De Novo Coding Variants Are Strongly Associated with Tourette Disorder

Highlights
- Exome sequencing links damaging de novo sequence variants with Tourette disorder
- De novo variants in approximately 400 genes contribute risk in 12% of clinical cases
- Recurrent de novo variants identify one high-confidence TD risk gene: WWC1
- Gene discovery will exponentially increase as additional cohorts are sequenced

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In Brief
Gene discovery by identifying recurrent de novo variants with whole-exome sequencing has proven effective in neurodevelopmental disorders like autism, epilepsy, and intellectual disability. Willsey et al. apply this approach to Tourette disorder, associate de novo variants, and identify genes.

Willsey et al., 2017, Neuron 94, 486–499
May 3, 2017 © 2017 Elsevier Inc.
http://dx.doi.org/10.1016/j.neuron.2017.04.024
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SUMMARY

Whole-exome sequencing (WES) and de novo variant detection have proven a powerful approach to gene discovery in complex neurodevelopmental disorders. We have completed WES of 325 Tourette disorder trios from the Tourette International Collaborative Genetics cohort and a replication sample of 186 trios from the Tourette Syndrome Association International Consortium on Genetics (511 total). We observe strong and consistent evidence for the contribution of de novo likely gene-disrupting (LGD) variants (rate ratio [RR] 2.32, p = 0.002). Additionally, de novo damaging variants (LGD and probably damaging missense) are over-represented in probands (RR 1.37, p = 0.003). We identify four likely risk genes with multiple de novo damaging variants in unrelated probands: WWC1 (WW and C2 domain containing 1), CELSR3 (Cadherin EGF LAG seven-pass G-type receptor 3), NIPBL (Nipped-B-like), and FN1 (fibronectin 1). Overall, we estimate that de novo damaging variants in approximately 400 genes contribute risk in 12% of clinical cases.

INTRODUCTION

Tourette disorder (TD) is an often-disabling developmental neuropsychiatric syndrome characterized by persistent motor and vocal tics. Onset is typically in early childhood, and estimates of the worldwide prevalence are between 0.3% and 1% (Centers for Disease Control and Prevention, 2009; Robertson, 2008; Scharf et al., 2015). The vast majority of children and adults who present for medical attention have other impairing co-occurring psychiatric disorders, including obsessive-compulsive disorder (OCD) (do Rosário and Miguel Filho, 1997; Ghanizadeh and Mosallaei, 2009; Hounie et al., 2006), attention-deficit/hyperactivity disorder (ADHD) (Burd et al., 2005; Leckman, 2003; Roessner et al., 2007), and mood and anxiety disorders (Cavanna et al., 2009; Hirschtritt et al., 2015). Rates of OCD-like conditions, such as trichotillomania and pathologic skin picking (Lochner et al., 2005), are likewise elevated.

Current treatments for tics and TD have limited efficacy and pharmacotherapies may carry significant long-term adverse effects. A fundamental obstacle to identifying novel therapeutic
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