

Variation in Genes Regulating Male Reproductive Development In Relation to Anogenital Distance Measurements, Potential Markers of In Utero Androgenization

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Purpose: Single nucleotide polymorphisms (SNPs) in genes regulating male reproductive tract development have been associated with male genitourinary abnormalities, but no studies have examined the relationship between SNPs and novel anogenital measurements such as anogenital distance (AGD), anoscrotal distance (ASD), and penile width (PW).

Methods: We examined whether common variation in 34 SNPs within genes regulating male genital development (*AR*, *ESR1*, *ESR2*, *CTGF*, *CYR61*, *INSL3*, *RXFP2*, *ATF3*) is associated with AGD, ASD, and PW in 106 healthy male infants (ages 2-34 months) from the multi-center Study for Future Families. DNA was extracted from buccal smears, and we used linear regression models to assess the relationship between anogenital measurements and SNP genotypes with adjustment for covariates.

Results: We found that the rs2077647 G allele, located in a coding region of *ESR1*, was associated with a shorter AGD (-7.3mm, 95% CI -11.6 to -3.1). In addition, the rs10475 T allele, located in the 3' untranslated region of *ATF3*, was associated with a shorter ASD (-4.3mm, 95% CI -7.2, -1.4). We observed no association between PW and any SNPs examined.

Conclusions: We found that minor alleles for two SNPs within genes that are involved in estrogen mediated male genital development were associated with AGD and ASD. These results are preliminary but suggest that these measures may be intermediate phenotypes that form within the same developmental pathway as other abnormalities such as hypospadias and cryptorchidism. Future studies are needed to functionally validate that *ESR1* and *ATF3* are involved in the development of intermediate male phenotypes.