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Brief Review

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Brief Review: Increasing the Variance for Genes in RDS and Other Polygenic Disorders

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Abstract

I present two alternatives to simple gene frequency in testing for the potential association between different genes and polygenic traits. These are testing for molecular heterosis and testing for hidden variables such as the mother's age at the birth of her first child. They have the potential to identify genes that may have appeared to be unassociated with the phenotype and to increase the percent of the variance for other genes. With this added help an algorithm evaluating the additive effect of the 10 to 20 genes with the greatest percent of the variance may allow genetic testing for susceptibility to the RDS spectrum and other polygenic disorders.

Keywords

Polygenic traits, Molecular heterosis, Epistasis, Maternal age, Maternal age at the birth of the first child, Reward deficiency syndrome, Alcoholism, DRD2, DRD1, Genetic testing

Problem: High Heritability, Low Percent Variance

Many common disorders, including alcoholism and other disorders in the RDS spectrum, have been shown by twin studies to have a significant genetic component [1]. However, this does not mean that gene based diagnostic tests for a susceptibility to these disorders will soon be available.

In the past decades genome wide association (GWA) studies have shown that most common disorders with a strong genetic component, are inherited in a polygenic fashion with dozens or even hundreds of genes involved. Each gene usually accounts for a small percent of the total variance [2-4]. As a result, developing a diagnostic genetic test for these disorders will be very difficult and at a minimum will require algorithms examining the additive effect of many genes. Is there any way we can we improve on the chances of success?

It is very unusual that the combined or additive effect of the identified multiple genes comes anywhere near to accounting for the magnitude of the genetic component suggested by twin studies. There have been many theories to account for this missing genetic 'dark matter.' It cannot be accounted for by involvement of non-coding regions of DNA since the wide range of SNPs used in GWA studies also covers these regions. Epigenetic factors may be involved and since they are genetically influenced they can contribute to the total heritability.

In some cases, where association studies suggest that a given gene is either uninvolved or minimally involved, this result may be due more to the method of testing than the lack of a significant effect. In this note I call attention to two ways in which the genetic effect of individual genes or DNA regions may be missed

or be greatly underestimated. Correcting for these effects may enhance the chances of developing meaningful genetic tests for polygenic disorders. I review here two phenomena that may account for an unrealistically low estimate of the percent of the variance. These are 1. genetic heterosis and 2. the presence of unexamined hidden variables which can totally eliminate any observed effect of a given gene.

Genetic heterosis

This refers to a situation in which the association with a given phenotype is greater (or lesser) in the 1-2 heterozygotes than in the 1-1 or 2-2 homozygotes [5]. In plant genetics this is referred to as hybrid vigor. In our own work up to 50% of the associations we have studied the effect was greatest in the 1-2 heterozygotes. By definition, if the association is only examined at the allele level rather than by genotype, a heterosis effect will be missed. One example is the controversy over the association of the *DRD2 Taq* A1 allele in alcoholism.

In a reappraisal of the field, Gelernter et al. [6] reviewed 12 different studies, including the two initial studies of Blum et al. [7,8]. Gelernter et al. pointed out that when the two original studies of Blum et al. were excluded, the frequency of the A1 allele was the same in the subsequent 378 alcoholics (0.18) as in the 427 subsequent controls (0.18). They concluded that "when all studies subsequent to the original studies are considered there is no significant difference in *DRD2* A1 allele frequency between alcoholics and controls." However, when the possibility of heterosis is considered the conclusions are dramatically different. Thus, of the alcoholics, 7 were 1-1 (1.9%), 124 were 1-2 (32.8%), and 247 were 2-2 (65.3%). For the controls 27 were 1-1 (6.3%), 100 were 1-2 (23.4%) and 300 were 2-2 (70.3%). When all three genotypes were included in the analysis, $X^2 = 16.5$, $p = 0.00025$. When compared by heterosis groupings of 1-1 + 2-2 vs 1-2, $X^2 = 8.79$, $p = 0.003$. However, when compared by A1 allele frequency, $X^2 = 0.13$, $p = 0.98$. Thus, when compared by A1 allele frequency or prevalence of the A1 allele, it was concluded that the post Blum et al. studies were not significant. However, when heterosis is considered, the alcoholics showed a relative deficiency of the 1-1 and 2-2 genotypes and an excess of 1-2 heterozygotes compared to the controls, and these differences were highly significant ($p = 0.00025$) [9].

