Familial Resemblance for Muscle Phenotypes in the HERITAGE Family Study

JESUS RICO-SANZ[1], TUOMO RANKINEN[1], DENIS R. JOANISSE[2], ARTHUR S. LEON[3], JAMES S. SKINNER[4], JACK H. WILMORE[5], D. C. RAO[6], and CLAUDE BOUCHARD[1]

[1]Pennington Biomedical Research Center, Human Genomics Laboratory, Baton Rouge, LA; [2]Physical Activities Sciences Laboratory, Laval University, and Laval Hospital Research Centre, Ste-Foy, Québec, CANADA; [3]School of Kinesiology and Leisure Studies, University of Minnesota, Minneapolis, MN; [4]Department of Kinesiology, Indiana University, Bloomington, IN; [5]Department of Health and Kinesiology, Texas A & M University, College Station, TX; and [6]Division of Biostatistics and Department of Genetics and Psychiatry, Washington University School of Medicine, St. Louis, MO

ABSTRACT

RICO-SANZ, J., T. RANKINEN, D. R. JOANISSE, A. S. LEON, J. S. SKINNER, J. H. WILMORE, D. C. RAO, and C. BOUCHARD. Familial Resemblance for Muscle Phenotypes in the HERITAGE Family Study. *Med. Sci. Sports Exerc.*, Vol. 35, No. 8, pp. 1360–1366, 2003. **Introduction/Purpose:** We hypothesized that skeletal muscle histological and biochemical phenotypes aggregate within families. **Methods:** Nineteen families (78 Caucasians) from the HERITAGE Family Study participated in the study. Proportions and areas of Type I, IIA, and IIX muscle fibers, capillary density, and maximal enzyme activities were determined in biopsy samples from the vastus lateralis obtained in the sedentary state and after a 20-wk endurance-training program. **Results:** In the sedentary state, there was evidence for familial resemblance for Type I fiber area ($P = 0.007$), number of capillaries around Type I and Type IIA fibers ($P = 0.04$), and Type I and IIA fiber areas per capillary ($P = 0.01$ and $P = 0.04$, respectively). Significant familial aggregation ($0.05 > P > 0.0001$) was observed for maximal activities of enzymes of the energy production pathways. With regard to the training response, significant familial aggregation ($0.05 > P < 0.0001$) was observed for maximal activities of enzymes of the energy production pathways. **Conclusion:** These data provide evidence of familial aggregation for enzyme activities of the main energy metabolism pathways of the skeletal muscle in the sedentary state and in response to regular exercise. **Key Words:** ENZYME, CAPILLARY, MUSCLE FIBER, SEDENTARY, TRAINING

Familial factors could contribute to the variability in human skeletal muscle phenotypes. Based on reports before 1983, interindividual variation in fiber type proportions appeared to be strongly genetically determined (1,20). This view was supported by the findings of a twin study (16). However, high estimates of genetic heritability for fiber type distribution seemed to be inconsistent with the technical and sampling variance associated with the biopsy procedure (25). In addition, physical activity level, age, and gender contribute to the variation in the percentage of Type I fibers (3,8,23,26). Subsequently, it was shown that the genetic effect on muscle fiber type distribution was much lower (3) and the heritability of the proportion of Type I fibers was estimated to be about 50% (21).

Genetic and shared familial environmental factors can also influence the activity of muscle enzymes of different metabolic pathways. In earlier studies, Howald (12) showed less variation in MZ twins compared with DZ twins in glyceraldehyde-3P-dehydrogenase (GAPDH) and 3-hydroxyacyl-CoA-dehydrogenase (HADH), whereas Komi et al. (16) found no significant genetic effect for the activities of creatine kinase (CK), ATPase, myokinase, phosphorylase (PHOS), hexokinase (HK), and lactate dehydrogenase enzymes. On the other hand, 25–50% of the variance in phosphofructokinase (PFK; glycolysis) and oxaloglutarate dehydrogenase (OGDH; citric acid cycle) levels were explained by genetic factors in another study (3).

Few studies to date have evaluated the familial aggregation of muscle phenotype responses to exercise training. No significant genotype-training interaction effect was found for fiber type distribution at any time during two 15-wk endurance-training programs in pairs of MZ twins (11,24). On the other hand, in one of the studies, PFK, malate dehydrogenase (MDH), HADH, and OGDH showed a genotype-training interaction effect during the last 8 wk of training, whereas only PFK showed this effect during the first 7 wk (11). In the other study, using a high-intensity intermittent training program lasting 15 wk, Simoneau et al. (24) found significant genotype-training interaction effects for CK, hexokinase (HK), lactate dehydrogenase (LDH), MDH, and OGDH in 14 pairs of MZ twins.

