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SYMPOSIUM REVIEW

Genetic basis of inter-individual variability in the effects of exercise on the alleviation of lifestyle-related diseases

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Habitual exercise training, including a high-intensity interval walking programme, improves cardiorespiratory fitness and alleviates lifestyle-related diseases, such as obesity, hypertension and dyslipidaemia. However, the extent of improvement has been shown to differ substantially among individuals for various exercise regimens. A body of literature has demonstrated that gene polymorphisms could account for the inter-individual variability in the improvement of risk factors for lifestyle-related diseases following exercise training. However, the fractions of the variability explained by the polymorphisms are small (∼5%). Also, it is likely that the effects of gene polymorphisms differ with exercise regimens and subject characteristics. These observations suggest the necessity for further studies to exhaustively identify such gene polymorphisms. More importantly, the physiological and molecular genetic mechanisms by which gene polymorphisms interact with exercise to influence the improvements of risk factors for lifestyle-related diseases differentially remain to be clarified. A better understanding of these issues should lead to more effective integration of exercise to optimize the treatment and management of individuals with lifestyle-related diseases.

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Abbreviations ACE, angiotensin I-converting enzyme; ADRB2, adrenergic receptor β_2; BMI, body mass index; *FTO*, fat mass and obesity associated gene; SBP, systolic blood pressure; $\dot{V}_{O_2peak}$, peak aerobic capacity.

Lifestyle-related diseases, which include obesity, diabetes, dyslipidaemia, hypertension and cardiovascular disease, represent the greatest global health threat. Epidemiological and clinical evidence indicates that poor cardiorespiratory fitness is a major risk factor for lifestyle-related diseases (Sawada *et al.* 1993, 2003; Wei *et al.* 1999; Lakka *et al.* 2001). Thus, the excess energy intake and adoption of a sedentary lifestyle by modern people can result in a decline in cardiorespiratory fitness, leading to the epidemic emergence of lifestyle-related diseases. In addition, cardiorespiratory fitness generally deteriorates with advancing age. In this regard, middle-aged and older individuals constitute another high-risk group for lifestyle-related diseases. Conversely, increasing cardiorespiratory fitness can be an effective measure in the prevention and alleviation of lifestyle-related diseases. One commonly recommended approach for increasing cardiorespiratory fitness and for decreasing the risks of, or alleviating the symptoms of lifestyle-related diseases is habitual exercise training, a low-cost, non-pharmacological intervention that is available to the vast majority of people (Kraus *et al.* 2002; Pescatello *et al.* 2004; O'Gorman & Krook, 2008). However, it has also become evident that the

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extent of improvement with exercise training differs substantially among individuals, irrespective of whether it is a standardized or controlled exercise-training programme (Bouchard & Rankinen, 2001). To appreciate the effects of exercise on prevention and alleviation of lifestyle-related diseases fully, it is indispensable to clarify the basis of the inter-individual variability.

Predisposition to lifestyle-related diseases has a genetic basis. Gene polymorphisms influence inter-individual variability in the predisposition to obesity (Rankinen *et al.* 2006) and hypertension (Levy *et al.* 2009; Newton-Cheh *et al.* 2009). Likewise, the inter-individual variability in the effects of exercise on alleviation of lifestyle-related diseases may be influenced by gene polymorphisms. Indeed, previous studies have consistently demonstrated involvement of genetic polymorphisms in the improvement of disease-related phenotypes for various exercise regimens. A genetic association study for the effects found a small collection of genes that influence improvement of diseases following habitual exercise training (Table 1). However, more studies are required to explore this hypothesis and establish a definitive gene–exercise relationship. Here, we briefly review the current status of the study of genetic associations of the effects of exercise on lifestyle-related diseases, including data obtained from our own study, and discuss a future perspective.