This dramatic effect of examining heterosis versus allele frequency is seen in other phenotypes as well. Beckman and Fröhlander [10] observed heterosis for the allelic association of secretor blood group and psoriasis, C3 complement and glomerulonephritis, properdin B system and rheumatoid arthritis, and haptoglobin and cholesterol levels. The findings for the Ss blood group and psoriasis showed considerable similarity to the *D2A1* and alcoholism association noted above. Even though the S allele frequencies were not significantly different in the 287 controls (0.41) vs. the 115 psoriasis patients (0.49) (p = 0.09), there were dramatic differences in the frequency of Ss heterozygotes of 45.6% in the controls vs. 12.2% in the psoriasis patients ($p = 3 \times 10^{-11}$). This indicated that Ss heterozygosity had a strong protective effect against psoriasis (R.R. = 0.017). This effect was attributed to increased physiological variability in the heterozygotes.

A further example shows the heterosis effect at a physiological level (Figure 1) [9]. This indicates a strong heterosis effect for the highest inattention scores for dopamine *DRD2 Taq* 1 heterozygotes. Johnson et al. [11] noted a strong negative heterosis effect for CNS homovanilic acid levels and the *DRD2 Taq* 1 polymorphism. The lower the HVA levels the higher the inattention score with the lowest levels in the 1-2 heterozygotes (Figure 1B).

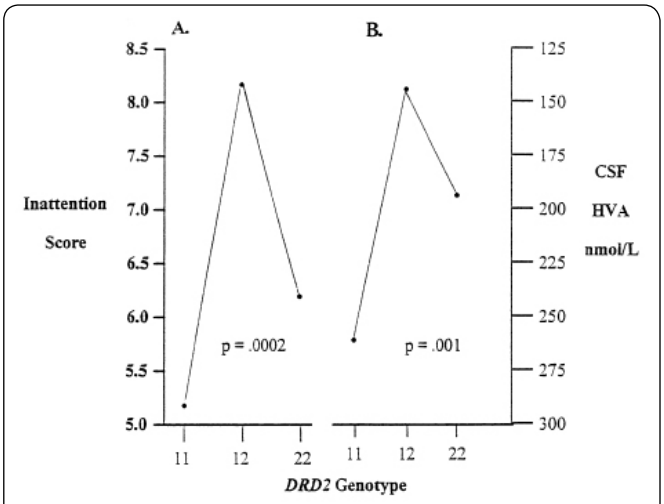

Figure 1: (A) Comparison of the relationship between DRD2 Taq1A genotypes and quantitative score for Inattention in Tourette syndrome probands and controls. (B) The relationship between DRD2 Taq1A genotypes and CSF HVA levels from Jönsson et al. (1997). Note the scale is inverted for the HVA levels. From Comings DE [9].

Failure to account for hidden variables

An association study between a given gene and a given phenotype may be negative or minimal if there is a hidden independent variable with associations in the opposite direction in two subgroups (Figure 2). If a sample is composed of two subgroups, A and B, and the 1 allele is associated with the phenotype in question in group A but the allele 2 is associated with the variable in group B - if the two groups are not examined separately the results will be negative. I have given examples of this effect for the association of the *DRD1* gene with stuttering and ocd where the hidden variable is the mother's age at the birth of the child or the mother's age at the birth of her first child [12]. We utilized the *DdeI* polymorphism of the *DRD1* gene described by Cichon et al. [13].

