**HERITAGE Family Study Review Paper**

**Supplementary Tables**

**Supplementary Table S1. HERITAGE Consortium Steering Committee**

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| Claude Bouchard, PhD; *Chairperson* | Laval University (until 1999); later Pennington Biomedical Research Center |
| Jacques Gagnon, PhD;  *Project Director* (1992-1999) | Laval University |
| Jean Paul Albert, MBA;  *Administrator* (1992-1999)  Tuomo Rankinen, PhD;  *Project Director* (1999-2012) | Laval University  Pennington Biomedical Research Center |
| Arthur S. Leon, MD | University of Minnesota |
| D. C. Rao, PhD | Washington University |
| James S. Skinner, PhD | Arizona State University (until 1995); Indiana University (1996+) |
| Jack H. Wilmore, PhD | The University of Texas at Austin (until 1997), later Texas A&M University, then back to The University of Texas at Austin after 2003. |

**Supplementary Table S2. HERITAGE Consortium Advisory Board (1992-2008)**

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| Elizabeth Barrett-Connor, MD | University of California, San Diego |  |
| Jean Davignon, MD | Clinical Research Institute of Montreal |  |
| E. Randy Eichner, MD  (1992-2002) | University of Oklahoma |  |
| Robert C. Elston, PhD | Louisiana State University and Case Western Reserve University |  |
| William L. Haskell, PhD | Stanford University |  |
| Rudy Leibel, MD  (2002-2008) | Columbia University |  |
| Eric Ravussin, PhD  (2002-2008) | Pennington Biomedical Research Center |  |

**Supplementary Table S3. HERITAGE Coordinating Centers, Clinical Centers, and Core Laboratories: List of Personnel**

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| **Laval University Consortium Coordinating Center and Clinical Center** | |
| PI: Claude Bouchard, PhD  Local Project Coordinator: Marcelle Lareau, MSc | |
|  |  |
| Jean-Paul Albert, MBA | Benoit Lamarche, PhD |
| Manon Baril, BSc | Claude Leblanc, MSc |
| Jean Bergeron, MD | Gilles Lortie, MD, PhD |
| Come S. Bouchard, MSc | Isabel Mercier, MSc |
| Anne-Marie Bricault, MSc | François Michaud, BSc |
| Yvon Chagnon, PhD | Chantal Paré, BSc |
| Jean-Pierre Despres, PhD | Louis Pérusse, PhD |
| Diane Drolet, MSc | Denis Prud’homme, MD, MSc |
| Jacques Gagnon, PhD | Jean-Aime Simoneau, PhD |
| My-Anh Ho-Kim, MSc | Germain Thériault, MD |
| Karen Horth, | Angelo Tremblay, PhD |
| Louise Laberge, | John Weisnagel, MD, PhD |
|  |  |
| **Washington University Data Coordinating Center** | |
| PI: D. C. Rao, PhD |  |
|  |  |
| Ping An, MD | Zhaohai Li, PhD |
| Ingrid B. Borecki, PhD | Stephen Mendel, PhD |
| Harry Cheng, MSc | Laura E. Mitchell, PhD |
| Gu Chi, PhD | Michael A. Province, PhD |
| Warwick Daw, PhD | Treva Rice, PhD |
| Habib El-Moalem, PhD | Kathryn A. Schallert, BSc |
| John O. Holloszy, MD | Kenneth B. Schechtman, PhD |
| Yuling Hong, MD | George P. Vogler, PhD |
| David J. Lerner, BSc |  |
|  |  |
| **Laval University Core Laboratories** | |
| ***Diabetes Research Unit*** | ***Lipid Research Center*** |
| André Nadeau, MD, PhD; Director | Paul Lupien, MD, PhD; Director |
| Yolande Montreuil, RN | Jean-Pierre Després, PhD |
| Gilles Tancrède, MSc | Sital Moorjani, PhD |
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| ***DNA and Cell Line Unit*** | ***Steroid Laboratory*** |
| France T. Dionne, PhD; Director | Alain Bélanger, PhD; Director |
| Monique Chagnon, ART | Simon Caron, MSc |
| Caroline Noel, BSc | Fernand Labrie, MD, PhD |
| Marie-Christine Thibault, PhD | Line Lavoie, MSc |
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| **University of Minnesota Clinical Center** | |
| PI: Arthur S. Leon, MD  Local Project Coordinator: Ava J. Walker, PhD | |
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| Marilyn Borkon, | Marcella Meyers, PhD |
| Fernando S. Branco, MD | James P. Norton, MSc |
| Erik J. Ekstrom, RD | Robert C. Serfass, PhD |
| Steve Gaskill, PhD | M. Katie Schmitz, MSc |
| William V. Mendoza, MD |  |
|  |  |
| **Arizona State University Clinical Center (Until1995)**  **Indiana University Clinical Center (1996+)** | |
| PI: James S. Skinner, PhD  Local Project Coordinator in Arizona: Kristine M. Wilmore, MA  Local Project Coordinator in Indianapolis: Joanne Krasnoff, PhD | |
|  |  |
| Kelly Enders, RN |  |
| Anna A. Jaskolska, PhD |  |
| Artur J. Jaskolski, PhD |  |
|  |  |
| **University of Texas at Austin Clinical Center** | |
| PI: Jack H. Wilmore, PhD  Local Project Coordinator: Philip R. Stanforth, MSc | |
|  |  |
| Melissa Domenick, MA |  |
| David W. Hayes, MD |  |
| Paul J. Roach, MD |  |

