yr (16 and 40 yr for offspring and 65 yr or less for parents) to avoid maturation (low end) and aging (high end) complications. Only five subjects were 16 yr of age. Second, individuals were required to be in good health to complete the test battery and the exercise training program. Third, families were required to be sedentary, defined at baseline as no regular physical activity over the previous 6 months, i.e., any activity lasting 30 min or more and involving an energy expenditure of at least 7 METs ($\geq$ 50 yr) or 8 METs ($<$50 yr) and occurring more than once a week. Families with some nonsedentary members were included provided that the nonsedentary individual(s) became inactive for at least 6 months. There were only six such cases in the entire HERITAGE Family Study cohort. Fourth, individuals with a body mass index (BMI) greater than 40 $kg \cdot m^{-2}$ were usually excluded because of metabolic abnormalities and exercise difficulties associated with extreme obesity. Fifth, individuals with resting blood pressures greater than 159 mm Hg for systolic and/or 99 mm Hg for diastolic were excluded. Finally, individuals with any condition or disease that was life-threatening or that could be aggravated by cycle exercise were excluded. As an example, definite or possible coronary heart disease and chronic or recurrent respiratory problems were bases for exclusion, as were uncontrolled endocrine and metabolic disorders, including diabetes or use of lipid-lowering drugs. A detailed list of exclusionary criteria was reported in the first paper on the HERITAGE Family Study (5).

Maximal oxygen uptake. Two maximal exercise tests were performed on separate days on a SensorMedics ergometrics 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 tests. The electrocardiogram was used to monitor heart rate. Gas exchange variables ($\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$, and RER) were recorded as a rolling average of three 20-s intervals. The criteria for $\dot{V}O_{2max}$ were RER $>$ 1.1, plateau in $\dot{V}O_2$ (change of $<$100 $mL \cdot min^{-1}$ in the last three 20-s intervals), and a heart rate within 10 $beats \cdot min^{-1}$ of the maximal level predicted by age. All subjects achieved a $\dot{V}O_{2max}$ by one of these criteria in at least one of the two tests. 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, which 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 10–12 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 tests 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 more than 5%, the higher $\dot{V}O_{2max}$ value was then 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% (20).

Table 1 shows the sample sizes, means, and standard deviations for the baseline $\dot{V}O_{2max}$ and for age, separately in each of four sex-by-generation groups (fathers, mothers, sons, and daughters). Based on a comparison of standard errors, significant sex differences and significant generation differences can be seen, with men having larger $\dot{V}O_{2max}$ values than women, and the younger generation having higher values than the older generation.

Body composition and anthropometry. Body mass was measured to the nearest 0.1 kg, using a balance beam scale. Hydrostatic weighing was used to assess body density according to the method of Behnke and Wilmore (2). At three of the clinical centers, the subject was instructed to exhale completely to the point of residual lung volume, at which point a load cell interfaced with a computer was used to obtain the underwater measurement of body mass. At the Laval University Clinical Center, the subject was allowed to exhale to a comfortable level, and the air remaining in the lungs was measured. Ten trials were obtained, and the three highest values were averaged. Residual lung volume was assessed out of water in a seated position using the oxygen-dilution principle, as described by Wilmore (22) and modified by Wilmore et al. (23), or in the water using the helium-dilution technique (13,15). A minimum of two trials were obtained, and a third trial was taken if the first two differed by more than 150 mL. An average of the two trials, or the two closest trials, was used in the correction for the residual lung volume in the estimation of body density. Relative body fat was estimated from body density using the equations of Siri (19) for Caucasian men and Lohman (10) for Caucasian women.

