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REVIEW ARTICLE

Review of the Studies on Exercise Genomics

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ABSTRACT

This study aimed to provide basic information for Genome and Exercise. Exercise Genomics was begun to investigate genetic differences that may affect fitness or performance at the DNA level in the 1990s. Recently the study of exercise genomics becomes very large. To provide the current results of the researches on exercise genomics, we review the recent publications and the controversy in the interpretation of the results from marker studies related to exercise genomics. Comparable reviews were currently published for weight loss treatment and drug-based therapy of type 2 diabetes. Other than the growing number of papers related to the influence of genetic polymorphisms on physical performance and adaptation to exercise training, not much is known regarding the practical use of genetic markers in exercise treatment and training.

＜Key-words＞
Exercise Genomics, Physical Activity, ACTNS3, APOE, ACE

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Ⅰ. The Roles of Genome in Relation to Exercise Science and Health

Exercise physiologists have conducted the studies and experiments on the physiological reactions or adaptation to various exercise stress and reported the results of those as the average values. However, such results that have been reported as the average values have shown the limitation that cannot explain the exercise response of each individual and the diversity of the levels of exercise adaptation. For example, the Heritage Family Study by Bouchard et al. in 1999 showed that there were the great differences among individuals in the maximal oxygen uptake during exercise. In particular, even though some subjects who participated in the twenty-week exercise program showed no or a little change of maximal oxygen uptake, the results were reported that the maximal oxygen uptake increased to 400ml after completing the twenty-week exercise program, which may cause the misunderstanding that all the people's maximal oxygen uptake increased after exercising. Moreover, according to the study of Bouchard and Rankinen(2001), there were the significant differences in the changes of blood pressure, heart rate and HDL cholesterol among individuals while doing aerobic exercise.

Conclusively, it is not reasonable to present the results with the average values in spite of the diversity of the physical reaction or adaptation to exercise stress. To explain the differences among individuals, we may significantly consider three factors; experimental error, environmental factor and genetic factor. Among those three factors, the individual differences in the results of exercise within the group may be explained by the genetic factor, because experimental error and environmental factor may be revised via experimental design or statistical analysis and more broadly the development of scientific technology or experimental technology. In this context, it is reasonable to assume that genetics may play a great role for exercise science and health.

Ⅱ. Exercise Genomics

Exercise genomics refers to the study of genetics related with the prescription of exercise and physical activity. The significance of genetic factors for exercise stress is backed up by the reactivity of various phenotype to exercise training and the identification of those genetic factors becomes the field of exercise genomics; that is, a person who has certain genetic traits may sensitively respond with certain exercise intervention in certain phenotypes and may not respond with certain other phenotype at all. For example, while some people's maximal oxygen uptake markedly increased, they didn't show the response to the control of blood pressure after implementing aerobic exercise; if such people went to hospital for the treatment of high blood pressure, they would find out that exercise training to blood pressure phenotype would be ineffective via genetic monitoring and the prescription for them would be changed. That is to say, it may

be very useful to know the genetic factor to enable to forecast the responses to exercise training for more efficient medical treatment.

To present exercise prescription, genetics may be applied to find optimum ways of exercise intervention for generally improving disease risk factors and the ability to perform sports in priority.

Ⅲ. The Recent Tendency of the Research on Exercise Genomics

1. The Summaries of Recent Research Achievements

The development of exercise genomics has been accelerated after 2000 just like other fields of genomics, when DNA base sequencing has begun to be generalized. For example, while 1) 20 studies on the endurance exercise performance and genetic test, 2) two studies on the traits of muscle strength or anaerobic power and genetics and 3) eight studies on the genetics in relation to the reactions to blood lipid and inflammatory markers were published by 2000, the range of the studies has been broaden and the number of 1), 2) and 3) had increased to 53 studies, 23 studies and 32 studies respectively between 2001 and 2005; since then the number of studies has continually increased. As the number of studies has steadily increased, there were four fields of the study that have shown visible research results as follows:

First, there is the field of the study on the nonsense mutation in the skeletal muscle gene that is known as ACTN3 (alpha-actinin-3) in fast twitch muscle fiber. Nonsense mutation results in the complete destruction of ACTN3 gene, but it doesn't cause muscular diseases to people who are homozygous for this mutation. Researchers have studied whether this mutation affects the muscle phenotype that doesn't cause diseases or not.

