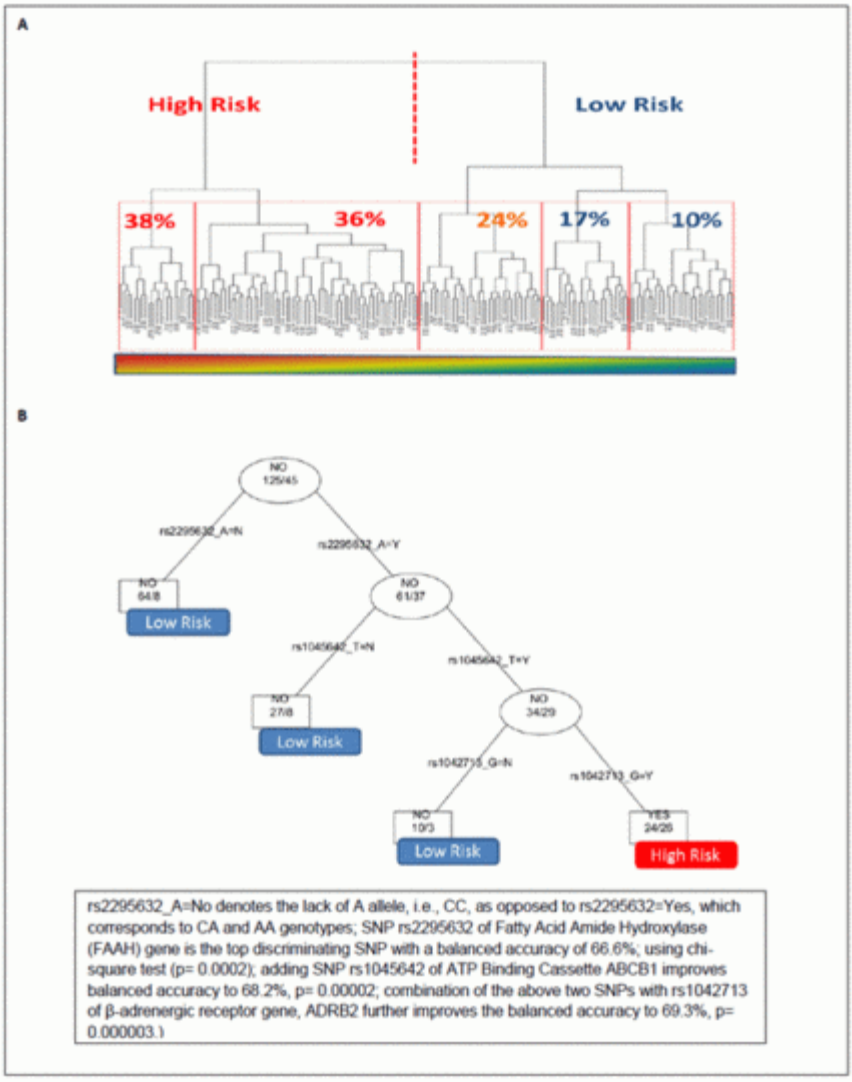
[OS1-85] Clinical Decision Algorithms based on Genetic and Non-genetic factors Predict risk of Postoperative Opioid-induced Respiratory Depression in Children

Chidambaran V, Sadhasivam S, Meller J, Biesiada J
Cincinnati Children's Hospital , Cincinnati , OH, United states

---

Introduction: A significant fraction of approximately 6 million children, who undergo painful surgeries in the US each year, experience inadequate pain relief and serious opioid-related side-effects. Opioid induced respiratory depression (RD),the most serious adverse effect, is responsible for upto 50% of postoperative respiratory failure events [1]. Twin studies have revealed significant heritability (30%) for RD from opioids [2]; non-genetic factors like female sex, race, and genetic risk factors like CYP2D6 variants have been described[3]. To translate genetic research finding to clinical practice, we need easy applicable clinical algorithms based on multivariate predictors. The aim of our study is to develop reliable models for the prediction of risk of morphine induced RD using genetic and non-genetic factors.
Methods: After appropriate IRB approval and consent, we conducted a prospective genotype-blinded trial in 263 children, aged 6-15 years, undergoing tonsillectomy, who received morphine as part of standard perioperative care. All patients were observed in the recovery room for morphine requirements, pain outcomes and occurrence of RD, our primary outcome, defined as a respiratory rate <10 breaths/ minute or persistent oxygen desaturation <92% requiring supplemental oxygen in the absence of clinically obvious upper airway obstruction. We genotyped all patients for 48 single-nucleotide polymorphisms (SNPs) in 15 genes known to be involved in the morphine pharmacokinetic and RD pathway using TaqMan assays. Genetic and non-genetic factors (race, sex, obstructive sleep apnea (OSA)) were analyzed for association with risk of RD and a stepwise risk-based algorithm was constructed using simple logical rules and decision tree approach.
Results: Of the 263 children, 219 were Caucasian and 44 African-American, 47% male and 47% had OSA. Using all SNPs and clinical variables, we were able to identify 5 clusters with the risk of RD increasing gradually from about 10% for the 'low risk cluster' to about 40% for the 'high risk clusters'(Fig 1A). Fig 1B shows an example - Fatty Acid Amide Hydroxylase (FAAH)gene variant is the top discriminating SNP and combining SNPs of ATP Binding Cassette (ABCB1) and β-adrenergic receptor gene, ADRB2 in a stepwise manner improves accuracy significantly.
Conclusion: Using centroids of defined clusters, we can achieve about 85% accuracy of high vs. intermediate vs. low risk assignment for postoperative morphine-induced RD in children. After appropriate and independent validations, genotype-based decision algorithms can help to proactively determine underlying risks and form an important step in clinical implementation of personalized analgesia.
References:
1.Fecho K et. al Therapeutics and clinical risk management. 2009;5:961-8.
2.Angst MS et. al,. Anesthesiology. 2012;117(1):22-37.
3.Niesters M et. al. British journal of anaesthesia. 2013;110(2):175-82

Figure 1: SNP signatures identify high vs. low risk subtypes among patients requiring post-surgical intervention; In panel A, percent of RD cases in each cluster is shown, and panel B shows that 3 SNPs allow capture of most of the signal as shown using a decision tree that classifies patients into low vs. high risk strata.



rs2295632_A=No denotes the lack of A allele, i.e., CC, as opposed to rs2295632=Yes, which corresponds to CA and AA genotypes; SNP rs2295632 of Fatty Acid Amide Hydroxylase (FAAH) gene is the top discriminating SNP with a balanced accuracy of 66.6%; using chi-square test (p= 0.0002); adding SNP rs1045642 of ATP Binding Cassette ABCB1 improves balanced accuracy to 68.2%, p= 0.00002; combination of the above two SNPs with rs1042713 of β-adrenergic receptor gene, ADRB2 further improves the balanced accuracy to 69.3%, p= 0.000003.)