Adjustments. $\dot{V}O_{2max}$ was analyzed under three separate sets of adjustments, one allowing only for age and sex effects, another allowing for the effects of age, sex, and body mass, and the last incorporating controls over the effects of age, sex, body mass, fat mass, and fat-free mass. $\dot{V}O_{2max}$ was adjusted using stepwise multiple regression procedures, separately in each of the four sex-by-generation groups. In summary, a given measure was regressed on a polynomial in the effects in a stepwise manner, retaining only those terms that were significant at the 5% level. Linear, simple quadratic, and simple cubic terms were allowed. The phenotypes used in the genetic analysis were defined as the residual scores from these regression analyses. In all three cases, the phenotype was standardized to a mean of zero and a standard deviation of one before analysis. Significant terms and percentages of variance accounted for in each of the sex-by-generation groups for each phenotype are given in Table 2. In the age and sex only regression, age terms were found to be significant in all groups except daughters, with 9.0–15.9% of the variance being accounted for by age effects in the other three groups. In the age, sex, and body mass regressions, age and body mass terms were significant in all four groups, with 24.3–39.2% of the variance accounted for. In the most extensive regression, age, body weight, and fat-free mass were found to have effects in all four groups, with fat mass also having an effect in sons. The percentage of variance accounted for here was quite large, ranging from 42.2 to 57.6% in the more complete adjustment procedure.

TABLE 2. Percent variance in $\dot{V}O_{2max}$ accounted for by data adjustment for covariate effects.

Effects Allowed	Group	Significant Terms*	% Variance
Age	Fathers	Age^3	15.9
	Mothers	Age	12.4
	Sons	Age	9.0
	Daughters	—	—
Age, weight	Fathers	Age^3, weight	39.2
	Mothers	Age, $weight^3$	24.3
	Sons	Age, weight, $Weight^2$, $weight^3$	33.0
	Daughters	Age, weight, $weight^2$	34.0
Age, weight, fat-free mass, fat mass	Fathers	Age, fat-free mass	56.8
	Mothers	Age, fat-free mass	42.2
	Sons	Age^3, $(fat\ mass)^2$, fat-free mass	57.6
	Daughters	Age, fat-free mass	48.3

* $P < 0.05$.

Familial correlation model. An ANOVA comparing the between-family to the within-family variances was first used to verify the hypothesis that the $\dot{V}O_{2max}$ aggregates in families without and with controls over body mass and body composition. The familial correlation model was based on four groups of individuals (fathers (*f*), mothers (*m*), sons (*s*), and daughters (*d*)), giving rise to eight interindividual correlations in three familial classes (one spouse (*fm*), four parent-offspring (*fs*, *fd*, *ms*, *md*), and three sibling (*ss*, *dd*, *sd*)). The maximum likelihood computer program SEGPATH (18) fitted the model directly to the family data under the assumption that the phenotypes within a family jointly follow a multivariate normal distribution. Null hypotheses were tested using the likelihood ratio test, which is the difference in minus twice the log-likelihoods (-2 ln L) obtained under the two different nested models. The likelihood ratio is approximately distributed as a χ^2, with the degrees of freedom being the difference in the number of parameters estimated in the two competing hypotheses. In addition to the likelihood ratio test, Akaike's (1) Information Criterion (AIC), which is -2 ln L plus twice the number of estimated parameters, was used to judge the fit of the nonnested models. The "best" model by AIC is the one with the smallest value.

The general model (model 1) and several null hypotheses were fitted to the data. Null hypotheses included tests for no sex differences in the offspring (i.e., model 2: $fs = fd$, $ms = md$, $ss = dd = sd$, $df = 4$), no sex differences in parents or offspring (i.e., model 3: $fs = fd = ms = md$, $ss = dd = sd$, $df = 5$), and no sex nor generation differences (i.e., model 4: $fs = fd = ms = md = ss = dd = sd$, $df = 6$). In model