**Supplementary Table S4. Listing of some of the most novel or impactful findings from the HERITAGE Family Study from 1995 to 2021**.

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| --- | --- | --- | --- | --- |
| **Novel or Impactful Findings** | **Trait(s)** | **Details** | **Citation(s)** | |
| **Heterogeneity of Training Responses** | | | | |
| Large inter-individual differences in phenotype responses to endurance training | VO2max | VO2max responses ranged from no gain to over 1 L/min [-5% to +48%] | Bouchard and Rankinen 2001;  Skinner, Jaskolski et al. 2001  Boule, Weisnagel et al. 2005 | |
| IVGTT traits | The proportion of subjects who had no change or decreases in IVGTT traits ranged from 42-55% |
| No correlation between baseline VO2max and its changes with training | VO2max | The correlation between baseline and delta VO2max was 0.08, with baseline levels after adjustments explaining only 2% of the variance in delta VO2max | Skinner, Jaskolski et al. 2001; Sarzynski, Ghosh et al. 2017 | |
| No aggregation of training responsiveness in individuals or subgroups | VO2max | There were low, average, and high VO2max responses across ages, both sexes, both ethnic groups, and levels of initial VO2max. | Skinner, Jaskolski et al. 2001 | |
| VO2max, %fat, AVF, insulin, HDL-C, small LDL, GlycA | Almost half of the cohort had at least one high response and one low response across seven cardiometabolic traits. There is a high degree of trait specificity in training responsiveness. | Barber BJSM in press | |
| Some unfavorable responses to endurance training | fasting insulin; HDL-C; TG; SBP | Prevalence of potentially "adverse" response in HERITAGE ranged from 6 to 9% for the four traits. | Bouchard Plos One 2012 | |
| **Familial Aggregation of Baseline Phenotype Levels** | | | | |
| Within-subject variability | VO2max | Within-subject standard deviation from measures repeated days and weeks apart range from 108 to 137 mL O2/min with CV of 4.1 to 5.0% | Wilmore, Stanforth et al, 1998; Skinner, Wilmore et al, 1999; Shephard, Rankinen et al, 2004; Sarzynski, Ghosh et al, 2017; plus unpublished data. | |
| Significant familial resemblance for intrinsic VO2max | VO2max | 2.7 times more variance between families than within families. Heritability of intrinsic VO2max was 51%, with significant maternal heritability (29%) | Bouchard, Daw et al. 1998 | |
| Significant familial aggregation for intrinsic submaximal VO2 | VO2 at 50W, 60%, 80% | Maximal heritability estimates ranged from 48-70% and 29-48% for maternal heritability | Perusse, Gagnon et al. 2001 | |
| Significant familial aggregation for intrinsic submaximal Q & SV | SV & Q at 50W and 60% VO2max | Maximal heritability estimates of 46% for SV and Q at 60% VO2max and 41% & 42% at 50W | An, Rice et al. 2000 | |
| Significant familial aggregation for visceral fat | AVF | Heritability of 47-48%, independent of total body fat | Rice, Despres et al. 1997 | |
| Higher heritability of resting BP in Black subjects | Resting SBP & DBP | Heritability of SBP & DBP were 68% and 56% in Black subjects vs 43% & 24% in White subjects. | Gu 1998 | |
| Significant familial aggregation for muscle enzyme activities | CK, PHOS, HK, PFK, GAPDH, LPL, CPT, HADH, CS, COX | Strong familial aggregation for activities of baseline muscle enzymes related to PCr, glycolytic, and oxidative metabolism. | Rico-Sanz, Rankinen et al. 2003; Rankinen, Bouchard et al. 2005 | |
| Significant familial aggregation for markers of oxidative stress | LDL-ox, C50-AAPH, TBARS, glutathione | Heritability for oxidative stress traits ranged from 31% to 44%. | Blache, Lussier-Cacan et al. 2007 | |
| **Familial Aggregation of Training Response** | | | | |
| Significant familial aggregation for VO2max training response | VO2max | Heritability was 47%, with maternal inheritance accounting for 28% | Bouchard, An et al. 1999 | |
| Significant familial aggregation for submaximal VO2 training response | VO2 at 50W, 60%, 80% | Heritability values ranged from 23% to 57% for the training response of submaximal measures of VO2 | Perusse, Gagnon et al. 2001 | |
| Significant familial aggregation of submaximal exercise BP and HR training responses | HR50, HR60%, SBP50 | Heritability for HR50, HR60%, SBP50 responses were 34%, 29%, 22%. Heritability for DBP traits and all HR and BP traits were lower in Black subjects | An, Perusse 2003 | |