Second, there is the field of the study on Alzheimer's disease. The outbreak and progress of Alzheimer's disease are related with genetic variation of ApoE gene. Researchers have focused on the interaction between physical activity and ApoE phenotype.

Third, there is the field of the study on world-class players' exercise performance. What makes excellent players? Genetic factor, remarkable motivation or appropriate training method? Or all of them are required to be excellent players? Those questions have motivated to identify the unique genetic factors that contribute for the exercise performance. The researchers on exercise genomics have conducted many studies on base-sequence variation of ACE gene and the ability to do diverse types of exercises and sports.

Fourth, there is the field of the study on the myostatin gene and skeletal muscle phenotype, particularly, the change of muscle mass.

<Table 1> The Summary of Research Achievements

	~ 2000	2000~ 2005
Endurance exercise performance	20 studies	53 studies
Muscle strength or anaerobic power	2 studies	23 studies
Blood lipid and inflammatory markers	8 studies	32 studies

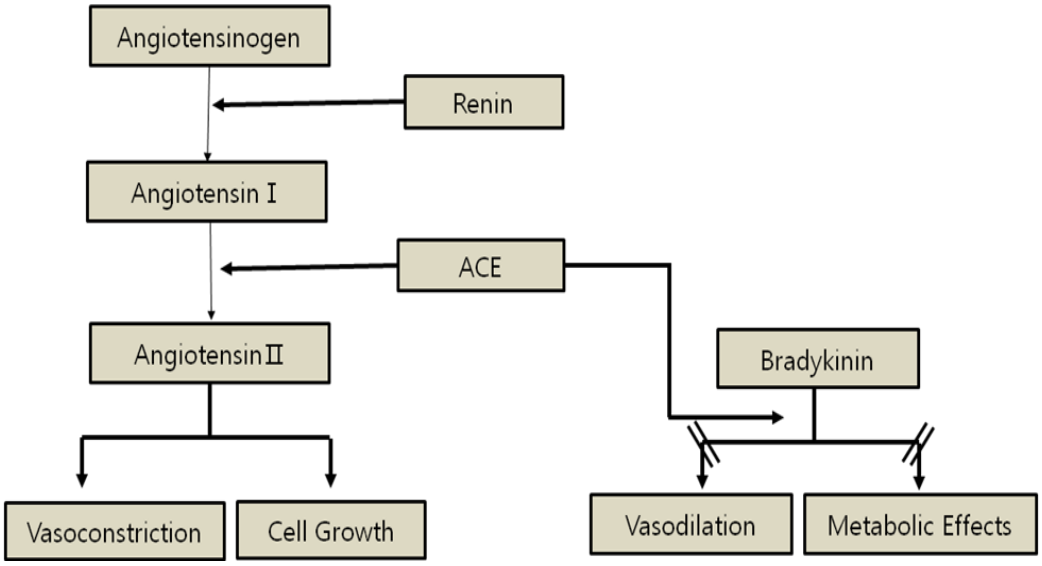
Source : Lee Samjun, Kim Sangho, Ran Won, Bak Jinhong, Lee Youngil, Seo Annold, La Seongmin & Choi Hyeonggyu(2008) Genetics: Primer for Exercise Science and Health, Daehan Media. Seoul

2. ACTN3 and Exercise Performance

It is expected that some studies on genetics may provide the fundamental information that would be the base of the research design in relation to genome, as they became to form the hypothesis that the influence may be given over various traits such as dominant trait, recessive trait and sex linked trait via newly-identified gene polymorphism.

