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Reply to Ménasché et al.

To the Editor:

It is gratifying to learn that Ménasché et al. (2002 [in this issue]) agree with our analysis of the phenotypic differences between patients with *RAB27A* mutations and those with *MYO5A* mutations. We leave it to *Journal* readers to decide if previous publications have "unequivocally established" these points. We do apologize for the error in table 1, which we recognized and have corrected in an erratum.

Perhaps we could make two additional points. First, Gaucher disease types I, II, and III represent examples of defects in a single gene resulting in different phenotypes, whereas Griscelli/Elejalde syndromes represent examples of defects in two different genes resulting in phenotypes with some similarities. Second, we wonder what nomenclature should be employed for these two disorders. Ménasché et al. continue to use Griscelli syndromes types 1 and 2. However, Griscelli's original cases exhibited immune deficiency (Griscelli et al. 1978), whereas Elejalde first recognized a distinct, neurologically based disorder (Elejalde et al. 1979). Perhaps Dr. Elejalde should be credited for the accuracy of his ascertainment.

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Family-Based Association Tests Incorporating Parental Genotypes

To the Editor:

The report "Parental Genotypes in the Risk of a Complex Disease" (Labuda et al. 2002) gives several interesting examples of how parental genotypes can contribute to children's disease risk—for example, through maternal effects during pregnancy or paternal effects during spermatogenesis. The authors note that if disease risk depends on parents' genotypes but not their child's genotype, then the distribution of genotypes in cases will not differ from the Mendelian expectation given their parents' genotypes. Hence, the traditional transmission disequilibrium test (TDT) using case-parent trio data will (correctly) not detect any association between individuals' genotypes and disease. The authors present an example in which the TDT provides no evidence of an association between a variant allele and disease (in fact, the point estimate for the odds ratio is 1.0), whereas a comparison of case subjects' genotypes to those of population control subjects does provide evidence of association (estimated odds ratio = 3.4). The authors then compare maternal and paternal genotypes to control subjects' genotypes and find evidence that the prevalence of the variant allele is higher in parents of case subjects than in population control subjects.

However, there are other analytic options in this case—namely, flexible statistical methods for case-parent trios which can test for parental-genotype effects. These have the advantage of being robust to population-stratification bias and, in some situations, are even more powerful for testing for parental-genotype effects than case-control studies (Starr et al. 2002).

The log-linear model developed by Weinberg et al. and Wilcox et al. can test for parental-genotype and parent-of-origin effects after adjusting for possible case-genotype effects (Weinberg et al. 1998; Wilcox et al. 1998). In principle, this model can also test parental-genotype × case-genotype interactions—which could be relevant;

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.