World Academy of Science, Engineering and Technology
International Journal of Bioengineering and Life Sciences
Vol:9, No:10, 2015

The Impact of P108L Genetic Variant on Calcium Release and Malignant Hyperthermia Susceptibility

Authors : Mohammed Althobiti, Patrick Booms, Dorota Fiszer, Philip Hopkins

Abstract : Malignant hyperthermia (MH) is a pharmacogenetic disorder of skeletal muscle. MH results from anaesthetics induced breakdown of calcium homeostasis. RYR1 and CACN1AS mutations represent the aetiology in ~70% of the MH population. Previous studies indicate that up to 25% of MH patients carry no variants in these genes. Therefore, the aim of this study is to investigate the relationships between MH susceptibility and genes encoding skeletal muscle Ca2+ channels as well as accessory proteins. The JSRP, encoding JP-45, was previously sequenced and novel genetic variants were identified. The variant p.P108L (c.323C > T) was identified in exon 4 and encodes a change from a proline at amino acid 108 to leucine residue. The variant P108L was detected in two patients out of 50 with 4% frequency in the sample population. The alignment of DNA sequences in different species indicates highly conserved proline sequences involved in the substitution of the P108L variant. In this study, the variant P108L co-segregates with the SNP p.V92A (c.275T > C) at the same exon, both variants being inherited in the same two patients only. This indicates that the two variants may represent a haplotype. Therefore, a set of single nucleotide polymorphisms and statistical analysis will be used to investigate the effects of haplotypes on MH susceptibility. Furthermore, investigating the effect of the P108L variant in combination with RYR1 mutations or other genetic variants in other genes as a combination of two or more genetic variants, haplotypes may then provide stronger genetic evidence indicating that JSRP1 is associated with MH susceptibility. In conclusion, these preliminary results lend a potential modifier role of the variant P108L in JSRP1 in MH susceptibility and further investigations are suggested to confirm these results.

Keywords : JSRP1, malignant hyperthermia, RyR1, skeletal muscle
Conference Title : ICBBMB 2015 : International Conference on Biochemistry, Biophysics and Molecular Biology
Conference Location : Chicago, United States
Conference Dates : October 08-09, 2015