COMMENTARIES

Single Nucleotide Polymorphisms (SNPs) in the IL-15 and IL-15R Genes are Associated with Predictors of the Metabolic Syndrome

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Introduction

The FAMuSS Study (Functional Polymorphisms Associated with Human Muscle Size and Strength) was designed to identify statistical associations between single nucleotide polymorphisms (SNPs) and the response of skeletal muscle to resistance exercise training. The FAMuSS study population consisted of men and women between the ages of 18 and 40 that had not performed strength training within 12 months prior to initiating the study. Participants performed 12 weeks of upper arm resistance training of the non-dominant arm only, using the dominant arm as an untrained control. Changes in muscle strength were assessed using isometric and dynamic contractions of the biceps while changes in muscle mass were quantified using MRI digitized images. Additionally, analysis of MRI images allowed the quantification of adipose tissue and bone within the upper arm. Predictors of the metabolic syndrome were analyzed, including: body weight, waist circumference measurements, resting blood pressure, the HOMA calculation, and serum measures of fasting glucose, insulin, cholesterol (total and LDL), and a coronary risk profile. Genotyping of selected SNPs were performed on a candidate list of genes.

Interleukin-15 (IL-15) is a recently discovered cytokine with numerous proposed roles in both lymphoid and non-lymphoid tissues. Transcript levels for IL-15 and the IL-15 receptor alpha chain (IL-15Rα) are widely distributed among tissue and cell types, including skeletal muscle [1]. Initial experiments using recombinant IL-15 protein suggested that IL-15 was an anabolic factor for skeletal muscle [2]. More recently, a muscle-to-adipose tissue signaling pathway has been proposed whereby IL-15 derived from skeletal muscle could have effects on adipose cells [3]. IL-15 may also have significant influence on both lipid and glucose metabolism, and therefore may prove useful as an anti-diabetogenic agent, as previously suggested [4]. These influences extend to contributing mechanisms of the metabolic syndrome, as alterations in cholesterol, triglycerides, and glucose tolerance are factors in the clinical definition of the metabolic syndrome presented by the International Diabetes Federation [5]. Additional factors included in the metabolic syndrome classification include: central obesity, hypertension, and presence of type II diabetes. IL-15 has also been associated with inflammatory diseases. For example, IL-15 protein is contained in the synovial fluid of patients affected with rheumatoid arthritis [6] and can stimulate osteoclastogenesis, thus contributing to bone resorption [7]. Atherosclerotic lesions also express IL-15 mRNA and protein and this expression may contribute to lymphocyte recruitment to the lesion sites [8].

Numerous SNPs have been identified in the human IL-15 gene and IL-15Rα genes. Previous studies have found associations between SNPs in the IL-15Rα gene and skeletal muscle responses to resistance exercise and obesity [9,10]. In the present study, we wanted to further examine these IL-15Rα SNPs in a larger sample size of subjects performing a unilateral resistance training program while including SNPs in the IL-15 gene. Based on the proposed roles of IL-15 and IL-15Rα identified above, we hypothesized that IL-15 and IL-15Rα genotypes would be associated with predictors of the metabolic syndrome as well as skeletal muscle and bone phenotypes examined at baseline and in response to RT.

Study Overview

This study was part of a multi-center investigation designed to uncover novel SNPs with associations to human muscle size and strength. Detailed methodology of the FAMuSS study has been presented previously [11]. DNA samples, obtained from subjects' white blood cells, were collected and used to perform SNP analyses. A review of the literature was performed to identify SNPs in the IL-15 and IL-15Rα genes that could potentially affect muscle phenotypes, metabolic syndrome predictors, and/or gene expression. SNPs in both coding regions as well as regulatory regions (i.e. 5'UTR, 3'UTR) of the IL-15Rα gene with previously established associations with muscle phenotypes were used in our analyses [10]. To date, there have been no SNPs described in coding regions that alter IL-15 structure or expression [12]. Therefore, we examined SNPs

in the 5' and 3' UTR regulatory regions of the IL-15 gene which had demonstrated associations with IL-15 expression levels and arthritis [12]. The two SNPs in the IL-15 gene analyzed in this study were in close LD, with a D' value of 0.84. We also observed strong LD values for the SNPs in the IL-15Rα gene, as follows: rs3136618 and rs2228059 – D'=0.93; rs2296135 and rs2228059 – D'=0.79; rs2296135 and rs3136618 – D'=0.80.