Although it appears that some level of familial inheritance affects the variation of muscle phenotypes, no examination of familial resemblance in skeletal muscle phenotypes has been performed in the sedentary state and in

Address for correspondence: Claude Bouchard, Ph.D., Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808; E-mail: bouchac@pbrc.edu.
Submitted for publication September 2002.
Accepted for publication February 2003.

0195-9131/03/3508-1360
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/01.MSS.0000079031.22755.63

response to an endurance-training program in nuclear families. The purpose of the present study was to examine the hypothesis that proportions and areas of the different muscle fiber types, muscle capillary supply, and enzyme activities of several metabolic pathways aggregate within families in the sedentary state and in response to exercise-training.

METHODS

Subjects

Seventy-eight subjects from 19 nuclear families of the HERITAGE Family Study participated in the study. All the families were investigated in the Quebec Clinical Center at Laval University. Subjects gave written consent to participate in the study and were advised of the risks and discomfort associated with the muscle biopsy. The study design, sample population, and protocol of the HERITAGE Family Study have been described earlier (2). The subjects were required to be between the ages of 17 and 40 yr for offspring, and less than 65 yr for parents. They were required to have been sedentary for at least 6 months. The study protocol was approved by each of the institutional review boards of the HERITAGE Family Study research consortium. Written informed consent was obtained from each participant.

Training Program

The training was conducted on cycle ergometers (Universal Aerobicycle, Cedar Rapids, IA). Subjects were endurance trained, three times a week, for 20 wk. The intensity of the exercise on cycle ergometers progressively increased from a heart rate corresponding to 55% of maximal oxygen uptake during the first 4 wk to 75% during the last 8 wk. The duration was also progressively increased from 30 $min \cdot d^{-1}$ during the first two weeks to 50 $min \cdot d^{-1}$, which was maintained from week 14 to the end of the program. A more detailed description of the training program can be found elsewhere (28). To maintain constant training heart rates, the ergometers were interfaced with a Mednet computer system (Universal Gym Mednet, Cedar Rapids, IA) to adjust automatically the power output to the individuals' heart rates. All training sessions were supervised on site.

Muscle Biopsy

Muscle biopsies were taken from the middle of the vastus lateralis, 12–16 cm above the patella and approximately 2 cm away from the epimysium by the percutaneous needle biopsy technique, applying suction as modified by Evans et al. (5). Each biopsy was partitioned into two pieces; one was frozen in isopentane cooled by liquid nitrogen and used for histochemistry, the other was employed for the determination of muscle enzyme activities and was flash frozen in liquid nitrogen.

Histochemical analysis. Based on the staining properties for myofibrillar adenosine triphosphatase, fibers were designated as Type I, Type IIA, and Type IIX according to the technique described by Mabuchi and Sréter (17). The mean muscle fiber area was determined by averaging the cross-sectional areas of 20 randomly selected fibers of each type. The number of capillaries around each of these fibers was counted to determine the capillary density and the area per capillary ratio in each fiber type.

Biochemical analysis. For the measurement of enzyme activities, tissue was homogenized in a glass-glass Duall homogenizer with 39 vol of ice-cold extracting medium (0.1 M Na-K-phosphate, 2 mM EDTA, pH = 7.2). Homogenate was transferred into 1.5-mL polypropylene tubes. This suspension was magnetically stirred on ice for 15 min and sonicated six times for 5 s at 20 W, on ice, with pauses of 85 s between pulses. The resulting homogenate was used for determination of maximal activity (V_{max}) of creatine kinase (CK; EC 2.7.3.2), phosphorylase (PHOS; EC), hexokinase (HK; EC 2.7.1.1), phosphofructokinase (PFK; EC 2.7.1.11), glyceraldehyde phosphate dehydrogenase (GAPDH; EC 1.2.1.12), 3-beta-hydroxyacyl CoA dehydrogenase (HADH; EC 1.1.1.35), carnitine palmitoyl transferase (CPT; EC 2.3.1.21), citrate synthase (CS; EC 4.1.3.7), and cytochrome *c* oxidase (COX; EC 1.9.3.1). Spectrophotometric techniques were conducted at 30°C, according to methods previously used (3,7). The V_{max} of enzymes were expressed in units (μmol of substrate per minute) per gram of wet weight tissue ($U \cdot g^{-1}$). In addition, lipoprotein lipase activity (LPL; EC 3.1.1.34) and the heparin releasable fraction of LPL were assayed as described by Taskinen et al. (30) and Simoneau et al. (27). LPL activity was expressed as nanomoles of FFA transformed/$min \cdot g^{-1}$ of wet weight muscle.