Stuttering

This sample was a group of patients with Tourette syndrome and two hidden variables were tested, the mother's age at the birth of the tested child (maternal age), and the age of the mother at the birth of her first child (maternal age 1st) (Figure 3). They were stratified by >= 25 years of age versus >= 26 years of age. Both maternal age (P = 0.02) and maternal age 1st (P <= 0.001) were significant for stuttering in males and females. For maternal age 1st, we tested whether the findings could be replicated in two separate, randomly chosen subsamples. Since stuttering is more common in males this was done by sorting the male cases by age and placing alternate cases in set 1 versus set 2. There was a reversal effect and an

epistatic effect in both sets. The *DRD1* x maternal age 1st born was significant in set 1 (F 3.08, P = 0.047) and set 2 (F 6.79, p <= 0.001) (Figure 2). When the two sets were combined the interaction was significant at P <= 0.001 (F 8.54).

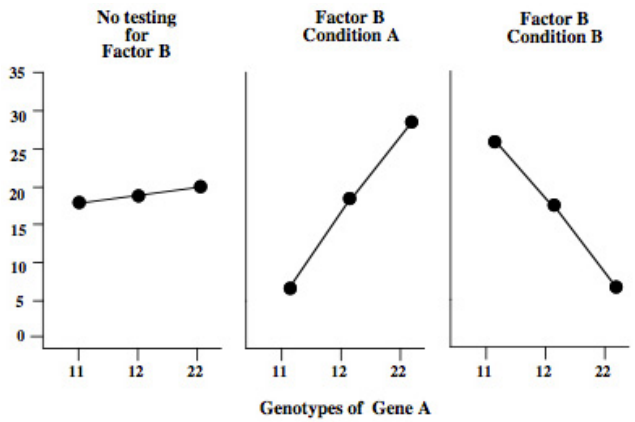

Figure 2: How a hidden variable B can negate the effect of a given gene on a specific phenotype. Here a subset of the test population (Factor B, condition A) shows a progressively greater effect from genotype 1-1 to1-2 to 2-2, while a second subset with condition B shows the opposite with a greater effect from genotype 2-2 to 1-2 to 1-1. When the test population is not divided into these subsets the gene appears to have no effect. From Comings DE and MacMurray JP [12].

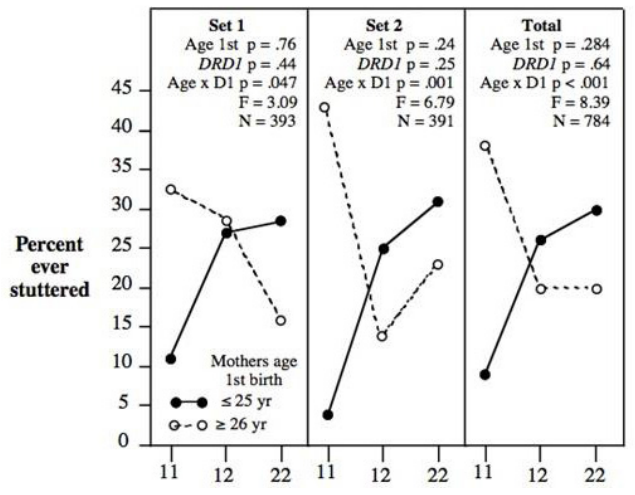

Figure 3: Two-way association of the DRD1 gene X maternal age 1st born versus stuttering. To test replication, the database was divided into two sets, 1 and 2. The results of the hierarchical ANOVA are shown at the top. In both sets there was a significant two-way association between DRD1 genotypes and stuttering. In subjects where maternal age 1st born was less than or equal to 25 years of age the genotype association was 2-2 > 1-2 > 1-1, while for those with a maternal age of greater than 25 years the association was in the opposite direction. From Comings DE and MacMurray JP [12].

