# Questions on Boehnke and Cox (1997) *American Journal of Human Genetics*.

Accurate Inference of Relationships in Sib-Pair Linkage Studies

1. When the paper was written, relative pair linkage studies were a popular strategy for complex trait gene mapping. How do relative pair linkage studies work? What are the consequences of misspecified relationships in relative pair linkage studies? Why are these studies no longer popular today?

2. Look in the *American Journal of Human Genetics* or in *Nature Genetics* for a complex trait linkage study and summarize its findings (how many families were analyzed, whether any linkage signals were discovered, etc.).

3. Do you think relationship estimation is important for the analysis of modern genetic association studies? Why?

4. The authors state that misspecified relationships can be identified based on incompatibilities with Mendelian inheritance, but only when additional family members are genotyped. What are these Mendelian incompatibilities? Why are additional family members required?

5. Consider a marker with genotypes A/A, A/B and B/B, each with frequency $p^2$, $2p(1-p)$ and $(1-p)^2$, where $p$ denotes the frequency of allele A. Consider a trio of individuals X, Y, Z … If we suppose that Z is the child of X and Y, but the three individuals are unrelated, what is the probability that their genotypes will be incompatible?

6. Most modern studies focus on single nucleotide polymorphisms, with only two alleles. Why? Which rows in table 1 are relevant for the analysis of single nucleotide polymorphisms? How would the simulation results change if the authors focused on single nucleotide polymorphisms instead of markers with 4 equally frequent alleles?

7. The authors identify the relationship $R$ that maximizes the probability of observed genotypes $P(X|R)$. What ingredients go into the calculation of this probability? If you preferred a Bayesian approach, how would you refine their approach?

8. How would you modify the proposed account to allow for the possibility of genotyping errors? If you are stuck, look for the work of Karl Broman.

9. Parent-offspring pairs and half-sibling pairs both share one chromosome identical by descent, on average. How can the proposed method distinguish between the two?

10. What struck you most about the paper?