TABLE 1. Descriptive statistics of sample population.

	Males (N = 43) Mean ± SD	Females (N = 35) Mean ± SD
Age (yr)	33.4 ± 15.6	32.0 ± 13.7
Body height (cm)	178.5 ± 7.0	161.6 ± 5.8
Body weight (kg)	83.1 ± 15.5	63.1 ± 10.3
Body mass index ($kg \cdot m^{-2}$)	26.0 ± 4.2	24.2 ± 3.5

Statistical Analysis

The effects of training in the entire cohort were determined by a paired *t*-test. A one-way ANCOVA was performed to test the hypothesis of familial aggregation. The *F*-ratio that compares the between-family with the within-family variances was used as an indicator of the familial resemblance. Because skeletal muscle phenotypes are influenced by age, sex, and BMI (14,19,26), these covariates were included in the ANCOVA model. The training responses were also adjusted for the baseline value of the phenotypes.

RESULTS

Table 1 shows the descriptive statistics for the subject population. Table 2 summarizes the results for maximal activities of the enzymes. Significant increases in maximal

TABLE 2. Descriptive statistics of the vastus lateralis muscle maximal enzyme activities.

Phenotype	Pretraining			Training Response				
	N	Mean	SD	*N*	Mean (Post-Pre)	SD	*t*	*P*
PCr metabolism								
CK	78	394.1	69.5	76	17.9	71.9	2.17	0.033
Glycolysis								
PHOS	78	20.3	5.0	75	0.9	3.9	2.07	0.042
HK	78	2.6	0.6	75	0.3	0.7	3.29	0.002
PFK	78	58.6	14.0	76	2.3	11.5	1.75	0.084
GAPDH	78	423.9	94.4	76	3.7	65.9	0.49	0.624
Oxidative metabolism								
PHLPL*	78	0.46	0.21	73	−0.04	0.21	1.74	0.086
IMLPL*	78	0.41	0.17	73	0.03	0.19	1.51	0.136
TLPL*	78	0.87	0.27	73	−0.01	0.28	0.29	0.773
CPT	78	0.12	0.03	76	0.03	0.04	6.33	<.0001
HADH	78	16.8	3.4	76	3.3	4.4	6.64	<.0001
CS	78	12.4	3.2	76	4.0	4.9	7.08	<.0001
COX	78	7.5	2.2	76	1.9	3.3	5.07	<.0001

Enzyme activities are expressed in units (micromoles of substrate/min) per gram of wet weight tissue ($U \cdot g^{-1}$).
* LPL activity is expressed as nanomoles of FFA transformed/min per gram of wet weight tissue.
PH, heparin releasable, IM, intramuscular, T, total.

enzyme activities were observed for CK ($P = 0.033$), PHOS ($P = 0.042$), HK ($P = 0.002$), and CPT, HADH, CS, and COX (all $P < 0.0001$). Tables 3 and 4 show the proportions of fiber types and capillary density of the vastus lateralis muscle in the sedentary state and their training responses. The percentage of Type I fibers increased and the proportion of Type IIX fibers decreased significantly after the endurance-training program. Statistically significant increases were observed after the training program in the capillary density of all fiber types, ranging from 0.55 ± 0.68 capillaries per fiber for Type IIX to 0.76 ± 0.72 capillaries per fiber for Type I (all $P < 0.0001$). Despite nonsignificant increases in the cross-sectional area of the muscle in all fiber types, the cross-sectional area of the fibers per capillary decreased in all fiber types by 125, 132, and 157 μm^2 per capillary in Type IIX, IIA, and I fibers (all $P < 0.001$), respectively.

Strong evidence for familial aggregation ($P < 0.05$ to $P < 0.0001$) was observed for maximal activities of key regulatory enzymes of the phosphagen ($F = 6.5$), glycolytic ($F = 2.6–6.8$), and oxidative ($F = 2.0–7.0$) pathways in the sedentary state (Table 5). The response to training for the enzymes of the phosphagen ($F = 4.1$), glycolytic ($F = 2.3–7.9$), and oxidative ($F = 2.4–7.0$) pathways also showed very significant familial aggregation ($P < 0.01$ to $P < 0.0001$) (Table 5). Figures 1a and 1b illustrate the heterogeneity within and between families for selected maximal enzyme activities of the phosphagen, glycolytic, and oxidative pathways in the sedentary state and for the training-induced responses, respectively.