Obsessive-compulsive score

Again the test subjects were patients with Tourette syndrome. The obsessive-compulsive score was based on the presence of twelve possible symptoms of obsessive and compulsive behaviors [12] (Figure 4). The scores ranged from 0 to 12 with a mean of 3.21, SD.3.1. Two-way interaction of the *DRD1* gene and different possible hidden variables with the obsessive-compulsive score in the TS database for males and females. Different panels represent different potential hidden variables: 1 = Maternal age. 2 = Maternal age 1st born. 3 = Paternal age. 4 = Paternal age 1st born. 5 = Mothers Grand-maternal age. 6 = Mothers Grand-maternal age 1st born. Solid lines, solid circles >= 25 years of age. Dotted line, open circles >= 26 years of age. The results of the hierarchical ANOVA are shown at the top of each panel. F = F ratio for the two-way interaction of gene by hidden variable. The N values ranged from 842 for panel 1 to 453 for panel 6. All were non-Hispanic Caucasians. The *DRD1* genotypes are shown at the bottom.

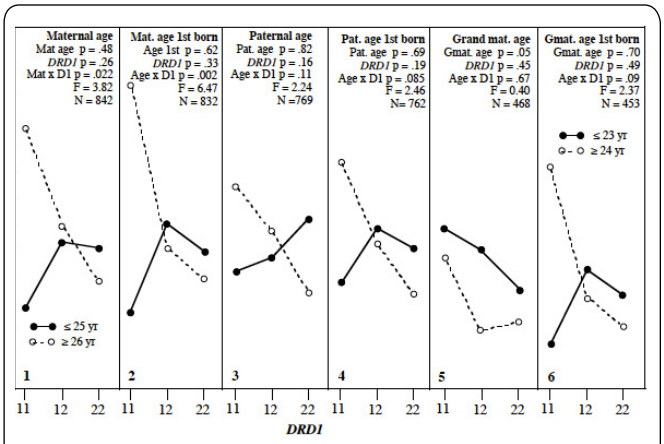

Figure 4: Two-way interaction of the DRD1 gene and different possible hidden parental age variables with the obsessive-compulsive score in a TS database. Different panels represent different potential hidden variables: 1. Maternal age; 2. Maternal age 1st born; 3. Paternal age; 4. Paternal age 1st born; 5. Mothers Grandmaternal age; 6. Mothers grand-maternal age 1st born. Solid lines, solid circles. <= 25 years. Dotted line, open circles. >= 26 years. The results of the hierarchical ANOVA are shown at the top of each panel. F = F ratio for the two-way interaction of gene by the hidden variable. The N values ranged from 842 for panels 1 to 453 for panel 6. All were non-Hispanic Caucasians. The DRD1 genotypes are shown at the bottom. From Comings DE and MacMurray JP [12].

One caution concerning the examination of the age at the birth of the first child is that since it adds a second variable it can reduce the power of the study. Increasing the sample size, and/or performing additional replication studies can compensate for this.

The reason these two entities are potentially so effective is not clear. In plant genetics heterosis is often referred to as hybrid vigor. Here the presence of two different genomes in the hybrid adds resilience to the plant. The reason molecular heterosis is so powerful may be similar – more diversity due to the presence of both the 1 and the 2 alleles may add to the strength (or weakness) of the phenotype.

The reason that dividing the sample by maternal age at the birth of the first child is a powerful hidden variable in some cases is not clear. First, it is important to have others replicate this finding in different phenotypes. That is not always easy since it requires access to this variable and this is not commonly available in data sets. This was available to us because we had complete pedigrees on all cases. A potential explanation is that there are a lot of co-variables, such as years of education, co-morbid conditions such as ADHD or learning disorders, and others that would contribute different genetic backgrounds of these two groups. It would be of interest to perform GWA studies comparing samples divided by this variable. For a more

detailed discussion of the many variables associated with the mother's age at the birth of her first child see Comings DE. [14].

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