

Genome-Wide Association Study Identifies *CDKN1A* as a Novel Locus Associated with Muscle Fiber Composition

Ekaterina A Semenova^{1,2}, Hirofumi Zempo³, Eri Miyamoto-Mikami⁴, Hiroshi Kumagai^{4,5},
Andrey K Larin¹, Rinat I Sultanov¹, Konstantin A Babalyan¹, Andrey V Zhelankin¹,
Takuro Tobina⁶, Keisuke Shiose⁷, Ryo Kakigi⁸, Takamasa Tsuzuki⁹,
Noriko Ichinoseki-Sekine^{4,10}, Hiroyuki Kobayashi¹¹, Hisashi Naito⁴, Jatin Burniston¹²,
Edward V Generozov¹, Noriyuki Fuku⁴, Ildus I Ahmetov^{1,12,13,14}

¹ Federal Research and Clinical Center of Physical-Chemical Medicine of Federal Medical Biological Agency, Russia.

² Volga Region State University of Physical Culture, Sport and Tourism, Russia. ³ Tokyo Seiei College, Japan.

⁴ Juntendo University, Japan. ⁵ University of Southern California, USA. ⁶ University of Nagasaki, Japan.

⁷ University of Miyazaki, Japan. ⁸ Josai International University, Japan. ⁹ Meijo University, Japan.

¹⁰ The Open University of Japan, Japan. ¹¹ Tsukuba University Hospital, Japan. ¹² Liverpool John Moores University, UK.

¹³ Plekhanov Russian University of Economics, Russia. ¹⁴ Kazan State Medical University, Russia.

Abstract

Muscle fiber composition is associated with physical performance, with endurance athletes having a high proportion of slow-twitch muscle fibers compared to power athletes. Approximately 45% of muscle fiber composition is heritable, however, single nucleotide polymorphisms (SNP) underlying inter-individual differences in muscle fiber types remain largely unknown.

Based on three whole genome SNP datasets, we have shown that the rs236448 A allele located near the cyclin-dependent kinase inhibitor 1A gene (*CDKN1A*) was associated with an increased proportion of slow-twitch muscle fibers in Russian ($n = 151$; $p = 0.039$), Finnish ($n = 287$; $p = 0.03$), and Japanese ($n = 207$; $p = 0.008$) cohorts (meta-analysis: $p = 7.9 \times 10^{-5}$). Furthermore, the frequency of the rs236448 A allele was significantly higher in Russian ($p = 0.045$) and Japanese ($p = 0.038$) elite endurance athletes compared to ethnically matched power athletes. On the contrary, the C allele was associated with a greater proportion of fast-twitch muscle fibers and a predisposition to power sports. *CDKN1A* participates in cell cycle regulation and is suppressed by the miR-208b, which has a prominent role in the activation of the slow myofiber gene program. Bioinformatic analysis revealed that the rs236448 C allele was associated with increased *CDKN1A* expression in whole blood ($p = 8.5 \times 10^{-15}$) and with greater appendicular lean mass ($p = 1.2 \times 10^{-5}$), whereas the A allele was associated with longer durations of exercise ($p = 0.044$) reported amongst the UK Biobank cohort. Furthermore, the expression of *CDKN1A* increased in response to strength ($p < 0.0001$) or sprint ($p = 0.00035$) training. Accordingly, we found that *CDKN1A* expression is significantly ($p = 0.002$) higher in the m. vastus lateralis of strength athletes compared to endurance athletes and is positively correlated with the percentage of fast-twitch muscle fibers ($p = 0.018$).

In conclusion, our data suggest that the *CDKN1A* rs236448 SNP may be implicated in the determination of muscle fiber composition and may affect athletic performance.