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Whole-Genome Analysis

To the Editor: In their article on a whole genome scan looking for SNPs associated with sporadic ALS, Dunckley *et al.* (August 3 issue)[1] consider finding ten SNPs that replicate over three studies unusual, based on unadjusted p-values of <0.05 in each study. We question the non-randomness of the result as presented, as it recalls the following "mysterious letter" effect [2]. In study one with 766,995 SNPs, one expects ~38,350 SNPs to meet the criterion by chance; 5% of that gives ~1,917 SNPs; 5% of that gives ~95 SNP expected to replicate over the three studies; the authors report ten. A major assertion is a Bonferroni adjusted p-value for marker FLJ10986 less than 0.05 in the first study. Computation of a Bonferroni p-value is the simple multiplication of the unadjusted p-value,1.8×10^{-5}, by the number of tests under consideration, 766,995, which, being greater than 1, is taken to be not significant. We are skeptical that any of the claims (See Figure 1) would replicate and the biological conclusions could be ex-post explanations to what appear to be random data.

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References

1. Dunckley, T., Huentelman, M.J., Craig, D.W. et al. Whole-genome analysis of sporadic amyotrophic lateral sclerosis. N Engl J Med 2007;357:1-14.
2. Taleb, N.N. *Fooled by Randomness: The Role of Chance in Life and in the Market, 2nd Rev Ed,* Random House, 2005; 157-158.

Figure 1

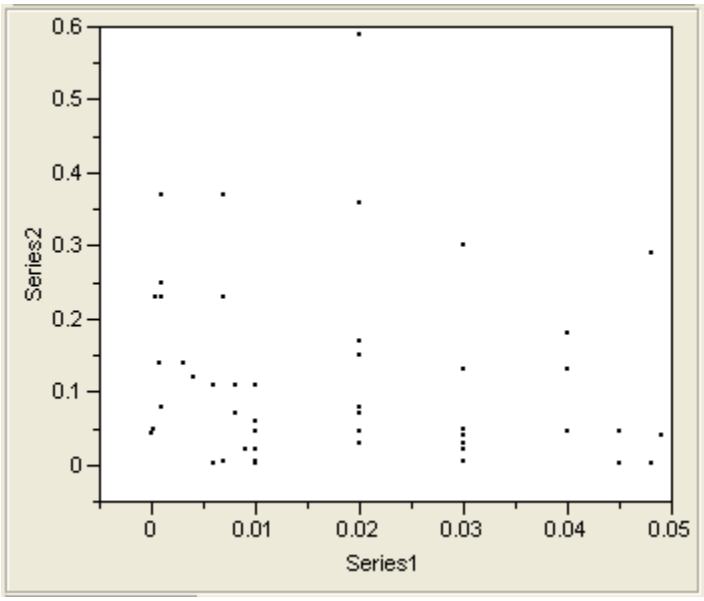

Figure 1. Plot of Series2 versus Series1 reported p-values. Small p-values for Series1 do not lead to small p-values for Series2.