Modulation of the Human Erythroid Plasma Membrane Calcium Pump (PMCA4b) Expression by Polymorphic Genetic Variants

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PMCA4b is an ATP-driven calcium pump encoded by the *ATP2B4* gene. This protein is responsible for several cellular functions and has a major role in maintaining low calcium levels in platelets and erythrocytes. In genome-wide association studies (GWAS) single nucleotide polymorphisms (SNPs) within a haplotype in the *ATP2B4* gene were associated with resistance to a severe form of malaria among children. Individuals that carry the minor haplotype show a decreased expression of PMCA4b in the red blood cell membrane. The genetic area of the haplotype is a predicted erythroid-specific enhancer region, but the molecular mechanisms of this regulation are not known.

Our aim was to examine the molecular mechanisms responsible for the association between the SNPs in the minor haplotype in the *ATP2B4* gene and the reduced expression of PMCA4b in erythroid cells.

To examine the promoter activity of the *ATP2B4* haplotype, four regions were examined separately in which the SNPs within the haplotype are located. HEK (human embryonic kidney) cells and erythroid cell lines HEL92 and K562 were transfected with luciferase-coding plasmids containing the examined regions. The potential promoter activity of the examined regions was determined by dual-luciferase assay.

Dual-luciferase measurements showed a large difference between the erythroid and HEK cell lines. The erythroid-specific regulatory region described by Lessard et al. (2017) showed a significant promoter activity in the HEL92 and K562 erythroid cell lines, while not in HEK cells. Measurements with the same haplotype region containing the minor SNPs showed a decreased level of promoter activity in erythroid cell lines.

Our results offer insights into the molecular mechanisms underlying the erythroid-specific regulation of the PMCA4b calcium transporter in the examined region. The results indicate that one of the examined regions has an erythroid-specific promoter activity that is decreased when two of the examined SNPs from the minor haplotype are present. The results may have a relevance in the susceptibility to malaria.

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