Tables 6 and 7 describe the familial aggregation for fiber types and capillary density phenotypes. There was evidence of a moderate familial aggregation for Type I fiber areas in the sedentary state ($F = 2.4$, $P = 0.007$) and Type IIX fiber areas in response to training ($F = 2.1$, $P = 0.03$). There was some evidence for familial resemblance in the number of capillaries around Type I ($F = 1.9$, $P = 0.039$) and Type IIA fibers ($F = 1.9$, $P = 0.044$), and in the fiber area per capillary in Type I ($P = 0.011$) and Type IIA fibers ($P = 0.042$) in the sedentary state. The number of capillaries per fiber and fiber areas per capillary (I and IIa) were not correlated in the present sample. No significant familial aggregation was found in the responsiveness to training for any of these phenotypes.

DISCUSSION

The present study examined the hypothesis that skeletal muscle phenotypes aggregate within families in the sedentary state as well as in the response to regular exercise. The results showed weak familial resemblance for fiber types, fiber areas, and capillary supply in the sedentary state, and in their responses to training. However, maximal enzyme activities of the phosphagen, glycolytic, and oxidative pathways appear to be influenced to a great extent by familial factors both in the sedentary state and for the changes induced by training.

TABLE 3. Descriptive statistics of the proportions and areas of the fiber types in the vastus lateralis muscle.

Phenotype	Pretraining			Training Response				
	N	Mean	SD	*N*	Mean (Post-Pre)	SD	*t*	*P*
Fiber type distribution								
% Type I	73	43.2	11.8	67	3.5	9.4	3.07	0.003
% Type IIA	73	36.8	8.9	67	1.8	9.9	1.5	0.140
% Type IIX	73	20.0	11.2	67	−5.4	10.3	4.49	<.0001
Fiber areas (μm^2)								
Type I	73	5500	1222	67	86	872	0.81	0.421
Type IIA	73	5027	1559	67	66	949	1.33	0.188
Type IIX	70	4172	1784	61	170	998	0.78	0.435

TABLE 4. Descriptive statistics of the capillary density in vastus lateralis muscle.

Phenotype	Pretraining			Training Response				
	N	Mean	SD	*N*	Mean (Post-Pre)	SD	*t*	*P*
Capillaries around fibers								
Type I	73	4.58	0.81	66	0.76	0.72	8.65	<0.0001
Type IIA	73	4.40	1.00	66	0.63	0.77	6.13	<0.0001
Type IIX	69	3.47	1.00	59	0.55	0.68	4.44	<0.0001
Area of Fibers per capillary (μm^2)								
Type I	73	1206	185	66	−157	171	7.48	<0.0001
Type IIA	73	1137	210	66	−132	182	5.88	<0.0001
Type IIX	69	1187	283	59	−125	251	3.78	<0.0001

Maximal Enzyme Activity

Sedentary state. A very significant familial aggregation was found for maximal activities of selected enzymes of the phosphagen, glycolytic, and oxidative pathways. The greater resemblance also observed in MZ twins compared with DZ twins for PFK, OGDH (3), GAPDH, and HADH activities suggests that the genotype plays a significant role in the activities of the enzymes of energy metabolism pathways. Moreover, all fractions of muscle LPL, which hydrolyzes chylomicron and VLDL triglycerides liberating fatty acids for uptake into muscle (9), were characterized by lower variation within families compared with between families. Thus, enzymes of high-energy phosphate, carbohydrate, and lipid metabolism appear to meaningfully aggregate within families in the sedentary state.

Response to training. Significant changes were observed in the maximal activities of CK, PHOSP, HK, CPT, HADH, CS, and COX after the HERITAGE training program. Although a 23-wk program produced a significant increase in the activities of HADH and malate dehydrogenase, 15-wk training programs increased CK, HK, PFK and LDH (24), and HK, PFK, LDH, MDH, HADH activities (11,22). The present findings indicate that the 20-wk training program was of sufficient duration and intensity to affect the phosphagen, glycolytic, and oxidative pathways.

There was significant familial aggregation for the training response of the enzymes of the energy metabolic pathways. Only the training response of the maximal activities of total and subfractions of LPL did not show familial resemblance. In one twin study, there were no significant differences in the intra-pair variance between MZ and DZ twins for the response to training of HK, GADPH, HADH, MDH, and SDH activities (12). However, training-induced changes in CK, HK, LDH, MDH, and OGDH activities and in the PFK/OGDH ratio were more similar within than between the pairs of MZ twins (24). A significant genotype-training interaction has also been observed for PFK during the first 7 wk of a training program in MZ twins, and for PFK, MDH, and HADH during the last 8 wk of training, whereas HADH showed a significant *F*-ratio of 5.4 for the genotype training interaction over the entire 15-wk program (11).