ACTN3 belongs to the alpha-actinin protein family that plays significant roles in many tissues. In the alpha-actinin protein family, there are two interesting proteins such as ACTN2 and ACTN3 that are mainly expressed in the skeletal muscular tissues. Skeletal muscles are composed of many muscular cells and those cells are divided into Type Ⅰ and Type Ⅱ according to various metabolic and contraction traits. Type Ⅰ muscle fiber is dominated by aerobic metabolism and its contractibility is lower than Type Ⅱ. Type Ⅱ muscle fiber has the high degree of contractility and many traits of anaeorobic metabolism. ACTN2 gene is expressed in all the fiber of skeletal muscle, but ACTN3 is found only in Type Ⅱ muscle fiber. In 1999, North and co-workers identified the nonsense polymorphism in ACTN3 gene, known as R577X(R577X polymorphism replaces arginine by stop codon). X/X genotype transporter results in the deficiency of ACTN3 protein in muscle fiber. Many studies on muscular diseases published in the mid-1990's identified the complete deficiency of ACTN3 gene, which is deeply related with the foot disease among muscular diseases. In particular, the deficiency of ACTN3 gene is deeply related with certain types of myatrophy. Thus, R577X mutation is useful to understand muscular diseases and it is intuitable that the mutation is a nonsense allele.

R577X polymorphism of ACTN3 gene results in the complete deficiency of ACTN3 protein in the X/X genotype transporter. People who have the complete deficiency of ACTN3 protein may not have muscular disease, but this kind of complete deficiency of Type Ⅱ muscle fiber protein may affect the exercise performance of their muscles or muscle-related phenotype.



<Figure1> Renin-angiotensin System

Source : Lee Samjun, Kim Sangho, Ran Won, Bak Jinhong, Lee Youngil, Seo Annold, La Seongmin & Choi Hyeonggyu(2008) Genetics: Primer for Exercise Science and Health, Daehan Media. Seoul.

3. ApoE and Cognitive Ability

Now the number of patients with Alzheimer's disease is assumed to be 20 million in the world and it became to be the commonest degenerative brain disease. The Alzheimer's disease that is one of senile dementia generally breaks out with mild forgetfulness at first in 60's; and then, causes the confusion with time or place, wandering, psychological disturbance and finally the personality changes. Ageing has been known as the major contributing factor of Alzheimer's disease, as it is estimated that the half of the population aged 80 years and over are at risk of this disease. Even though no medicine for this disease has been developed, it is critical to get early diagnosis, because it was found that the medication to activate nerve transmission is markedly effective to some patients.

ApoE ε4 allele is the powerful predictor of the outbreak of Alzheimer's disease; in particular, it is more powerful predictor in the homozygous transporter. Currently researchers have been intensively conducted the studies on gene-related modification factors; in particular, they have devoted their efforts to the studies on the probability of the improvement of ε4 allele that is highly associated with physical activity and cognitive decline.

4. ACE and Exercise Performance

Angiotensin-converting enzyme (ACE) gene comes in two alleles and is expressed by the insertion (I allele) and deletion (D allele) of 287 base pairs in the latter part of gene. ACE gene is expressed with three genetic polymorphisms; homozygous ACE II genotype

and heterozygous ACE ID genotype, which are insertion alleles and homozygous ACE DD genotype, which is a deletion allele (Montgomery et al, 1998; Jones et al, 2002). According to the precedent studies, ACE I allele was markedly presented among the endurance athletes (Montgomery et al., 1998) and ACE D allele among the sprint/power athletes. The studies in the aspect of diseases reported the high degree of association among the plasma angiotensinogen concentration, renin plasma activity, plasma ACE activity, BMI (Cooper et al., 1997) and obesity.

The reason that ACE in the renin-angiotensin system is important is because ACE became the candidate gene for the studies on the endpoints of cardiovascular system; but it doesn't refer to the phenotype to specific renin angiotensin system. ACE gene is one of the genes that have been most perfectly studied in terms of exercise performance phenotype.

5. Myostatin and Muscle Mass

Myostatin is found in the animal model and was identified as the negative regulatory element in the growth of skeletal muscle. Researchers could infer that such genetic mutation is the change by the normal growth of human muscle or the response to the various exercise stresses in terms of such importance of the growth regulatory element.

Ⅳ. Human Gene Map for Performance and Health-related Fitness Phenotype

It is reasonable to assume that many projects have been conducted for the accurate reviews of genetic study on genetic traits, looking at the current study results in the field of exercise performance and health-related fitness based on the efforts of many researchers. However, those projects may not be easy; that is to say, it is difficult to discuss various phenotypes in such a broad field of exercise performance and health-related fitness, for it is difficult to combine many kinds of exercises with various traits. In spite of such difficulty, Dr. Bouchard, who is the mastermind of this field, have presented the paper by reviewing all the papers of candidate genes using case-control and other designs published until the end of 2000; furthermore, Bouchard and co-workers have regularly updated it by reviewing all the newly published papers.

