# [OS2-92] Postoperative Respiratory Depression in Children is associated with Genetic Variants of Blood Brain Barrier Opioid Transporter, ABCB1

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Background
Tonsillectomy is one of the most common and significantly painful surgical procedures children undergo. Use of opioid pain medications accounted for a preponderance of post-tonsillectomy deaths and anoxic brain injuries. In February 2013, the FDA warned against the use of codeine (morphine pro-drug) in children undergoing tonsillectomy based on multiple reports of deaths and serious adverse effects irrespective of the CYP2D6 genotype and sleep apnea status. Opioids often worsen oxygen desaturations after tonsillectomy in children. Thus, adequate and safe postoperative pain management is essential.
Morphine is subject to efflux transport via P-glycoprotein transporter encoded by ABCB1 gene.. ABCB1 polymorphisms (Figure 1a) may affect blood brain barrier transport of morphine and, therefore, individual response to its central analgesic and adverse effects. This study aims to determine specific associations between common ABCB1 genetic variants and analgesic efficacy and clinically important adverse outcomes associated with intravenous morphine in American children undergoing tonsillectomy.
Methods
A homogeneous group of 263 children undergoing tonsillectomy who received intravenous morphine as part of standard perioperative care were genotyped for ABCB1. The association between 5 single-nucleotide polymorphisms (SNPs) of ABCB1 and the primary safety endpoints, respiratory depression, and respiratory depression resulting in prolonged stay in Post Anesthesia Recovery Room (PACU) were evaluated. The secondary outcome was postoperative morphine requirement.
Results
ABCB1 polymorphism, rs9282564, was significantly associated with increased risk of morphine related respiratory depression in PACU in both 219 white and 44 black children (Table 1). Specifically, in a combined race analysis compared to children with GA genotype, children with GG genotype of rs9282564 had 4.7 fold increase in the odds of respiratory depression resulting in prolonged stay in PACU (95% CI: 2•-10•8, p=0•0002) (Figure 1b); increased postoperative morphine requirement was associated with CC genotype of the ABCB1 polymorphism, rs2229109 (p=0•02) (Figure 2).
Conclusion
ABCB1 rs9282564 polymorphism is associated with increased risk of morphine related respiratory depression resulting in prolonged stays in PACU in children undergoing tonsillectomy. Awareness of genetic variations of drug responsiveness can lead to tailored drug selection on the basis of a patient’s genetic makeup and dose adjustment, which are likely to prevent adverse drug reactions.

**Table 1. Respiratory depression (RD) and prolonged PACU stay due to RD by genotypes**

| | | White Children | | | | | Black Children | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **ABCB1 SNP** | | N | RD % | p | Prolonged PACU due to RD% | p | N | RD % | p | Prolonged PACU due to RD% | p |
| **rs9282564** | **GG** | 2 | 100 | **0.04** | 100 | **<0.01** | 0 | - | 0.20 | - | **0.04** |
| | **GA** | 46 | 17 | | 20 | | 3 | 67 | | 67 | |
| | **AA** | 171 | 16 | | 8 | | 41 | 27 | | 10 | |