Fiber Types

Sedentary state. The results of the present study showed that familial factors do not exert a major influence on fiber type proportions in the sedentary state. The various types of fibers in human skeletal muscle are visible before 20 wk of gestation (4,6), with a progressive appearance of Type I fibers around 18–19 wk and Type IIA and IIX fibers during the last 3 months of pregnancy (6). At birth, 15–20% of the fibers appear to be undifferentiated (4). There are changes in the fiber type distribution and cross-sectional area up to 17 yr of age (29). During adolescence, the upper leg muscles increase the proportion of Type II, whereas the lower leg muscles increase the proportion of Type I fibers (29). The first results from MZ and DZ twin studies appeared to strengthen the hypothesis that the genotype determines fiber type proportions (16). However, the relatively high technical variance of the biopsy technique (25), in addition to the findings suggesting a contribution from the physical activity level (23), provoked a reexamination of this hypothesis. It has been subsequently proposed that the

TABLE 5. Familial aggregation of maximal enzyme activities in the vastus lateralis muscle.

Phenotype	Pretraining			Training Response		
	N	*F*	*P*	*N*	*F*	*P*
PCr metabolism						
CK	78	6.5	<0.0001	76	4.13	<0.0001
Glycolysis						
PHOS	78	6.76	<0.0001	75	2.42	0.007
HK	78	2.65	0.003	75	4.42	<0.0001
PFK	78	3.41	0.0002	76	2.34	0.009
GAPDH	78	4.89	<0.0001	76	2.68	0.003
Oxidative metabolism						
PH_LPL	78	2.05	0.021	73	1.79	0.054
IM_LPL	78	2.22	0.012	73	1.66	0.080
T_LPL	78	2.01	0.024	73	1.35	0.197
CPT	78	5.02	<0.0001	76	3.95	<0.0001
HADH	78	4.39	<0.0001	76	7.03	<0.0001
CS	78	5.62	<0.0001	76	5.41	<0.0001
COX	78	5.08	<0.0001	76	3.30	0.0004

