XENOBIOTIC METABOLISM GENES AND CLUBFOOT

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Idiopathic or isolated clubfoot is a common orthopedic birth defect that affects approximately 135,000 children worldwide. It is characterized by equinus, varus and adductus deformities of the ankle and foot. Correction of clubfoot involves months of serial manipulations, castings and bracing, with surgical correction needed in forty percent of cases. Multifactorial etiology has been suggested in numerous studies with both environmental and genetic factors playing an etiologic role. Maternal smoking during pregnancy is the only common environmental factor that has consistently been shown to increase the risk for clubfoot. Moreover, a positive family history of clubfoot and maternal smoking increases the risk of clubfoot twenty fold. These findings suggest that genetic variation in smoking metabolism genes may increase susceptibility to clubfoot. Based on this reasoning, we interrogated eight candidate genes, chosen based on their involvement in phase 1 and 2 cigarette smoke metabolism. Twenty-two SNPs and two null alleles in eight genes (CYP1A1, CYP1A2, CYP1B1, CYP2A6, EPHX1, NAT2, GSTM1 and GSTT1) were genotyped in a dataset composed of nonHispanic white and Hispanic multiplex and simplex families. Only one SNP in CYP1A1, rs1048943, had significantly altered transmission in the aggregate and multiplex NHW datasets (p=0.003 and p=0.009). Perturbation of CYP1A1 by rs1048943 polymorphism causes an increase in the amount of harmful, adduct forming metabolic intermediates. A significant gene interaction between EPHX1 and NAT2 was also found (p=0.007). This interaction may affect the metabolism of harmful metabolic intermediates. Additionally, marginal interactions were found for other xenobiotic genes and these interactions may play a contributory role in clubfoot. Importantly, for CYP1A2, significant maternal (p=0.03; RR=1.24; 95% CI: 1.04-1.44) and fetal (p=0.01; RR=1.33; 95% CI: 1.13-1.54) genotypic effects were identified suggesting that both maternal and fetal genotypes impact normal limb development. No association was found for maternal smoking status and tobacco metabolism genes. Together, these results suggest that
xenobiotic metabolism genes may play a contributory role in the etiology of clubfoot regardless of maternal smoking status and may impact foot development through perturbation of tobacco metabolic pathways.