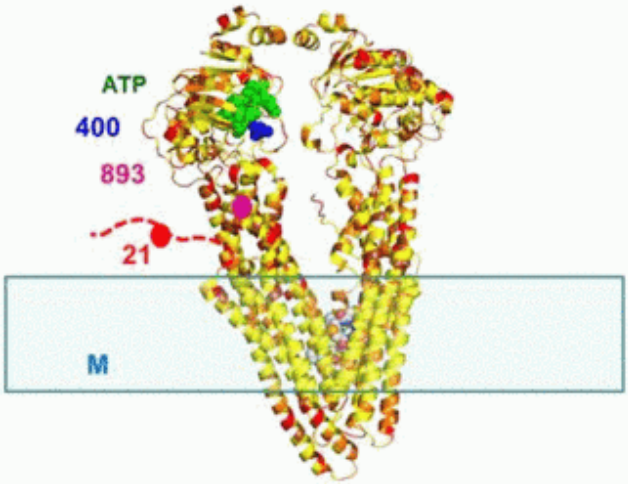


**Figure 1a. 3D structure of ABCB1 with polymorphisms**

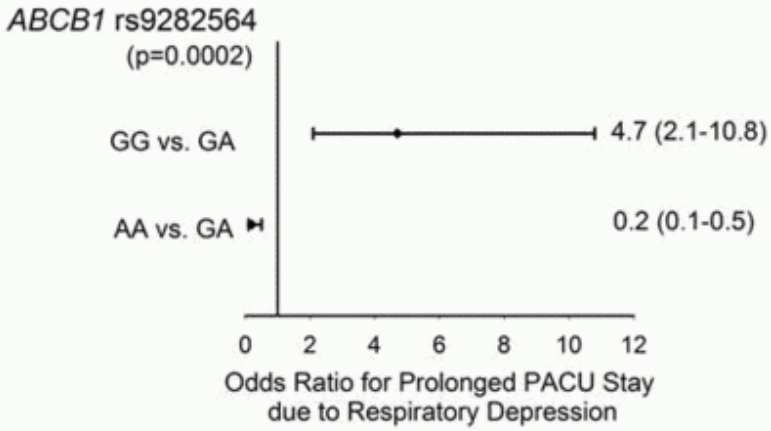


**Figure 1b. ABCB1 genotype and risk of Respiratory Depression**

**Figure 1. ABCB1 Transporter Variant is Associated With Respiratory Depression in White and Black Children**

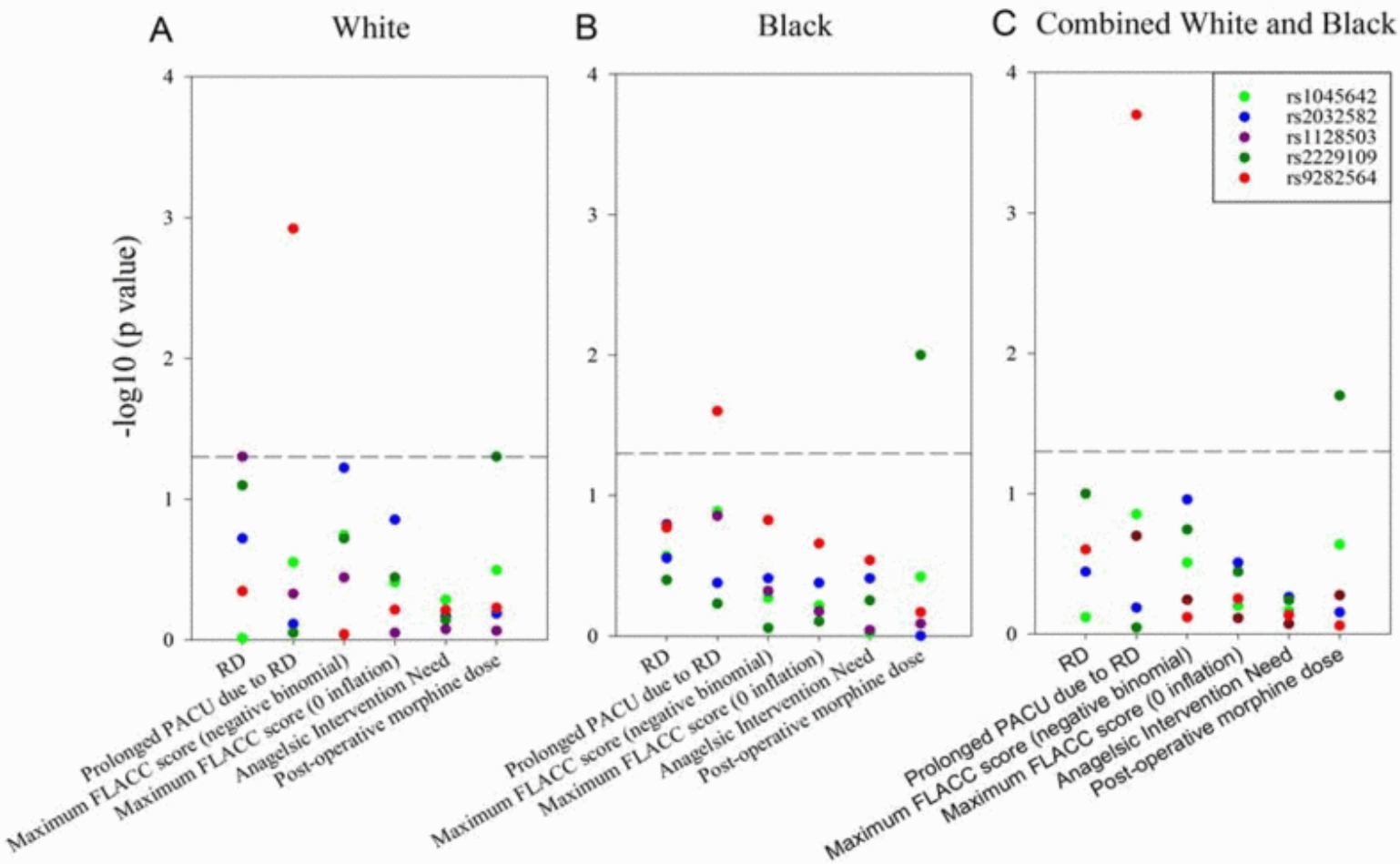


**Figure 2. Genetic associations between 5 ABCB1 polymorphisms and Clinical Safety and Efficacy Outcomes**