Gene polymorphisms underlie the inter-individual variability in alleviation of lifestyle-related diseases following exercise training

There is a body of literature demonstrating associations between gene polymorphisms and exercise-training responsiveness of risk factors for lifestyle-related diseases (Table 1). Candidate genes come from a variety of functional categories. Several gene polymorphisms were reported to be associated with responsiveness of several risk factors. Angiotensin I-converting enzyme (ACE) is a dipeptidyl carboxypeptidase that plays an important role in blood pressure regulation and electrolyte balance. A polymorphism of the human *ACE* gene was identified in which the deletion rather than the insertion of a 287 bp fragment in intron 16 of the gene is associated with high tissue ACE activity (Danser *et al.* 1995). This insertion/deletion polymorphism influences not only the cardiovascular response (Hagberg *et al.* 1999), but also changes in body composition following exercise training (Montgomery *et al.* 1999). However, some gene–exercise interaction effects failed to be replicated in other studies. These facts imply a complex interrelationship among gene polymorphisms, exercise and lifestyle-related diseases. For more information, the interested reader can also refer to an excellent recent review on this topic (Bray *et al.* 2009).

Effects of high-intensity interval walking training are also dependent on gene polymorphisms

'High-intensity interval walking' is an aerobic exercise that improves cardiorespiratory fitness and alleviates lifestyle-related diseases in middle-aged and older individuals (Nemoto *et al.* 2007). We investigated the effects of a high-intensity interval walking training intervention in middle-aged and older Japanese females. Average initial values of this population ($n = 217$; 41–86 years of age; mean age, 63.3 years) for peak aerobic capacity ($\dot{V}_{O_2peak}$), body mass index (BMI) and systolic blood pressure (SBP) were 20.5 ml kg^{-1} min^{-1}, 23.7 kg m^{-2} and 133.3 mmHg, respectively. After 10 months of high-intensity interval walking training, the parameters improved significantly to 25.6 ml kg^{-1} min^{-1} ($\dot{V}_{O_2peak}$), 23.0 kg m^{-2} (BMI) and 130.3 mmHg (SBP). Among the 217 subjects, 57 had an initial BMI $\geq$ 25 kg m^{-2}, which is the threshold value for the clinical diagnosis of obesity in Japan. Eighty-two had an initial SBP $\geq$ 140 mmHg, which is the threshold value for the clinical diagnosis of hypertension in Japan. Importantly, improvement was prominent for these subjects. In the obese subjects, BMI decreased significantly from 27.6 to 26.4 kg m^{-2}. In the hypertensive subjects, SBP decreased significantly from 148.3 to 140.9 mmHg. However, the change scores in these parameters differed substantially among individuals (Fig. 1).

Next, a study was performed to determine the association between the change score and gene polymorphisms. Most of these polymorphisms were reported to be associated with inter-individual variability in the effects of exercise on the improvement of obesity or hypertension (Table 1). Our results, however, failed to replicate the gene–exercise interaction effects or pre- and post-training values for most polymorphisms. This discrepancy may be partly explained by differences in the exercise regimen, such as type (e.g. aerobic or endurance), strength, frequency and duration. The gene–exercise interaction would also be influenced by subject characteristics, such as ethnicity, age, sex, energy intake and baseline physical activity. A single nucleotide polymorphism (SNP), rs1042713, in the adrenergic receptor β_2 (*ADRB2*) gene (also known as a Gly16Arg polymorphism) was found to be associated with the change score in BMI in obese subjects (Fig. 2). The Arg allele was associated with a greater reduction of BMI following exercise training. This polymorphism explained 12.5% of the inter-individual variability in change scores following exercise training. This result was consistent with one of the previous reports (Garenc *et al.* 2003), but inconsistent with the other report (Sakane *et al.* 1999), in which the Gly allele was associated with a greater reduction in body weight, implying intricate gene–exercise interaction.