In results, Human Gene Map for Performance and Health-related Fitness Phenotype appeared in the Medicine and Science in Sports and Exercise in 2001 and has been updated with addition and emendations every year. Thanks to his efforts of reviewing the papers, the first human gene map for physical performance and health-related fitness traits appeared. Such the human gene map has been updated with addition and emendations; therefore, the tables have become to be broader and the list of such papers has been printed via positive gene- linkage analyses in terms of various phenotypes. Even though the papers that had reported negative results were reviewed and the list of such papers was printed in the year when they were published, such genes were excluded

from the gene map and such papers were also excluded from the updated papers. At first, the review aimed to present the history of genetics in the field of performance and health-related fitness phenotypes until the end of 2000; in addition, gene map intended to present the summarization of the most recent studies on broad range of phenotypes in the field of exercise performance and health-related fitness. The most recent gene map that is valid for the review(Rankinen Bray et al., 2006) identified that 170 genes and its region are positively related with traits. 29 genes and their regions that were reported in the first human gene map in 2001 have been remarkably developed. The greater growth in the field of the human gene map for exercise performance and health-related fitness phenotypes is expected via these reviews.

Ⅴ. The Summaries of the Studies on Exercise and Genome in 2012

1. The Summaries of Research Tendency

- A small number of excellent articles on exercise genomics issues were published in 2012.
- New reports on variants in ACTN3 and ACE
  → increased the level of uncertainty regarding their true role in skeletal muscle metabolism and strength.
- Positive effects of regular physical activity on body mass index as assessed by their FTO genotype.
- The serum level of triglycerides / the risk of hypertriglycemia
  : SNP in the NOS3 ↔ Physical activity level
- SNPs at the RBPMS, YWHAQ, and CREB1 loci
  : strong predictors of changes in submaximal exercise heart rate

2. Physical Activity Behavior and Exercise Intolerance

- No new major human studies related to the molecular genetics of human physical activity behavior.
- Genomewide quantitative trait loci(QTLs) screening for wheel-running phenotype in mice and the first animal model targeting a specific mutation causing McArdle disease were published in 2012.
  → important contributions to the knowledge base for human studies.

3. Muscle Strength and Power

- Less clarity in our understanding of the influences of specific genes on skeletal muscle strength-related traits.
- Multiple articles examined the ACTN3 R577X polymorphism and the possible importance of the X/X genotype on cellular or metabolic aspects of skeletal muscle(Vincent et al, 2012)

・A study examining the influence of testosterone and androgen receptor gene(AR) CAG repeat polymorphism in 183 young and old man : free testosterone was associated with knee extensor muscle strength (Polland et al, 2012).

4. Cardiorespiratory Fitness and Endurance Performance

1) Study1

・the association of elite athlete status and the ACTN3 R577X polymorphism: the odds ratio(OR) of a "world-class" athlete having the XX genotype versus the RR+RX genotype was 3.74 compared with "national" level athletes (Eynon et al, 2012).

2) Study 2

・the response to an exercise program of submaximal exercise capacity(the HERITAGE Family study)

: a QTLs on chromosome 13q12

indicators of submaximal exercise capacity

→ (the strongest evidence being for the training-induced changes in VO_2 at 60% of max)

(Rice, 2012).

3) Study 3

・verify whether the rs6552828 polymorphism in the acyl-coenzyme A synthetase long-chain family member 1 gene(ACSL1) was associated with elite endurance athlete status

⇒a strong marker of VO_{2MAX} trainability in GWAS

: a marginal association was observed in Chinese male athletes but not in females or in male athletes from Spain

(Bouchard et al, 2011).

4) Study 4

・investigated the influence of uncoupling protein 2(UCP2) and 3(UCP3) polymorphisms on training-related changes in two different cohorts undergoing controlled physical training sessions

: the UCP2 866G>A variant was nominally associated with the DE response to training(Dhamrait SS, 2012)

* Delta efficiency (DE)

a measure of skeletal muscle contraction efficiency

☞current exercise training trend increase work related power and capacity

⇓

work efficiency (reduce the energy cost)

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