5, all eight correlations were equated ($fm = fs = fd = ms = md = sd = ss = dd$, $df = 7$). Several models were also included to test for maternal inheritance, where mother-offspring and offspring-offspring correlations are expected to be equal. In particular, model 6 ($ms = md = sd = ss = dd$, $df = 4$) tests for a maternal mode of inheritance without any assumptions on the father's contributions. Maternal inheritance was further tested under the assumptions that the father-offspring correlations were independent of sex (model 7: $fs = fd$, $ms = md = sd = ss = dd$, $df = 5$), that the father's contribution is entirely environmental (model 8: $fm = fs = fd$, $ms = md = sd = ss = dd$, $df = 6$), and that the father-offspring and father-mother correlations are zero (model 9: $fm = fd = fs = 0$, $ms = md = sd = ss = dd$, $df = 7$). Finally, additional null hypotheses testing the strength of the familial resemblance were conducted by familial class, including no spouse resemblance (i.e., model 12: $fm = 0$, $df = 1$), no parent-offspring resemblance (i.e., model 11: $fs = fd = ms = md = 0$, $df = 4$), and no sibling resemblance (i.e., model 10: $ss = dd = sd = 0$, $df = 3$). Each null hypothesis was tested by a likelihood ratio comparison to the general model, and a parsimonious model was derived by combining all nonrejected null hypotheses. The AIC was used to select the "best" sex hypothesis from among the nonnested sex models.

RESULTS

An analysis of variance was implemented to test for aggregation in families, with adjusted $\dot{V}O_{2max}$ as the dependent variable and family ID as the independent variable. The results of the ANOVA are presented in Table 3. The *F*-ratios indicate that there are about 2.6 to 2.9 times more variance between families than within families in the adjusted $\dot{V}O_{2max}$ phenotypes. About 40% of the variance in $\dot{V}O_{2max}$ is accounted for by family lines, which clearly shows that $\dot{V}O_{2max}$ aggregates in families.

The model-fitting results are shown in Table 4 for each of the adjusted $\dot{V}O_{2max}$ phenotypes. For the age- and sex-adjusted phenotype, the hypotheses of no sex differences in parents or offspring (model 3) and no sex nor generation differences (model 4) are rejected, as are the hypotheses of no significant sibling (model 10) and no parent-offspring (model 11) correlations. Although the four maternal inheritance models (model 6–9) fit the data based on likelihood ratio tests, the AIC suggests that model 8, in which the father-offspring correlations are assumed to be environmental rather than genetic, is the most parsimonious (AIC = 8.9). For $\dot{V}O_{2max}$ adjusted for age, sex, and body weight, the results remain about the same, i.e., significant sibling and parent-offspring correlations with no significant spouse resemblance and with a maternal model (model 8) being the most parsimonious (AIC = 7.9)

TABLE 3. Familial aggregation of $\dot{V}O_{2max}$ adjusted phenotypes from the comparison of the between-family and the within-family variance components.

Variable	R-Square	*F* Value	*P*
Age-sex adjusted $\dot{V}O_{2max}$	0.41	2.87	0.0001
Age-sex-weight adjusted $\dot{V}O_{2max}$	0.39	2.63	0.0001
All covariate-adjusted $\dot{V}O_{2max}$	0.41	2.72	0.0001

After correcting for fat-free mass, fat mass, and body mass, as well as age, the tests for no sibling (model 10) and no parent-offspring (model 11) correlations were rejected, with model 5 (all 8 correlations equal) considered the best by AIC. Since the spouse correlation did not seem to be significantly different from 0 (model 12), two additional hypotheses were tested, one by combining model 4 (no sex nor generation differences) with model 12 (no spouse correlation) and the other by combining model 7 with model 12. Model 5, with all correlations equal, provided the best fit (AIC = 4.0), although model 8 also fits quite well. Among the maternal hypotheses tested (model 6–9), model 8, with the father's contribution explained by familial environment, provided the best fit (AIC = 4.6).

Parameter estimates (correlations ± SE) under the general and parsimonious models are summarized in Table 5. For the most extensively adjusted phenotype, in addition to the most parsimonious results, the best maternal model is also provided for comparison. The maximal general heritability, defined as the most comprehensive estimator of the familial transmission, was estimated as twice the average of the 7 correlations for related individuals (i.e., all except fm) and is given for all models in Table 5. For the maternal models, the maximal maternal inheritance was taken to be the common mother-offspring, offspring-offspring correlations. For the most parsimonious models, the maximum general heritability ranged from 51 to 59%. For the maternal models, the maximum maternal heritability ranged from 29 to 36%. Figure 1 depicts the distribution of the age, sex, body weight, fat mass, and fat-free mass adjusted $\dot{V}O_{2max}$ phenotype within and between families. In this instance, the maximal heritability, which includes genetic and nongenetic causes of the familial aggregation, accounted for 51% of the total adjusted phenotypic variance.