Table 1. Gene polymorphisms reported to be associated with inter-individual variability in responsiveness to exercise training

Gene name	Gene symbol	dbSNP ID	Location of SNP	Effect of SNP	Phenotype	Selected reference
Fat mass and obesity associated gene	*FTO*	rs9939609*	intron 1	—	BMI	Andreasen *et al.* (2008)
Insulin induced gene 2	*INSIG2*	rs7566605	5′ upstream (−10)	—	Fat volume	Orkunoglu-Suer *et al.* (2008)
Uncoupling protein 1	*UCP1*	rs1800592*	5′ upstream (−3826)	—	Body weight	Kogure *et al.* (1998)
Uncoupling protein 3	*UCP3*	rs1800849*	5′ upstream (−36)	—	BMI	Otabe *et al.* (2000)
Peroxisome proliferator-activated receptor α	*PPARA*	rs1800206	exon 5	L162V	Fat volume	Uthurralt *et al.* (2007)
Peroxisome proliferator-activated receptor δ	*PPARD*	rs2267668	intron 2	—	$\dot{V}_{O_2peak}$	Stefan *et al.* (2007)
Peroxisome proliferator-activated receptor γ	*PPARG*	rs1805192	exon 2	A12P	Body weight	Lindi *et al.* (2002); Ostergard *et al.* (2005)
Cytochrome P450, family 19, subfamily A, polypeptide 1	*CYP19A1*	(TTTA)*n* repeat polymorphism	intron 4	—	BMI, fat mass, % body fat	Tworoger *et al.* (2004)
Catechol-*O*-methyltransferase	*COMT*	rs4680	exon 4	V158M	% body fat	Tworoger *et al.* (2004)
Lipoprotein lipase	*LPL*	rs328*	exon 9	S474X	BMI	Garenc *et al.* (2001)
Adrenergic receptor β_2	*ADRB2*	rs1042713*	exon 1	R16G	Body weight, BMI, % body fat	Sakane *et al.* (1999); Garenc *et al.* (2003)
		rs1042714*	exon 1	Q27E	% body fat	Meirhaeghe *et al.* (1999); Corbalán *et al.* (2002); Phares *et al.* (2004)
Adrenergic receptor β_3	*ADRB3*	rs4994*	exon 1	R64W	Body weight, % body fat	Yoshida *et al.* (1995); Phares *et al.* (2004)
Guanine nucleotide-binding protein β_3	*GNB3*	rs5443	exon 10	aberrant splicing	Obesity, fat mass, % body fat	Rankinen *et al.* (2002); Grove *et al.* (2007)
Ectonucleotide pyrophosphatase/ phosphodiesterase	*ENPP1*	rs1805101	exon 4	K171Q	BMI	Park *et al.* (2008)
Angiotensin I-converting enzyme	*ACE*	I/D polymorphism*	intron 16	—	Diastolic blood pressure, fat mass	Hagberg *et al.* (1999); Montgomery *et al.* (1999)

* Polymorphisms examined in our study.
dbSNP ID: reference single nucleotide polymorphism identifier in SNPs database of NCBI (http://www.ncbi.nlm.nih.gov/SNP)
SNP: single nucleotide polymorphism
BMI: body mass index
VO_{2peak}: peak aerobic capacity

Towards comprehensive identification of polymorphisms for effects of exercise training

In order to attain full comprehension of intricate gene–exercise interaction in alleviation of lifestyle-related diseases, two major subjects need to be achieved in the future. Firstly, it is necessary to exhaustively identify candidate gene polymorphisms associated with alleviation of lifestyle-related diseases following exercise training. So far, most of the studies have employed a candidate gene approach, in which only one or a few specific genes of interest were examined. The choice of candidate polymorphisms has primarily been based on the hypothesis that the polymorphisms, which determine the predisposition to lifestyle-related diseases, would also be a determinant of recovery feasibility from the diseases following exercise. This hypothesis was true for several genes, such as *ACE* (Rush & Aultman, 2008) and fat mass and obesity associated gene (*FTO*) (Frayling *et al.* 2007). However, it might not always be the case. Furthermore, the sample sizes in previous studies were generally too small (∼1000) to provide adequate statistical power. Currently, a genome-wide association study, which allows simultaneous examination of over 50 000 polymorphisms without accompanying hypothesis in thousands of subjects, is becoming the main strategy to analyse the genetic basis of predisposition to lifestyle-related diseases (The Wellcome Trust Genome Case Control Consortium, 2007). This approach confirmed the results obtained by the candidate gene approach with more strict statistical conditions. More importantly, it resulted in successful discoveries of hundreds of new SNPs for lifestyle-related diseases (Thorleifsson *et al.* 2008; Willer *et al.* 2009; Levy *et al.* 2009; Newton-Cheh *et al.* 2009), implying the greatest promise also for comprehensive identification of polymorphisms for even more intricate gene–exercise interaction in alleviation of the diseases.

