4. Discussion

Genetic variations of the human *ABCB1* gene have been the most extensively studied. More than 50 SNPs and insertion/deletion polymorphisms in the *ABCB1* gene have been reported. However, information is still limited with respect to the actual effect of these genetic polymorphisms on the function of the ABCB1 protein.

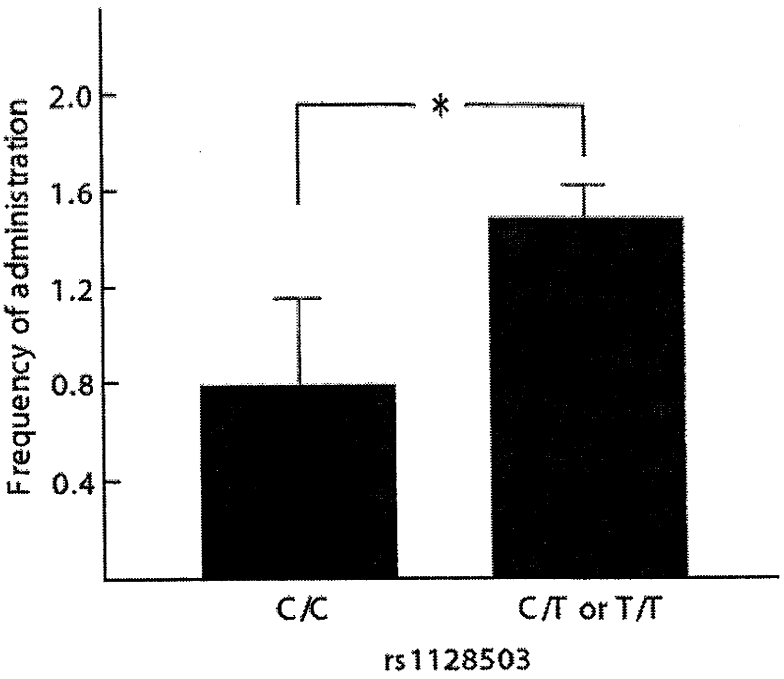

Figure 1. Association between frequency of rescue analgesic administration and *ABCB1* rs1128503. The data are presented as mean ± SEM. Asterisk indicates significant difference (*$p < 0.05$).

In the present study, we analyzed three *ABCB1* gene polymorphisms in a Japanese population who underwent major open abdominal surgery under combined general and epidural anesthesia. Previous studies have reported associations between the rs1045642, rs2032582, and rs1128503 SNPs and methadone doses required for effective treatment of heroin dependence [20].

Methadone is a μ-opioid receptor agonist used for treating opiate dependence and is also a substrate of the transporter P-glycoprotein that is encoded by the *ABCB1* gene, similar to other opioids. Therefore, we chose these three *ABCB1* SNPs for the present association study.

We found associations between the *ABCB1* gene polymorphism (rs1128503) and frequency of rescue analgesic administration. A significant main effect of the *ABCB1* rs1128503 SNP on the frequency of rescue analgesic administration was observed when the C/C genotype was compared with the combined C/T and T/T genotypes (Figure 1). Blood levels of opioids are reported to depend on the activity of the ABCB1 protein, and the activity of the ABCB1 protein in patients requiring more rescue analgesics may be higher than in other patients. This hypothesis suggests that the activity of the ABCB1 protein in patients with the C/C genotype may be lower than in patients with the C/T and T/T

genotypes. rs1128503 is a synonymous variant that does not result in a change in amino acid sequence. It is located in exon 12 and within one of the intracellular loops of the protein, adjacent to an ATP-binding/utilization domain. rs1128503 may affect translation regulation, RNA stability, or other molecular mechanisms.

For our ANOVA, the desirable sample size was calculated as 158 for the effect size 0.25 to achieve 80% power. This suggests that the sample size of 129 in the present study might be insufficient to detect reliably moderate differences between the SNP genotypes. Further investigations with larger samples may reveal further associations between the *ABCB1* polymorphism and sensitivity to opioids.

In the present study, the data from patients who received NSAIDs not as main analgesics, but rather as rescue analgesics, were also analyzed. The amount of NSAIDs administered as rescue analgesics during the 24 h postoperative period were converted to the equivalent dose of systemic pentazocine. This study, therefore, investigated the relationship between *ABCB1* polymorphisms and sensitivity to opioids, not NSAIDs.

5. Conclusion

The present study analyzed *ABCB1* polymorphisms (rs1045642, rs2032582, rs1128503) in a Japanese population who underwent major open abdominal surgery under combined general and epidural anesthesia. We found an association between the *ABCB1* gene polymorphism rs1128503 and frequency of rescue analgesic administration. This study suggests that specific ABCB1 variants may have clinical relevance by influencing the opioid doses required. The present findings will contribute to future personalized pain treatment.

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