Available online at www.sciencedirect.com

ScienceDirect

www.onlinepcd.com

Personalized Preventive Medicine: Genetics and the Response to Regular Exercise in Preventive Interventions

Claude Bouchard[a,*], *Ligia M. Antunes-Correa*[b], *Euan A. Ashley*[c,d], *Nina Franklin*[e], *Paul M. Hwang*[f], *C. Mikael Mattsson*[c,g], *Carlos E. Negrao*[b,h], *Shane A. Phillips*[e], *Mark A. Sarzynski*[a], *Ping-yuan Wang*[f], *Matthew T. Wheeler*[c,d]

[a]*Human Genomics Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA, USA*
[b]*Heart Institute (InCor), Medical School, University of Sao Paulo, Sao Paulo, Brazil*
[c]*Center for Inherited Cardiovascular Disease, Division of Cardiovascular Medicine, Stanford University, Stanford, CA, USA*
[d]*Cardiovascular Institute, Stanford University School of Medicine, Stanford, CA USA*
[e]*Department of Physical Therapy, Department of Medicine, Integrative Physiology Laboratory, University of Illinois at Chicago, Chicago, IL, USA*
[f]*National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA*
[g]*The Swedish School of Sport and Health Sciences, Stockholm, Sweden*
[h]*School of Physical Education and Sport, University of Sao Paulo, Sao Paulo, Brazil*

ARTICLE INFO

Keywords:
Personalized medicine
Individual differences
Genetics
Mitochondria
Endothelium

ABSTRACT

Regular exercise and a physically active lifestyle have favorable effects on health. Several issues related to this theme are addressed in this report. A comment on the requirements of personalized exercise medicine and in-depth biological profiling along with the opportunities that they offer is presented. This is followed by a brief overview of the evidence for the contributions of genetic differences to the ability to benefit from regular exercise. Subsequently, studies showing that mutations in *TP53* influence exercise capacity in mice and humans are succinctly described. The evidence for effects of exercise on endothelial function in health and disease also is covered. Finally, changes in cardiac and skeletal muscle in response to exercise and their implications for patients with cardiac disease are summarized. Innovative research strategies are needed to define the molecular mechanisms involved in adaptation to exercise and to translate them into useful clinical and public health applications.

As physical activity (PA) energy expenditure has diminished and sedentary pursuits have increased, a number of physical and psychosocial ailments related to inactivity have become manifest. The phenomenon was first documented by the seminal studies of Morris et al.[1,2] on occupational PA and risk of coronary heart disease (CHD) in London public transportation workers in the 1950s. Since then, a large

Statement of Conflict Interest: see page 344.

* Address reprint requests to Claude Bouchard, Human Genomics Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA 70806, USA.
E-mail address: claude.bouchard@pbrc.edu (C. Bouchard).

http://dx.doi.org/10.1016/j.pcad.2014.08.005
0033-0620/

Abbreviations and Acronyms

ACSL1 = Acyl-CoA synthetase long-chain family member 1

CREB1 = cAMP responsive element binding protein 1

CHD = Coronary heart disease

CRF = Cardiorespiratory fitness

CVD = Cardiovascular disease

GWAS = Genome-wide association studies

FMD = Flow-mediated dilation

HF = Heart failire

HR50 = Heart rate at 50 W

IGF-1 = Insulin-like growth factor 1

IL = Interleukin

KIF5B = Kinesin family member 5B

LFS = Li-Fraumeni syndrome

mtDNA = Mitochondrial DNA

MZ = Monozygotic

NO = Nitric oxide

NFAT = Nuclear calcineurin/ nuclear factor of activated T-cells

p53 = Tumor protein 53

^{31}P-MRS = P-31 magnetic resonance spectroscopy

PA = Physical activity

PCr = Phosphocreatine

QTL = Quantitative trait loci

SERCA2 = Sarcoplasmic/ endoplasmic reticulum Ca2+ ATPase 2

SNPs = Single nucleotide polymorphisms

TNF-α = Tumor necrosis factor-α

VO_{2Max} = Maximal oxygen consumption

number of epidemiological studies have confirmed that PA level and cardiorespiratory fitness (CRF) are associated with the risk of mortality, morbidities, and the risk factor profile for common chronic diseases.[3–11] Moreover, a body of data from randomized, controlled exercise interventions and other experimental studies has established that regular exercise produces favorable changes in commonly recognized risk factors for cardiovascular disease (CVD), type 2 diabetes, and other conditions.[12–16]

The health benefits of a physically active lifestyle are typically evaluated with reference to mean response of a given risk factor or outcome to an exercise program. This approach fails to recognize that there are considerable inter-individual differences in responses to any exercise program.[17,18]

Issues related to this overarching theme organized around five topics are addressed in the present report. First, a brief expose of the requirements of personalized exercise medicine and of in-depth biological profiling is presented. This is followed by a summary of the evidence for the contributions of genetic differences to the ability to benefit from regular exercise. Third, studies showing that mutations in *TP53* influence exercise capacity in mice and humans are succinctly described. This is followed by a section on the evidence for the effects of acute and regular exercise on endothelial function in healthy individuals and patients with CVD. Finally, the changes in cardiac and skeletal muscle in response to regular exercise and their implications for patients with cardiac disease are summarized.

Genomic implications for PA

The completion of the Human Genome Project and the subsequent expansion of genetic studies to genome-wide association studies (GWASs) and whole genome and whole exome sequencing have led to a new era in genetics. Though still in its infancy, personalized genomics and related personal omics profiling, encompassing epigenomics, pharmacogenomics, transcriptomics, proteomics, metabolomics, and antibody profiling, will allow for the deep biological profiling of humans in the face of PA.

Personalized genomics and beyond

Previous investigators have examined in a clinical context the whole genome sequence of an apparently healthy individual[19] and provided personalized results. Common disease variants were interpreted and estimated effect sizes aggregated to provide an estimate of the future risk of developing common diseases such as diabetes, CHD, hypertension, or osteoporosis. In addition, the genome was evaluated for evidence of rare variants associated with rare diseases associated with potential increased risk of sudden death, fracture, or metabolic disease. Evaluation of the whole genome sequence also allowed for elucidation of genetic differences, which may predispose to adverse or differential drug responses. Further work demonstrated the incremental value of phasing genomic information among a family to improve interpretability.[20] Evaluation of common disease risk alleles showed that common alleles, as expected, can be differentially dispersed among family members so that high- and low-risk offspring may be seen from average-risk individuals, even in the absence of new genetic variation. Similarly, without targeted genotyping, individual family members who carry risk alleles of manifest rare diseases can be easily inferred.

Integrated personal omics profiling using a combination of genomic, transcriptomic, proteomic, metabolomics, and antibody profiling has been described in an apparently healthy individual.[21] Repeated measures of metabolic, antibody, and transcript profiles allowed time-resolved discrimination of subject-environment interactions and identification of novel processes associated with changes in health status. Furthermore, cross-sample and cross-platform validation improved confidence of variant calls and in many cases proved the direct effects of genomic variants on transcript and proteomic profiles. While the extent of omic profiling demonstrated by Chen et al. has not been achieved at a cohort or population scale, the opportunities and limitations of multiscale phenotyping have yet to be fully evaluated. Efficient data reduction methods and validation to improve inference and causality will be required to allow omics profiling to reach common usage. Integrating genomic and omics profiling into research, clinical practice, and PA will require continued improvements in the efficiency of data generation as well as further optimization of nascent bioinformatics tools.

Genomic implications for PA and exercise training

Prior and current research on the genetics of exercise training is covered in other sections of this report. Findings from many