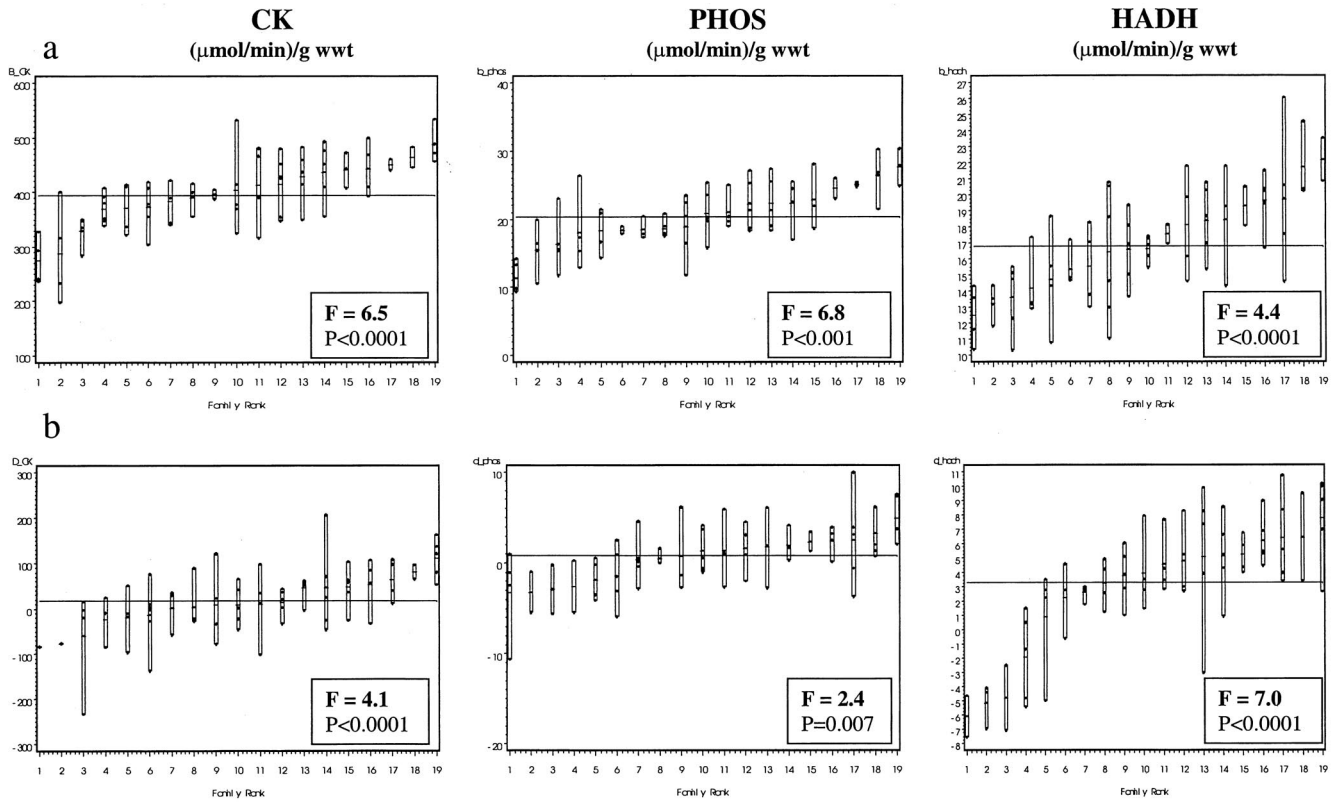

FIGURE 1—Familial aggregation for regulatory enzymes of the phosphagen (CK), glycolytic (PHOS), and oxidative pathways (HADH) in (a) the sedentary state and (b) the response to training.

genetic component for Type I fibers is around 45% (21). These observations are compatible with the results of the present study, which indicate that familial factors do not contribute strongly to fiber type proportion in humans.

The cross-sectional area of muscle fibers could also be potentially determined by familial factors. The activity level has been found to add to the variation of the cross-sectional areas of the fibers (10). In the present study, the variance between families compared with within families was significant only with respect to the area of Type I fibers, and there was no significant familial resemblance for the percentage of the area occupied by the different fibers in the sedentary state.

Response to training. The exercise training program of the present study provoked a significant increase of 3.5% units in Type I fibers, whereas the Type IIX fibers decreased by 5.4% units. Several training studies before the early 1980s showed that regular exercise did not induce changes in percent Type I fibers (20). However, several studies have since found changes in fiber type proportions after training or detraining suggesting that muscle fiber type proportions can adapt to the environmental stress of regular exercise (23). In the present study, the response of these muscle phenotypes to 20 wk of endurance training did not seem to aggregate significantly within families, indicating that environmental factors play an important role in the plasticity of skeletal muscle fiber type distribution and area.

Capillary Density

Sedentary state. Oxidative and glycolytic skeletal muscle fibers differ in capillary density (13). In agreement with these observations, the more glycolytic Type IIX fibers had about 25% less capillaries compared with the oxidative

TABLE 6. Familial aggregation of the proportions and areas of the fiber types in the vastus lateralis muscle.

	Pretraining			Training Response		
Phenotype	***N***	***F***	***P***	***N***	***F***	***P***
Fiber types						
%Type I	73	1.62	0.094	67	0.62	0.854
%Type IIA	73	0.54	0.920	67	1.81	0.057
%Type IIX	73	1.27	0.251	67	1.13	0.355
Fiber areas						
Type I	73	2.43	0.007	67	1.27	0.258
Type IIA	73	1.28	0.245	67	1.05	0.429
Type IIX	70	1.31	0.224	61	1.14	0.358

TABLE 7. Familial aggregation of the capillary density in vastus lateralis muscle.

Phenotype	Pretraining			Training Response		
	N	*F*	*P*	*N*	*F*	*P*
Capillaries around fibers						
Type I	73	1.90	0.0390	66	1.65	0.0918
Type IIA	73	1.87	0.0438	66	1.75	0.0697
Type IIX	69	0.91	0.5628	58	0.99	0.4933
Area of fibers per capillary						
Type I	73	2.31	0.0108	66	0.93	0.5432
Type IIA	73	1.88	0.0419	66	0.65	0.8352
Type IIX	69	1.30	0.2349	58	0.75	0.7371

fibers in the present study. To our knowledge, no other study has evaluated the familial aggregation of the skeletal muscle capillary density. Our results showed significant familial resemblance for the capillary density only in Type I and IIA fibers in the sedentary state. The ratio of the area of these fibers per capillary also showed significant familial aggregation in the sedentary state. Our results therefore suggest that the genotype and/or familial environment remain important factors in the development of capillary supply to the oxidative skeletal muscle fibers during adulthood.

