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Reply to Merz et al.

To the Editor:

The "ASHG "Statement on Professional Disclosure of Familial Information" is the result of 2 year's work and consultation. While relying on both the President's Commission and I.O.M. reports, it also examined the issue from an international, comparative perspective.

The literature and cases cited were but examples of a growing realization that genetic information is not only personal but necessarily familial. Reiterating and reinforcing the ethics of physician-patient confidentiality formed the basis of our statement. The ethical-legal privilege of disclosure may be exercised if certain conditions are met.

It is in the decision to respect (or not respect) the patient's refusal to allow disclosure that the health professional, like all professionals, enjoys the concomitant freedoms and responsibilities inherent in that very status. The statement provides a framework not only for reflection and guidance in complex situations but also for human reactions that cannot always be foreseen or contractually arranged by consent or refusal prior to the availability of test results.

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LOD Scores, Location Scores, and X-Linked Cone Dystrophy

To the Editor:

In a previous issue of the *Journal*, Bergen and Pinckers (1997) described a novel locus for X-linked progressive cone dystrophy, on Xq27, which was assigned in a single large pedigree. However, there appear to be two weaknesses in the data presented.

First, there is an apparent anomaly in the LOD scores obtained for the family showing linkage. The most significant two-point LOD score was only 2.6; yet, multipoint linkage analysis gave a LOD score of 10.8. Multipoint analysis functions to combine data from those parts of the family that were uninformative for one or more markers into a maximally informative haplotype. As such, a multipoint analysis seems unlikely to give a result so much larger than the two-point LOD scores for the markers used to calculate it. As a rough rule of thumb, when estimating the LOD score that a pedigree should give, each informative meiotic event contributes ~0.33 to the LOD score, if no recombination occurs. Examination of the pedigree studied by Bergen and Pinckers (1997) revealed 14 meioses informative for the disease, which, on the basis described above, should give at best a maximum LOD score of ~4.6. I, therefore, repeated the analysis described in their article, using the alleles given. By assuming equal frequencies, I obtained results similar to those given in table 3 of their article. On the basis of the multipoint analysis, however, the graph shown in figure 2 of their article evidently is in fact a plot of location scores (the natural log) rather than of LOD scores ($\log_{10}$). To obtain the LOD score, the location score is divided by 4.6. Therefore, the true LOD score obtained from this analysis was 2.35, not 10.8.

Although not stated by Bergen and Pinckers (1997), I assumed that the markers presented in table 3 of their article are in the order in which they occur on the chromosome. If this is the case, then markers DXS297 and DXS998 lie in the 3-cM gap between DXS292 and DXS1123. Under that assumption and, again, when equal allele frequencies were assumed, my multipoint analysis with the alleles shown for markers DXS292, DXS297, DXS998, DXS1123, and DXS1113 gave a maximum LOD score of 3.38, at DXS998. Repetition of this analysis, with allele frequencies estimated from the six unrelated chromosomes sampled in the family, gave a LOD score of only 2.46. In conclusion, these data do indeed suggest a locus for X-linked cone dystrophy in this region but with rather less significance than Bergen and Pinckers have stated.

A second weakness in the article is the assertion that this locus maps to Xq27. An examination of published maps of the area (NIH/CEPH Collaborative Mapping Group 1992; Gyapay et al. 1994) provides some information but does not confirm a location on Xq27. DXS292 and DXS297, which mark the proximal boundary of the interval, are placed in Xq27-28, whereas DXS998, which is within the interval, is only 3 cM from the distal tip of the 1994 Généthon X-chromosome map (Gyapay et al. 1994). As such, for this locus, placement on Xq28 seems equally likely, which would place the locus in very close proximity to the red and green opsin genes (RCP and GCP, respectively).

In table 1 of their article, Bergen and Pinckers (1997) summarize the phenotypes resulting from the GCP and