Dear Editor,

In your recent fine symposium on Tourette syndrome (TS), Walkup[1] struggles with the relationship between TS and the many other disorders commonly comorbid with TS. Table 4, in addition to attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), lists major depression, separation anxiety disorder, social phobia, generalized anxiety disorder, posttraumatic stress disorder, bipolar disorder, pervasive developmental disorders, substance abuse, oppositional defiant disorder (ODD), conduct disorder (CD), and others. We have previously shown that most of these symptom complexes are significantly increased in frequency in the TS relatives of TS probands, compared with relatives without TS.[2-6] This rules out ascertainment bias and suggests these conditions all share one or more common etiologies. In Table 3, Walkup[1] proposes nine possible explanations for this range of comorbidity, including TS being the cause, a risk factor for, or a precursor for other psychiatric disorders; or other psychiatric disorders being the cause, a risk factor for, or a precursor to TS. I suggest that none of these nine possibilities accurately portrays the real reason for these comorbidities and that the following sentence is all that is needed to explain both Tables 3 and 4: "Psychiatric disorders, including TS, are polygenically inherited and each share many, but not all, genes in common." To keep things simple, this concept is illustrated in Figure 1 just for TS, ADHD, and OCD, but the concept applies to all comorbid conditions. Thus, depending on the polygenic mix individuals can have TS only, ADHD only, OCD only, TS + ADHD, TS + OCD, or TS + ADHD + OCD. The higher the genetic loading, the greater the risk they will have all three.

Polygenic disorders are due to the additive effect of multiple genes, each accounting for a small percent of the variance.[7,8] Lod score and most other linkage techniques lack the power to identify genes with such small effects.[9] This explains why none of the linkage studies of TS have identified any TS genes. In contrast, association studies do have the power to identify genes with such small effects.[9] With this technique we have identified over 20 genes for dopamine, serotonin, norepinephrine, γ-aminobutyric acid, and other neurotransmitters and neuropeptides that have a significant additive effect on ADHD in TS probands.[10-12] Tics per se, CD, ODD, and other comorbid conditions used a subset of these genes. I have suggested elsewhere that because polygenic disorders are much more common than single gene disorders, and because they are caused by the additive effect of multiple genes, the gene defects must be fundamentally different than the mutations causing single gene disorders[7,8,13]—ie, they must be common and they must have only a moderate effect on gene function. If they had a major effect, they would be single gene disorders. As a corollary to this, I have suggested that all

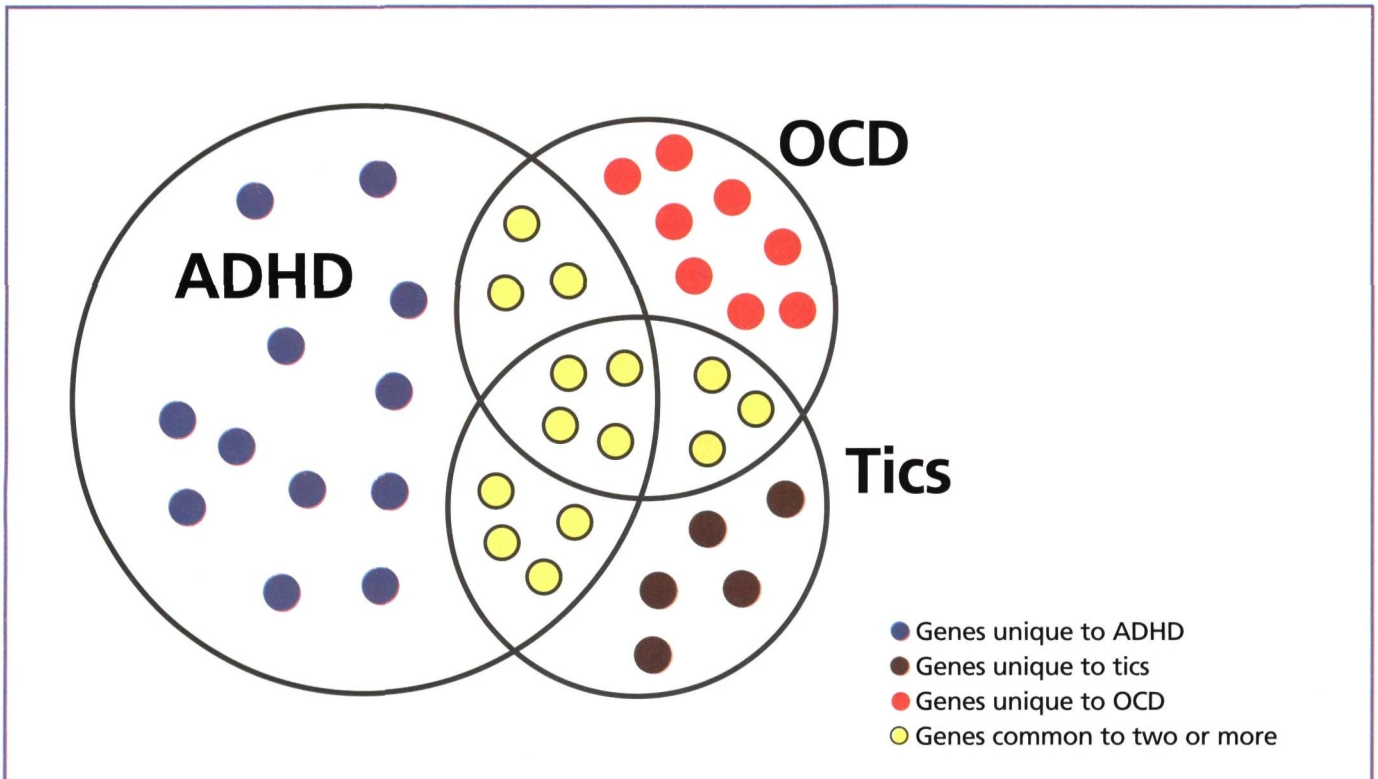

FIGURE 1. Diagram illustrating the concept of Tourette syndrome as a polygenic disorder sharing some but not all genes in common with comorbid disorders such as attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). To develop ADHD, OCD, or tics an individual must inherit some, but not necessarily all, of the genes in the respective circles.

https://doi.org/10.1017/S1092852900011488 Published online by Cambridge University Press

genes come in a wide range of common hypofunctional and hyperfunctional variants.[14] As a result, everyone is at risk to inherit a number of these variants. When the number passes a certain threshold and the genes affect the function of neurotransmitters and neuropeptides, the person is at risk to develop a range of behavioral disorders. The greater the genetic loading for these variants, the greater the severity of the disorder—and the greater the number and likelihood of comorbid conditions.

Segregation analyses of TS, using only tics or OCD as the phenotype, have suggested TS is inherited as an autosomal dominant or codominant trait.[15] While some have suggested that I define TS differently than others, I use the same *Diagnostic and Statistical Manual of Mental Disorders* criteria for diagnosing TS probands. However, if TS is consistently and significantly associated with a wide range of other phenotypes that share similar hypofunctional and hyperfunctional genetic variants, and this spectrum of phenotypes is not taken into account in the segregation analyses, then the true polygenic nature of TS is likely to be missed. One way around these flawed segregation analyses is to examine the individual genes themselves, as we have done.

These issues are important because the identification of the genes involved in TS, as well as other psychiatric disorders, will provide significant insight into their cause and effective treatment. If the wrong models and the wrong techniques are used, these genes will never be identified.

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https://doi.org/10.1017/S1092852900011490 Published online by Cambridge University Press