Response to training. Capillaries proliferated significantly in all fiber types after training. Our results are in agreement with those of others who showed that training provokes higher capillary density in human muscle (15). As the capillary density appears to be regulated as a function of the oxygen demand irrespective of the fiber types (18), the present findings indicate that all fiber types were metabolically stressed during training. Increased capillarization and decreased ratio of the cross-sectional area of the fibers per capillary increases oxygen extraction, oxygen conductance, blood flow, and maximal oxygen uptake rate of the exercising muscle (18). One could hypothesize that changes in capillary density in skeletal muscle provoked by exercise training are influenced by familial factors. However, in the present study, no indication for familial aggregation was found for the capillary density response to training. Exposure to high metabolic demands could play a more significant role than familial factors *per se* in the microcirculation adaptation to training.

In conclusion, the present family study showed very significant familial aggregation for maximal enzyme activities of the main energy metabolism pathways in the sedentary state and in the responsiveness to regular exercise. However, no compelling evidence for familial resemblance for fiber types and capillary supply, and their adaptation to a moderate-intensity exercise-training program was observed. Clearly, this is one of the largest studies of its kind, and yet the sample size (19 families) was too small to detect anything but large familial effects. Therefore, it is unclear at this time whether the lack of significance for some phenotypes is due to the small sample size, a small size effect, or is truly the case. Moreover, the data do not allow to test for sex-specific effects due to the sample size limitation. Whether the familial aggregation observed in the present set of families of white ancestry would apply to other ethnic groups cannot be addressed with the data of this HERITAGE Family Study supplementary project.

This paper is dedicated to the memory of the late Jean-Aimé Simoneau, Ph.D., who coordinated this ancillary project of the HERITAGE Family Study.

The HERITAGE Family Study is supported by the NHLBI through Grants HL45670 (to C.B.), HL47323 (to A.S.L), HL47317 (to D.C.R), HL47327 (to J.S.S.), and HL47321 (to J.H.W.). Arthur S. Leon is partially supported by the Henry L. Taylor endowed Professorship in Exercise Science and Health Enhancement. Claude Bouchard is partially supported by the George A. Bray Chair in Nutrition.

REFERENCES

1. Annex, B. H., C. E. Torgan, P. Lin, et al. Induction and maintenance of increased VEGF protein by chronic motor nerve stimulation in skeletal muscle. *Am. J. Physiol.* 274:H860–H867, 1998.
2. Bouchard, C., A. S. Leon, D. C. Rao, J. S. Skinner, J. H. Wilmore, and J. Gagnon. The HERITAGE Family Study: aims, design, and measurement protocol. *Med. Sci. Sports Exerc.* 27: 721–729, 1995.
3. Bouchard, C., J. A. Simoneau, G. Lortie, M. R. Boulay, M. Marcotte, and M. C. Thibault. Genetic effects in human skeletal muscle fiber type distribution and enzyme activities. *Can. J. Physiol. Pharmacol.* 64:1245–1251, 1986.
4. Colling-Saltin, A. S. Enzyme histochemistry on skeletal muscle of the human foetus. *J. Neurol. Sci.* 39:169–185, 1978.
5. Evans, W. J., S. D. Phinney, and V. R. Young. Suction applied to a muscle biopsy maximizes sample size. *Med. Sci. Sports Exerc.* 14:101–102, 1982.
6. Farkas-Bargeton, E., M. F. Diebler, M. L. Arsénio-Nunes, R. Wehrlé, and B. Rosenberg. Histochemical, quantitative and ultrastructural maturation of human fetal muscle. *J. Neurol. Sci.* 31:245–259, 1977.
7. Gauthier, J. M., R. Theriault, G. Theriault, Y. Gelinas, and J. A. Simoneau. Electrical stimulation-induced changes in skeletal muscle enzymes of men and women. *Med. Sci. Sports Exerc.* 24:1252–1256, 1992.
8. Glenmark, B., G. Hedberg, and E. Jansson. Changes in muscle fibre type from adolescence to adulthood in women and men. *Acta Physiol. Scand.* 146:251–259, 1992.
9. Goldberg, I. J., and M. Merkel. Lipoprotein lipase: physiology, biochemistry, and molecular biology. *Frontiers Biosci.* 6:388–405, 2001.
10. Haggmark, T., E. Jansson, and E. Eriksson. Fiber type area and metabolic potential of the thigh muscle in man after knee surgery and immobilization. *Int. J. Sports Med.* 2:12–17, 1981.
11. Hamel, P., J. A. Simoneau, G. Lortie, M. R. Boulay, and C. Bouchard. Heredity and muscle adaptation to endurance training. *Med. Sci. Sports Exerc.* 18:690–696, 1986.
12. Howald, H. Ultrastructure and biochemical function of skeletal muscle in twins. *Ann. Hum. Biol.* 3:455–462, 1976.
13. Hudlicka, O., M. Brown, and S. Egginton. Angiogenesis in skeletal and cardiac muscle. *Physiol. Rev.* 72:369–417, 1992.