DISCUSSION

These results, based on the baseline data from Caucasian subjects of the HERITAGE Family Study, support the findings of previous family studies that suggested the presence of significant familial resemblance for $\dot{V}O_{2max}$ measured in sedentary subjects. We estimated in the past that about 10–40% of the variance of the adjusted $\dot{V}O_{2max}$ phenotypes could be accounted for by family relationships (3). In the present study, familial correlations were computed in intact nuclear families that included only confirmed sedentary individuals. Although the contributions of genetic and familial environment cannot be fully quantified separately based on this approach, inferences about their respective contributions to the phenotypic variance can be made by inspection of the pattern of familial correlations. For example, a pattern of significant correlations among siblings and between parents and offspring, but not between spouses, would suggest that the familial resemblance is primarily due to genetic factors, while the presence of a significant spouse correlation in addition to parent-offspring and sibling re-

TABLE 4. Model-fitting summary for the three $\dot{V}O_{2max}$ adjusted phenotypes.

Model	df	$\dot{V}O_{2max}$ Adjusted for Age and Sex			$\dot{V}O_{2max}$ Adjusted for Age, Sex, and Weight			$\dot{V}O_{2max}$ Adjusted for All Covariates		
		χ^2	*P*	AIC	χ^2	*P*	AIC	χ^2	*P*	AIC
(1) General model				16.0			16.0			16.0
(2) *fs=fd, ms=md, ss=dd=sd*	4	4.41	0.354	12.4	2.95	0.566	10.9	0.47	0.976	8.5
(3) *fs=fd=ms=md, ss=dd=sd*	5	11.61	0.041	17.6	6.36	0.273	12.4	1.03	0.960	7.0
(4) *fs=fd=ms=md=ss=dd=sd*	6	13.34	0.038	17.3	6.37	0.383	10.4	1.42	0.965	5.4
(5) *fm=ms=fd=sd=fs=md=ss=dd*	7	13.89	0.053	15.9	6.75	0.456	8.7	1.96	0.962	4.0
(6) *ms=md=dd=sd=ss*	4	1.37	0.850	9.4	3.16	0.531	11.2	0.45	0.979	8.4
(7) *fs=fd, ms=md=dd=sd=ss*	5	4.66	0.458	10.7	3.86	0.571	9.9	0.48	0.993	6.5
(8) *fm=fs=fd, ms=md=dd=sd=ss*	6	4.86	0.562	8.9	3.86	0.695	7.9	0.63	0.996	4.6
(9) *fm=fs=fd=0, ms=md=dd=sd=ss*	7	8.36	0.302	10.4	9.45	0.222	11.4	8.34	0.304	12.9
(10) ss=dd=sd=0	3	29.62	<0.001	39.6	17.00	0.007	27.0	19.29	<0.001	29.3
(11) fs=fd=ms=md=0	4	29.59	<0.001	37.6	23.63	<0.001	31.6	17.91	0.001	25.9
(12) *fm=0*	1	2.78	0.095	16.8	3.09	0.079	17.1	3.53	0.060	17.5
Parsimonious model										
(8)	6	4.86	0.562	8.9	3.86	0.695	7.9	0.63	0.996	4.6
(5)	7							1.96	0.962	4.0
(4) and (12)	7							4.70	0.697	6.7
(7) and (12)	6							3.11	0.795	7.1

TABLE 5. Familial correlations and heritability estimates.