IL-15 and IL-15Rα SNPs and Associations with Predictors of the Metabolic Syndrome

Significant associations with SNPs in the regulatory elements (1st intron, 3'UTR) of the IL-15 gene were observed with predictors of the metabolic syndrome. The T-allele for a SNP (rs1589241) located in the 1st intron was associated with higher values for serum cholesterol and LDL in female subjects and BMI and HOMA in male subjects. Fasting glucose and BMI were lower in males with a copy of the T-allele for rs1057972, located in the 3'UTR. When analyzing SNPs in the IL-15Rα gene, a copy of the C-allele for the rs2228059 SNP, located in the 3rd exon, was associated with lower values of serum triglycerides in males.

IL-15 and IL-15Rα SNPs and Associations with Muscle, Strength, and Bone Phenotypes

Significant associations between SNPs in the IL-15Rα and IL-15 genes and muscle, strength, and bone phenotypes were observed in our sample population. A copy of the A-allele for rs2228059, located in the 3rd exon of the IL-15Rα gene, was associated with higher skeletal muscle volume but lower muscle quality measured at baseline in males. Females with a copy of the C-allele for rs2296135, located in the 3'UTR of the IL-15Rα gene, gained more isometric strength after the 12-week resistance training program. Males with a copy of the T-allele for rs1057972, located in the 3'UTR of the IL-15 gene, showed greater improvements in the 1 repetition maximum strength test following the 12 week program. In females, a copy of the A-allele for rs2296135, located in the 3'UTR of the IL-15Rα gene, was associated with a greater baseline total bone volume. Higher values for baseline cortical bone volume in females were associated with a copy of the A-allele for rs2228059, located in the 3rd exon of the IL-15Rα gene.

Discussion

Our data highlight novel, gender-specific associations between predictors of the metabolic syndrome, specifically, total cholesterol, LDL, BMI, fasting glucose, and HOMA measures and SNPs in the IL-15 and IL-15Rα genes. Baseline demographic data showed significant differences in body mass, height, and BMI when comparing female and male subjects. Based on this observation, all phenotype and serum markers were analyzed separately in males and females. These associations are interesting in light of the proposed role of muscle-derived IL-15 on lipolysis and glycogenolysis [3]. A copy of the T-allele for rs1589241 (IL-15 gene) was associated with a higher BMI value as well as a higher HOMA measurement in males. Published data suggests that muscle-derived IL-15 is able to promote lipolysis. Therefore, it is conceivable that a copy of the T-allele for rs1589241 could alter levels of IL-15 leading to a reduction in lipolysis and, consequently, a higher BMI value. Furthermore, a copy of the same allele is associated with higher HOMA values, indicative of an increase in insulin resistance. Collectively, these data suggest that IL-15 and IL-15Rα may have roles in the etiology of the metabolic syndrome.

In addition to the roles of IL-15 addressed above, this cytokine has lymphocyte chemotactic properties and can act as a non-specific lymphocyte growth factor [1,13]. Atherosclerosis is recognized as an inflammatory disease and atherosclerotic lesions from humans and mice have been shown to contain IL-15 mRNA protein [8]. This expression of IL-15 may recruit lymphocytes to the site of the lesion, thus promoting the disease. Polymorphisms within regulatory elements of genes have the potential to alter expression levels of mRNA, although we did not test the effects of these specific SNPs on expression levels of IL-15 and Il-15Rα in this study. It is conceivable that individual SNPs or haplotypes in the IL-15 and IL-15Rα genes could alter expression levels and place individuals at an increased risk for high cholesterol and/or progression of atherosclerotic lesion development through lymphocyte recruitment. These hypotheses, along with the novel SNP associations revealed in this study, remain to be tested.

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