| Significant familial aggregation for submaximal Q & SV training responses | SV & Q at 50W and 60% VO2max | Heritability ranging from 24 to 38% for SV and Q at 50W and 60% VO2max | An, Rice et al. 2000 | |
| Significant familial aggregation of inter-individual variation in plasma lipid responsiveness to training | TC, TG, LDL-C, apoB, HDL-C, HDL2-C, HDL3-C, apoA-I | Heritability ranged from 25% to 38% for lipid response traits. Exceptions were for heritability levels near 60% for changes in apoB in Blacks and HDL2-C in Whites and a lack of heritability for change in LDL-C in Black subjects | Rice, Despres et al. 2002 | |
| Significant familial aggregation for training response of markers of oxidative stress | LDL-ox, C50-AAPH, TBARS, glutathione | Heritability for oxidative stress training response traits ranged from 35% to 84% | Blache, Lussier-Cacan et al. 2007 | |
| Significant familial aggregation for training response of muscle enzyme activities | CK, PHOS, HK, PFK, GAPDH, CPT, HADH, CS, COX | Strong familial aggregation found for training response of muscle enzymes related to PCr, glycolytic, and oxidative metabolism | Rico-Sanz, Rankinen et al. 2003; Rankinen, Bouchard et al. 2005 | |
| **Ethnic and sex differences in responses to training** | | |  | |
| Training responses of submaxmial exercise measures of hemodynamic  traits differed by sex and ethnic groups | HR, SBP, DBP at 50W | Submaximal HR, SBP, DBP decreased with training, with greater reductions in women compared to men and in Black and older subjects compared to White and younger subjects. | Wilmore, Stanforth 2001 pp 10-116 | |
| a-vO2 diff, SV, Q, and VO2 at 50W | Black men did not increase a-vO2 diff at 50W. Thus, on average Black men had greater increases in SV50 and smaller decreases in Q50 compared with White men to achieve similar VO250. | Wilmore, Stanforth 2001 MSSE pp 99-106 | |
| Significant sex interactions for insulin sensitivity response to training | Si | Insulin sensitivity increased by 10% in the total cohort, with the increase larger in men than women (16% vs 5%). | Boule, Weisnagel et al. 2005 | |
| Significant ethnic and sex differences in lipid, lipoprotein, and lipase activity responses to training | ApoA-I, HDL2-C | ApoA-I increased more in women than men, in Black than White subjects, and in offspring than in parents. Black subjects experienced greater increases in HDL2-C compared to White subjects. | Leon, Rice et al. 2000 | |
| LPL activity | LPL activity increased in all subgroups except Black men. | Bergeron, Couillard et al. 2001 | |
| **Response of other traits to training** |  |  |  | |
| Little influence of endurance training on markers of oxidative stress | LDL-ox, C50-AAPH, TBARS, antioxidants, and aminothiols | Only erythrocyte resistance to hemolysis significantly changed with training, which interacted with smoking status (smokers did not experience beneficial effects of training on erythrocytes), and was significant in women only. | Blache, Lussier-Cacan et al. 2007 | |
| No change in RMR with training . | RMR via indirect calorimetry | Sample size (N=77) was larger than previous studies. No change in RMR at 24 or 72 hrs post-training. | Wilmore, Stanforth et al. 1998 | |
| Favorable changes in clinically relevant lipoprotein subfractions in response to training | NMR-based lipoprotein subfractions | Large HDL-P and LDL-P increased, while small LDL-P and all VLDL subfractions and VLDL-P size decreased with training. These findings were not captured with traditional lipid profiling (i.e., TG and LDL-C did not change in total sample). | Sarzynski, Burton et al. 2015 | |
| **Genome-wide linkage studies of baseline and response phenotypes** | | | | |
| Identification of QTLs for baseline VO2max and for VO2max response | VO2max | QTLs on 4q, 8q, 11p, and 14q reported for baseline VO2max. QTLs on 1p, 2p, 4q, 6p, and 11p identified for change in VO2max. | Bouchard, Rankinen et al. 2000 | |
| Dense mapping of four QTLs identified strong candidate genes for submaximal exercise capacity and hemodynamic responses to training | SV50, HR50 | Titin, kinesin family member 5B, cAMP responsive element binding protein 1, *MIPEP* and *SGCG* genes identified as strong candidates for changes in submaximal SV and HR and submaximal exercise capacity. | Rankinen, Rice et al. 2003; Argyropoulos, Stutz et al. 2009; Rankinen, Argyropoulos et al. 2010; Rice, Sarzynski et al, 2012 | |