Parameter	$\dot{V}O_{2max}$ Adjusted for Age and Sex		$\dot{V}O_{2max}$ Adjusted for Age, Sex, and Weight		$\dot{V}O_{2max}$ Adjusted for All Covariates		
	General	Most Parsimonious	General	Most Parsimonious	General	Most Parsimonious	Best Maternal/ Mitochondrial
fm	0.18 ± 0.10	0.14 ± 0.08	0.19 ± 0.10	0.17 ± 0.07	0.18 ± 0.11	0.26 ± 0.05	0.21 ± 0.07
fs	0.23 ± 0.09	[0.14]*	0.20 ± 0.09	[0.17]*	0.23 ± 0.09	[0.26]*	[0.21]*
fd	0.05 ± 0.10	[0.14]	0.13 ± 0.09	[0.17]	0.20 ± 0.09	[0.26]	[0.21]
ms	0.32 ± 0.09	0.36 ± 0.06	0.26 ± 0.09	0.29 ± 0.06	0.26 ± 0.09	[0.26]	0.29 ± 0.06
md	0.41 ± 0.07	[0.36]*	0.35 ± 0.07	[0.29]*	0.30 ± 0.09	[0.26]	[0.29]
ss	0.38 ± 0.12	[0.36]	0.18 ± 0.15	[0.29]	0.27 ± 0.14	[0.26]	[0.29]
dd	0.40 ± 0.10	[0.36]	0.17 ± 0.15	[0.29]	0.27 ± 0.13	[0.26]	[0.29]
sd	0.35 ± 0.09	[0.36]	0.31 ± 0.07	[0.29]	0.32 ± 0.08	[0.26]	[0.29]
Maximal general heritability**		59%		52%		51%	53%
Maximal maternal/mitochondrial heritability**		36%		29%			29%

* Parameters in square brackets were equated to a preceding parameter.
** See text for computation of maximum heritabilities.

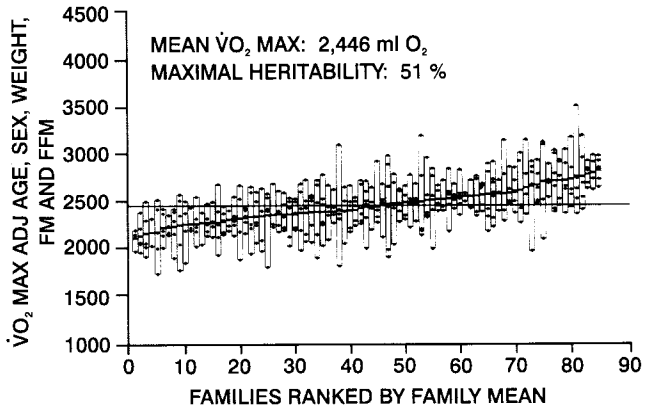

Figure 1—Age, sex, weight, fat mass, and fat-free mass adjusted $\dot{V}O_{2max}$ phenotype (*y* axis) plotted against family rank (i.e., families ranked by family mean). The adjusted $\dot{V}O_{2max}$ value for each individual was calculated as the residual from the regression model plus the group mean. Each family is enclosed within a box, with individual data points plotted as *dots* and each family mean as a *dash*. The *horizontal reference line* is the group mean (value noted in the inset). The maximal heritability shown in the inset is taken from Table 5.

semblance would suggest that shared familial environment is also important.

The correlations presented in Table 5 were derived from the most parsimonious models. They indicate significant spouse correlations for the three $\dot{V}O_{2max}$ phenotypes ($0.14 \leq r \leq 0.26$), suggesting that nongenetic factors contribute to the familial aggregation of $\dot{V}O_{2max}$. These spouse correlations are similar to those of Montoye and Gayle (14) and Lesage et al. (9) who reported correlations of 0.18 and 0.22, respectively, for direct measures of $\dot{V}O_{2max}$ adjusted for the proper concomitants. In their recent study of the inheritance of physical fitness in young (10-yr-old) twin pairs and their parents, Maes et al. (12) reported a spouse correlation of 0.42 for unadjusted $\dot{V}O_{2max}$. Significant spouse resemblance was also observed with other aerobic performance phenotypes. In the Quebec Family Study (16) and in the Canada Fitness Survey (17), spouse correlations of 0.21 and 0.17, respectively, have been reported for PWC_{150} adjusted for age, gender, and body mass. These results and those of other studies are therefore remarkably consistent and suggest that nongenetic factors certainly contribute to the interindividual differences in aerobic performance phenotypes. They imply that any genetic heritability estimate of $\dot{V}O_{2max}$ based on nuclear family data alone is inflated by nongenetic contributions.

