Am. J. Hum. Genet. 71:1237–1238, 2002

Griscelli Syndrome Types 1 and 2

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To the Editor:

In a recent report, Anikster et al. (2002) identified a *RAB27A* (MIM 603868) deletion in a kindred with Griscelli syndrome (GS) (MIM #214450). Several patients from this kindred displayed neurological manifestations related to the hemophagocytic syndrome (HPS). On the basis of their study, the authors suggest "that the neurological involvement in these patients with GS occurs secondarily to the hemophagocytic syndrome and that patients with primary CNS complications and *MYO5A* (MIM 160777) mutations have a related disorder, namely, Elejalde syndrome." This assertion is certainly correct but surprisingly is presented as new and as an "alternative explanation." Several previously published reports have unequivocally established that neurological manifestations occurring in patients with GS and caused by *RAB27A* mutation are related to lymphocyte infiltration of the CNS (Ménasché et al. 2000; Pastural et al. 2000; de Saint Basile and Fischer 2001), whereas patient(s) with GS caused by *MYO5A* mutations exhibit a primary neurological disease, potentially described as Elejalde syndrome, and is unrelated to the hematopoietic lineage, as also observed in *Myo5a* mutant *dilute* mice (Pastural et al. 1997, 2000; Sanal et al. 2000; de Saint Basile and Fischer 2001; Ivanovich et al. 2001). The common finding of both conditions is albinism that results from the same mechanism—a defective release of melanosome content to neighboring cells, such as keratinocytes in the skin. MyoVA and Rab27A have been shown to interact in the same molecular pathway, resulting in melanosome transport on actin filament to dock at plasma membrane (Marks and Seabra 2001; Hume et al. 2002; Provance et al. 2002; Seabra et al. 2002). There should not be any confusion left, since patients with partial albinism and manifestations of HPS, with or without neurological involvement, should be screened for *RAB27A* mutations and treated accordingly, whereas those with partial albinism and a primary neurological disease without HPS should be screened for *MYO5A* mutations, as discussed elsewhere (Ménasché et al. 2000)

There are numerous examples of conditions grouped under the same umbrella name (such as "Gaucher disease type I to III") because of shared biological mechanisms, but that have different outcomes and treatments. Griscelli syndromes 1 and 2 are other examples.

Incidentally, in table 1 of the Anikster et al. report, the *dilute* and *ashen* murine models have been inverted, potentially causing some confusion.

Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for Griscelli syndrome [MIM #214450], RAB27A [MIM 603868], and MYO5A [MIM 160777])

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0002-9297/2002/7105-0026$15.00

Am. J. Hum. Genet. 71:1238, 2002

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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0002-9297/2002/7105-0027$15.00

Am. J. Hum. Genet. 71:1238–1239, 2002

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;