UNC
GILLINGS SCHOOL OF
GLOBAL PUBLIC HEALTH

BIOSTATISTICS SEMINAR

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Methods for finding risk-related X chromosome variants

The X chromosome has been largely neglected in genome-wide association studies (GWAS), in part because the analyst has had limited methodological options. We consider identifying risk-related single nucleotide polymorphisms (SNP markers) on the X, in the context of case-parent studies. Our method, the parent-informed likelihood ratio test for the X chromosome (PIX-LRT), enables estimation of relative risks, is robust against population stratification, and takes advantage of parental genotype information and the sex of the affected offspring. Under *parental allelic exchangeability* (PAE) for the X, the parents of affected offspring provide an independent replication sample, which augments the conditional information based on transmission distortion to the affected offspring. For each offspring sex we can combine the parent-level and the offspring-level information to form a likelihood ratio test statistic; we then combine the statistics for the two sexes to form a single composite test statistic, which offers better power than existing methods. Maternal SNP effects can also influence risk through prenatal effects on the developing fetus, regardless of which alleles were transmitted by the mother to her offspring. Previously, using triads alone, no method of testing for maternally-mediated effects of variants on the X had been developed that did not require an assumption of Hardy-Weinberg Equilibrium (HWE). We extend PIX-LRT to identify maternal X-chromosome SNP effects under PAE. Finally, we consider the identification and estimation of multi-SNP effects. For case-parent triads, X-chromosome haplotype phases can be inferred. With that exact phase information, under parental haplotype exchangeability one can extend PIX-LRT from a two-allele problem to a k-allele problem, where the “alleles” are now the existing haplotypes at the locus under study and a conditional logistic model uses pseudo-siblings. We illustrate our methods using data from over 2000 triads in which the affected offspring have an oral cleft. (*This is based on work by Clarice R. Weinberg, Min Shi, and Alison Wise*)

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3:30 pm - 4:30 pm

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