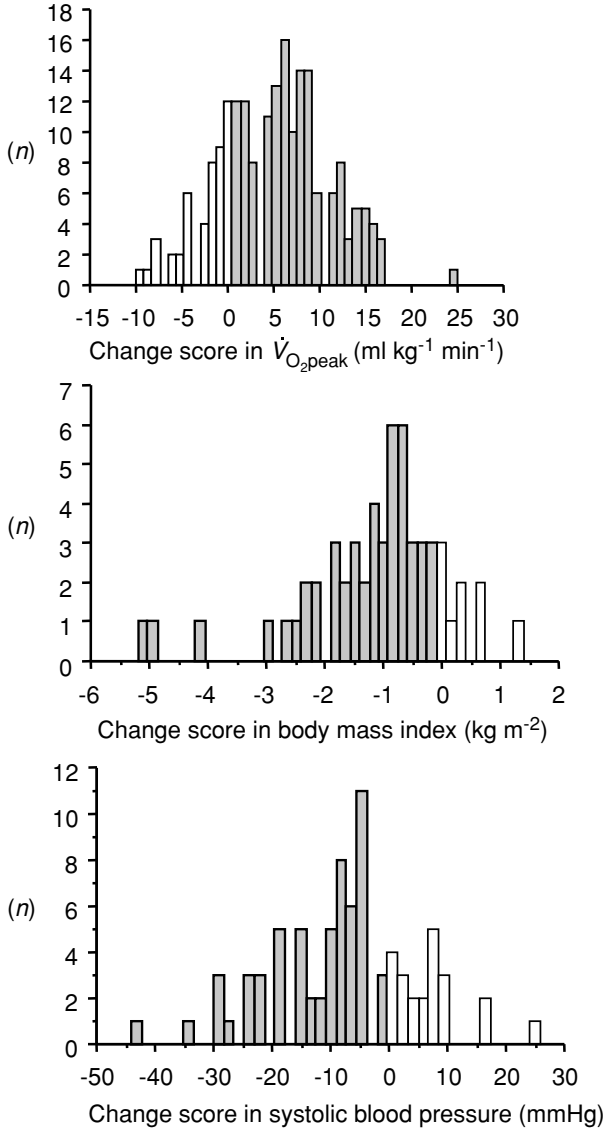

Figure 1. Distribution of change score in $\dot{V}_{O_2peak}$ (n = 217), body mass index in obese subjects (BMI ≥ 25 kg m^{-2}; n = 57) and systolic blood pressure in hypertensive subjects (SBP ≥ 140 mmHg; n = 82) after 10 months of high-intensity interval walking exercise training
Grey bars represent subjects with improvement, whereas open bars represent subjects with no change or aggravation.