Because no distinction can be made between genetic and familial nongenetic inheritance with the approach used in

the present study, and because of the presence of significant spouse correlations for the various $\dot{V}O_{2max}$ phenotypes, the heritabilities reported in Table 5 have to be considered as "maximal" heritabilities. These heritabilities were found to range from 51 to 59%, depending on the type of adjustment performed. Despite the fact that we consider these estimates as "maximal" heritabilities inflated by familial nongenetic contributions, they are lower than those reported from twin studies (6–8,12,21). These discrepancies between family and twin data emphasize the need to interpret with caution the heritability estimates derived only from twins, even when they are based on large sample sizes and derived from an appropriate modeling of the data.

A unique feature of the present study is that we specifically addressed the issue of maternal inheritance by testing four different models in which we forced mother-offspring and sibling correlations to be equal. In the first model (model 6), the spouse and the father-offspring correlations were allowed to vary, while in the others (models 7–9), constraints were imposed on some of them. In model 7, we tested whether the father-offspring correlations differed with the sex of the offspring by forcing father-son and father-daughter correlations to be equal. In model 8, we tested the hypothesis that the father-offspring correlations were due to familial environment rather than genetic factors by forcing the father-son and the father-daughter correlations to be equal to the spouse correlation. Finally in model 9, we assumed that the familial aggregation was entirely explained by maternal inheritance by forcing the father-offspring and spouse correlations to be equal to zero. Our results indicate that for the three adjusted $\dot{V}O_{2max}$ phenotypes, maternal inheritance with the father's contribution being environmental represented the best model for age- and sex-adjusted as well as for age-, sex-, and body mass-adjusted $\dot{V}O_{2max}$. Although complex maternal autosomal and sex-chromosome inheritance mechanisms could be proposed to account for the maternal inheritance pattern in the presence of a negligible paternal transmission, the most likely explanation is one based on a mitochondrial DNA contribution. Based on the present results, we estimated that the "mitochondrial" heritability is in the range of 30–35%. To the best of our knowledge, this is the first evidence of maternal/mitochondrial inheritance for $\dot{V}O_{2max}$, although familial data published 10 yr ago, but based on a smaller sample of families, were suggestive of such a pattern (9).

Mitochondrial inheritance represents a situation in which a maternal influence on a phenotype is attributable to the mother, the maternal effect being ascribed to the fact that mitochondrial DNA is transmitted by the mother to the fertilized zygote with the father having no such contribution. In the context of a family study such as the present one, however, one cannot rule out the possibility that the observed maternal effect is partially mediated by mitochondrial DNA but also by long lasting *in utero* maternal influences, genetic influences solely expressed through the chromosomes of maternal descent, or nongenetic contributions of the mother to variations in $\dot{V}O_{2max}$. The issue needs to be investigated at the DNA level, particularly mitochondrial DNA, so that the molecular differences responsible for this maternal effect can be identified and their influences on the phenotype described.

The observation of a significant maximal heritability in the presence of a surprisingly large maternal/mitochondrial inheritance component needs to be considered in light of the fact the subjects of the present study were all sedentary and untrained. The evidence for familial aggregation of $\dot{V}O_{2max}$ and for a contribution of maternal/mitochondrial inheritance may markedly differ for moderately or highly trained individuals. One cannot rule out, for instance, that sequence variation in mitochondrial DNA exerts a more profound influence on maximal aerobic power phenotypes among individuals who are characterized by sustained sedentariness, low level of familiarity with the exercise test, and low maximal cardiac output and oxygen delivery capacity.

In summary, the maximal heritability of $\dot{V}O_{2max}$ adjusted for age, sex, and body mass reaches about 50% of the residual variance. However, due to the presence of a significant spouse correlation, it is obvious that the genetic heritability is less than 50%. The data of the HERITAGE Family Study also reveal that maternal influence, perhaps mitochondrial inheritance, accounts for as much as 30% of the familial transmission. These estimates are essentially unchanged when the $\dot{V}O_{2max}$ of the sedentary subjects was further adjusted for body composition.

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