for example, in the study of complications during pregnancy such as preeclampsia (Kilpatrick 1999).

The log-linear model is equivalent to a conditional logistic analysis comparing the case to appropriately defined "pseudo-sibling controls" (Kraft 2002). If the gene under study is assumed not to play a direct role in an individual's risk of disease (or to be linked to any other such gene), then to test for an indirect role of maternal genotype (say) each case subject should be compared to a pseudo-sibling control subject whose mother has the genotype of the case subject's father. That is, if the genotypes of the mother and father are G_m and G_f, respectively, then the conditional logistic likelihood for the family is

$$\frac{e^{\beta Z(G_m)}}{e^{\beta Z(G_m)} + e^{\beta Z(G_f)}},$$

where $Z(\cdot)$ is some dominance coding.

This approach (reasonably) assumes that, given the set of parental marker genotypes $\{G_1,G_2\}$, it is equally likely that $G_m = G_1$ or G_2. In other words, "the frequency of heterozygous mothers married to homozygous variant fathers is the same as the frequency of heterozygous fathers married to homozygous variant mothers, and so on" (Wilcox et al. 1998). Furthermore, since this likelihood permutes the genotypes of "the parent contributing to disease risk" and the "the parent not contributing to disease risk," it cannot estimate joint effects of both parents' genotypes. However, for many diseases, only the mother (father) will plausibly contribute to a child's disease risk.

Although the case-parent trio analysis conditions on the parents' genotypes and hence is robust to population stratification bias, the analysis comparing parental genotypes to population-based controls is not (although Labuda et al. [2002] argue that this may not be an issue for the particular data they analyze in their report). Furthermore, even when there is no population stratification, the latter analysis is something of an "apples and oranges" comparison, as the exposure of interest is not the control subject's genotype, but his or her parent's genotype. The control's genotype serves as a surrogate for his or her parent's. In a simulation study with 175 unmatched case and control subjects (1,000 replicates), we found that the odds ratio comparing case subjects' maternal genotypes to control genotypes underestimated the odds ratio associated with each variant maternal allele by 11% (variant allele frequency 0.25; baseline probability of disease 14%; odds ratio per variant maternal allele 2). Of course, the data Labuda et al. (2002) analyzed did not contain parental genotype information for the controls. But if one were to design a case-population control study to detect the effects of maternal (paternal) genotypes, then one should plan to collect information on controls' maternal (paternal) genotypes.

Finally, figure 1*a* is misleading in that case subjects' parents are not representative of population controls if individuals' genotypes are associated with disease or there is population stratification.

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Regarding "Parental Genotypes in the Risk of a Complex Disease"

To the Editor:

Labuda et al. (2002) have proposed that parental genotypes might play a role in the causation of complex diseases. They seem unaware that this idea has been considered by others (e.g., Lande et al. 1989) and that methods have been developed to test for parentally mediated genetic effects, both for a dichotomous phenotype (Mitchell 1997; Weinberg et al. 1998; Wilcox et al.

1998) and for a quantitative phenotype (van den Oord 2000).

Furthermore, some of the assessments made by Labuda et al. miss the mark. They assume (see their fig. 1) that under scenario A, where the offspring genotype is the one that "counts," the parents of affected children will resemble control parents with respect to the gene under study. This ignores the fact that the genotypes of parents and their children are correlated. Just as the parents of offspring with Huntington disease will differ from population controls in their prevalence of the allele for Huntington disease, parents of offspring who have a complex disease will tend to differ from population controls. Thus, the case-control analyses reported in table 1 of Labuda et al. (2002) are not specific to parentally mediated genetic effects.

There are other reasons, biologic and technical, to doubt the interpretation offered by Labuda et al., who suggest that their data support a parent-mediated effect of *CYP2E1*5* on risk of childhood acute lymphoblastic leukemia. First, the mechanisms by which the maternal and paternal genotypes would influence offspring phenotype are very different (i.e., in utero environment vs. DNA replication errors that produce genetically abnormal sperm). It thus seems unlikely that the etiology of a given condition would be related to both maternal and paternal effects of a single gene. Rather, similar "effects" of the maternal and paternal genotypes, on the basis of case-control parental data, seem more likely due to the selection of a biased control group or to offspring-mediated effects that have confounded the comparison of the (correlated) parental genotypes. Thus, the data offered by Labuda et al., which show very similar odds ratios for the mother and for the father, may be seen more plausibly as reflecting either a systematic bias in the control group or a chance finding.

The final issue is analytic. The odds ratio parameter estimated by the case-control analysis is not the same as that estimated by transmissions. Labuda et al. evidently used a standard method for paired data, calculating the ratio of counts for discordant transmission pairs based on heterozygous parents. This approach estimates the relative penetrance for carriers of a single copy of the variant allele under a gene dose model in which the relative penetrance for two copies is the square of that for one copy. By contrast, in their case-control analysis, Labuda et al. use carrier status, which presumes a dominant model. The paired estimator based on transmissions can be shown to be biased toward 1.0 under such a model. Even if the two analyses were estimating the same parameter, there is considerable overlap in the CIs for the two estimates. For these reasons, the results presented by Labuda et al. (2002) should be seen as providing only very weak evidence for a parent-mediated effect of *CYP2E1*5*.

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Reply to Comments by Kraft and Wilson and by Weinberg and Mitchell on "Parental Genotypes in the Risk of a Complex Disease"

To the Editor:

Kraft and Wilson (2002 [in this issue]) point out that there are other analytical options to a joint application of case-control and TDT analysis in our study of the effect of parental genetics in the risk of a complex disease. They propose a "pseudo-sibling controls" design as an alternative to the approach proposed earlier by Weinberg and colleagues (1998) to study parental effects in case-parent trios. However, these tests are directed to evaluate the effect within a presumed model and are not designed to estimate joint effects of both parents' genotypes, which appeared to be the case with our data. Our study, inspired by original experimental observations, led us to understand the underlying genetic effects