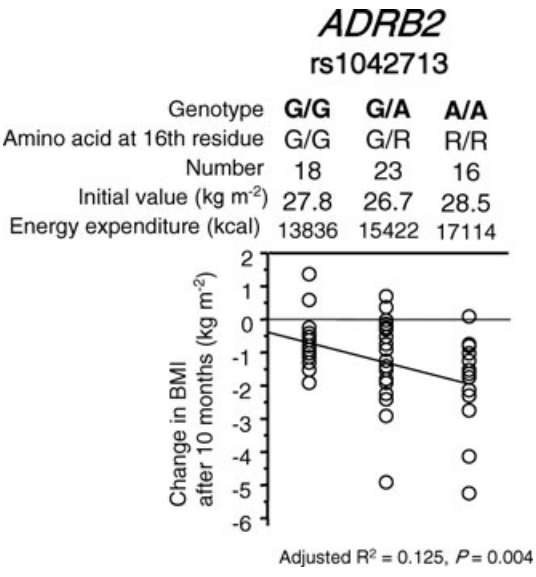

Figure 2. Association of a SNP rs1042713 in the *ADRB2* genes and change in BMI in obese subjects (BMI ≥ 25 kg m^{-2}; n = 57) after 10 months of high-intensity interval walking training
Stepwise multiple regression analysis was employed. This figure shows the result drawn by a simple linear regression analysis. Average initial values for BMI and energy expenditure from high-intensity walking were not statistically different between genotypes. The change score in BMI was not correlated with age or initial BMI value.

Towards elucidation of the mechanisms for the genotype-dependent effects of exercise training

Secondly, the physiological and molecular genetic mechanisms by which the variations in the genes exert genotype-dependent differential effects on alleviation of lifestyle-related diseases following exercise training remain to be clarified. Habitual exercise training induces multiple adaptations within skeletal muscle. Also, exercise training elicits improvements in endothelium-dependent dilatation or reduces sympathetic activity. Thus, exercise training is considered to elicit metabolic as well as physiological reprogramming systemically, which contributes to alleviation of lifestyle-related diseases. Alterations in actions of plenty of genes through epigenetic modification, changes in expression level and stability of transcripts, post-translational modification of gene products and other mechanisms undoubtedly underlie this reprogramming process. Common gene polymorphisms may have only a negligible or subtle influence on gene functions in sedentary conditions. Exercise training may amplify the differential effects between polymorphic alleles, which then manifest as differences in responsiveness to exercise between individuals (Fig. 3). Indeed, a few studies have demonstrated that nucleotide polymorphisms caused differences in gene expression level after exercise training (Prior *et al.* 2006; Oberbach *et al.* 2008). This, in addition to other possibilities, should be studied in the future. This would be achieved by integration of data obtained from two different approaches. Firstly, responses of each candidate polymorphic gene to exercise training should be carefully examined at various levels from DNA to a mature protein product. A second useful approach is transcriptome, proteome and physiome analysis, which would give a comprehensive picture of physiological dynamics occurring after exercise training.

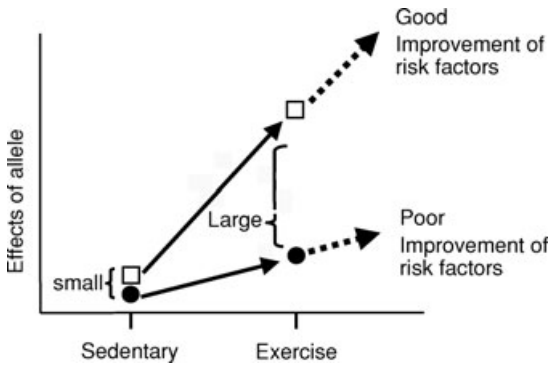

Figure 3. Proposed model of allele–exercise interaction for alleviation of lifestyle-related diseases

Conclusion

It is evident that gene polymorphisms play a crucial role in determination of the improvement of risk factors for lifestyle-related diseases following exercise training. Full comprehension of gene polymorphism–exercise interaction in alleviation of the diseases should help in the development of individualized training programmes to optimize the treatment and management of subjects with lifestyle-related diseases. It should also provide clues as to which pathways to target with agents that mimic or potentiate the effects of exercise for the treatment of lifestyle-related diseases (Narkar *et al.* 2008; Hawley & Holloszy, 2009).

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Author contributions

All authors contributed to the conception and design of the study, interpretation of data and drafting and revising the manuscript. M.M. performed experiments and analysed the data. K.H. performed experiments. A.S. analysed the data. Y.T. performed experiments. T.M. performed experiments. H.N. performed experiments. All authors approved the published version of the manuscript. All the experiments were done at the Institute on Aging and Adaptation, Shinshu University Graduate School of Medicine.

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