14. KERN, P. A., R. B. SIMSOLO, and M. FOURNIER. Effect of weight loss on muscle fiber type, fiber size, capillarity, and succinate dehydrogenase activity in humans. *J. Clin. Endocrinol. Metab* 84: 4185–4190, 1999.
15. KLAUSEN, K., L. B. ANDERSEN, and I. PELLE. Adaptive changes in work capacity, skeletal muscle capillarization and enzyme levels during training and detraining. *Acta Physiol. Scand.* 113:9–16, 1981.
16. KOMI, P. V., J. H. VIITASALO, M. HAVU, A. THORSTENSSON, B. SJÖDIN, and J. KARLSSON. Skeletal muscle fibres and muscle enzyme activities in monozygous and dizygous twins of both sexes. *Acta Physiol. Scand.* 100:385–392, 1977.
17. MABUCHI, K., and F. A. SRÉTER. Actomyosin ATPase. II. Fiber typing by histochemical ATPase reaction. *Muscle Nerve* 3:233–239, 1980.
18. POOLE, D. C., and O. MATHIEU-COSTELLO. Relationship between fiber capillarization and mitochondrial volume density in control and trained rat soleus and plantaris muscles. *Microcirculation* 3:175–186, 1996.
19. PROCTOR, D. N., W. E. SINNING, J. M. WALRO, G. C. SIECK, and P. W. LEMON. Oxidative capacity of human muscle fiber types: effects of age and training status. *J. App. Physiol.* 78:2033–2038, 1995.
20. SALTIN B., and P. D. GOLLNICK. Skeletal muscle adaptability: significance for metabolism and performance. In: *Skeletal Muscle*, L. D. Peachey, R. H. Adrian, and S. R. Geiger (Eds.). Bethesda, MD: American Physiological Society, 1983, pp. 555–631.
21. SIMONEAU, J. A., and C. BOUCHARD. Genetic determinism of fiber type proportion in human skeletal muscle. *FASEB J.* 9:1091–1095, 1995.
22. SIMONEAU, J. A., G. LORTIE, M. R. BOULAY, et al. Human muscle enzyme alterations after aerobic and anaerobic training. *Can. J. Appl. Sport Sci.* 8:217, 1983.
23. SIMONEAU, J. A., G. LORTIE, M. R. BOULAY, M. MARCOTTE, M. C. THIBAULT, and C. BOUCHARD. Human skeletal muscle fiber type alteration with high-intensity intermittent training. *Eur. J. Appl. Physiol. Occup. Physiol.* 54:250–253, 1985.
24. SIMONEAU, J. A., G. LORTIE, M. R. BOULAY, M. MARCOTTE, M. C. THIBAULT, and C. BOUCHARD. Inheritance of human skeletal muscle and anaerobic capacity adaptation to high-intensity intermittent training. *Int. J. Sports Med.* 7:167–171, 1986.
25. SIMONEAU, J. A., G. LORTIE, M. R. BOULAY, M. C. THIBAULT, and C. BOUCHARD. Repeatability of fibre type and enzyme activity measurements in human skeletal muscle. *Clin. Physiol.* 6:347–356, 1986.
26. SIMONEAU, J. A., G. LORTIE, M. R. BOULAY, M. C. THIBAULT, G. THERIAULT, and C. BOUCHARD. Skeletal muscle histochemical and biochemical characteristics in sedentary male and female subjects. *Can. J. Physiol. Pharmacol.* 63:30–35, 1985.
27. SIMONEAU, J. A., J. H. VEERKAMP, L. P. TURCOTTE, and D. E. KELLEY. Markers of capacity to utilize fatty acids in human skeletal muscle: relation to insulin resistance and obesity and effects of weight loss. *FASEB J.* 13:2051–2060, 1999.
28. SKINNER, J. S., K. M. WILMORE, J. B. KRASNOFF, et al. Adaptation to a standardized training program and changes in fitness in a large, heterogeneous population: the HERITAGE Family Study. *Med. Sci. Sports Exerc.* 32:157–161, 2000.
29. TAMBOVTSEVA, R. V., and I. A. KORNIENKO. [Development of various types of muscle fibers in the quadriceps femoris and the soleus during human ontogenesis]. *Arkh. Anat. Gistol. Embriol.* 91:96–99, 1986.
30. TASKINEN, M. R., E. A. NIKKILÄ, J. K. HUTTUNEN, and H. HILDEN. A micromethod for assay of lipoprotein lipase activity in needle biopsy samples of human adipose tissue and skeletal muscle. *Clin. Chim. Acta* 104:107–117, 1980.