| **First GWAS of exercise response traits** | |  |  | |
| GWAS of VO2max response to endurance training | VO2max | 39 SNPs were associated at p<1.5x10-4, with a panel of 21 SNPs accounting for 49% of the variance in VO2max trainability. | Bouchard, Sarzynski et al. 2011 | |
| GWAS of submaximal HR response to training | HR50 | 40 SNPs associated at p<9.9x10-5, with top hit 8x10-7. Nine SNPs accounted for the genetic variance of the submaximal exercise HR response to training. | Rankinen, Sung et al. 2012 | |
| **Molecular signatures of exercise response derived from integrative analyses of genomic and transcriptomic profiles** | | | | |
| Muscle gene expression and SNP signatures predict VO2max response to endurance training | VO2max | Genome-wide baseline muscle gene expression and validation identified a 29-RNA signature that predicted changes in VO2max. Candidate genes from this predictor and the literature led to a 11 SNP signature that explained 23% of the variance in VO2max trainability. | | Timmons, Knudsen et al. 2010 |
| Combined genome-wide and transcriptome-wide analysis identifies SNPs associated with TG response to training | TG | GWAS identified 4 SNPs accounting for the genetic variance of TG response, while molecular signature based on the baseline expression of 11 genes predicted 27% of TG changes in response to training. An 8-SNP score comprised of 4 SNPs each from transcriptomics and GWAS was the strongest predictor of TG training response. | Sarzynski, Davidsen et al. 2015 | |
| GWAS and transcriptional signature of insulin sensitivity response to training | Si | Integrative analysis of functional genomic and transcriptomic profiles identified combined variation in genes linked to cholinergic, calcium, and chemokine signaling associated with Si training response. MEF2A transcription factor was the most significant candidate driving the transcriptional signature associated to ∆Si, strengthening the relevance of calcium signaling in exercise training-mediated Si response. | Takeshita, Davidsen et al. in press | |
| **Proteomic signatures of VO2max and its trainability** | | |  | |
| Plasma protein signature of cardiorespiratory fitness level | VO2max | Elastic net regression identified 115 proteins highly correlated (r2=0.80) with measured VO2max, which was replicated in the validation dataset, with an r2 of 0.71 (Figure 9). | Williams, Kivimaki et al. 2019 | |
| Plasma proteins associated with intrinsic VO2max and its trainability | VO2max | 147 proteins were associated with baseline VO2max, while 102 baseline proteins were associated with changes in VO2max, with minimal overlap (only 5 proteins) between protein sets. A baseline 56 protein signature improved prediction of VO2max response (AUC 0.84) compared to a model of only clinical variables (AUC 0.62). | Robbins, Peterson et al. 2021 | |
| **Bioinformatics explorations of intrinsic VO2max and its trainability** | | |  | |
| Integrative pathway analysis of VO2max response to training GWAS | VO2max | Using GWAS results followed by candidate gene prioritization and pathway analysis, pathways related to calcium signaling, energy sensing and partitioning, mitochondrial biogenesis, angiogenesis, immune functions, and regulation of autophagy and apoptosis were identified as key mechanisms through which the physiological responses of VO2max to training are mediated. | Ghosh, Vivar et al. 2013 | |
| Genetics and biology underlying intrinsic VO2max | VO2max | A bioinformatics pipeline applied to VO2max data in the sedentary state suggests four loci related to cardiovascular physiology (*ATE1, CASQ2, NOTO, and SGCG*), four loci related to hematopoiesis (*PICALM, SSB, CASQ2, and CA9*), four loci related to skeletal muscle function (*SGCG, DMRT2, ADARB1,and CASQ2*), and eight loci related to metabolism (*ATE1, PICALM, RAB11FIP5, GBA2, SGCG, PRADC1, ARL6IP5, and CASQ2*) as candidates for human variability in cardiorespiratory fitness among sedentary adults. | Ghosh, Hota et al. 2019 | |
| **Metabolomic biomarker of training responsiveness** | | | | |
| DMGV is a biomarker of metabolic response to endurance training | Fasting glucose, insulin and lipids | Baseline levels of plasma DMGV associated with lack of improvement in HDL traits. DMGV levels decreased with training and were positively correlated with several lipid, glucose and insulin traits | | Robbins, Herzig et al, 2019 |