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Web-based phenotyping for Tourette Syndrome: Reliability of common co-morbid diagnoses

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ABSTRACT

Collecting phenotypic data necessary for genetic analyses of neuropsychiatric disorders is time consuming and costly. Development of web-based phenotype assessments would greatly improve the efficiency and cost-effectiveness of genetic research. However, evaluating the reliability of this approach compared to standard, in-depth clinical interviews is essential. The current study replicates and extends a preliminary report on the utility of a web-based screen for Tourette Syndrome (TS) and common comorbid diagnoses (obsessive compulsive disorder (OCD) and attention deficit/hyperactivity disorder (ADHD)). A subset of individuals who completed a web-based phenotyping assessment for a TS genetic study was invited to participate in semi-structured diagnostic clinical interviews. The data from these interviews were used to determine participants' diagnostic status for TS, OCD, and ADHD using best estimate procedures, which then served as the gold standard to compare diagnoses assigned using web-based screen data. The results show high rates of agreement for TS. Kappas for OCD and ADHD diagnoses were also high and together demonstrate the utility of this self-report data in comparison previous diagnoses from clinicians and dimensional assessment methods.

1. Introduction

Tourette Syndrome (TS) is a childhood-onset neuropsychiatric disorder marked by the occurrence of multiple motor tics and at least one phonic tic for a period of more than a year (American Psychiatric Association, 2000). The reported prevalence of TS is 0.3–0.7% internationally (Scharf et al., 2015) and affects males more frequently than females at a rate of 3 or 4 to 1 (Robertson, 2008; Scharf and Pauls, 2008). TS symptom severity generally waxes and wanes, typically beginning between ages 5 and 7, intensifying between ages 10 and 12, and diminishing in strength thereafter (Conelea et al., 2014). While many individuals experience a marked decrease in tic symptoms in adulthood, for others, symptoms persist (Ludolph et al., 2012; Tamara, 2013).

The disease burden of TS is high. In a recent study, adults with TS reported lower quality of life (QOL) than was reported by "healthy" adults and scored significantly higher on scales of depression and anxiety than the general population (Conelea et al., 2014). This may be due in part to the high prevalence of comorbid psychiatric

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disorders, predominantly obsessive compulsive disorder (OCD) and attention deficit/hyperactivity disorder (ADHD), which occur at rates of 30–50% and 30–90% respectively (Bloch et al., 2006; Coffey et al., 2000; Freeman, 2007; Hirschtritt et al., 2015).

Etiological studies have demonstrated a complex relationship between TS, OCD, and ADHD, both phenotypically and genetically (Davis et al., 2013; Gunther et al., 2012; Mathews and Grados, 2011; McGrath et al., 2014; O'Rourke et al., 2011; Stewart et al., 2006; Yu et al., 2015). Additionally, recent evidence suggests that TS, OCD, and ADHD are polygenic, meaning many genes contribute jointly to their symptom expression (Davis et al., 2013; Gratten et al., 2014). Therefore, studies attempting to identify specific, genome-wide significant TS-related genes necessitate large sample sizes, typically in the range of thousands to tens of thousands (O'Rourke et al., 2009; Scharf et al., 2013). As with other neuropsychiatric disorders, sample collection has been a rate-limiting factor in TS genetic research. Traditionally, recruitment of appropriate participants has taken place through TS specialty clinics, which tend to be located in large urban areas and therefore have a limited referral base. In addition, phenotypic data have historically been obtained through lengthy structured interviews, creating a substantial participant burden at a high cost of time and resources.

To address these obstacles, we have developed a web-based phenotyping measure, the *T*ourette *I*nternet-implemented *Que*stionnaire, (TIQue) (Egan et al., 2012) for online recruitment of participants throughout the United States. Not only does this measure allows individuals who do not live near a TS specialty clinic to participate, it also enables efficient, cost-effective collection of TS phenotype data, including tic symptoms, severity, and information about comorbid conditions. This information is entered directly by the participants into the TIQue through a secure web-site.

Following the initial phase of web-based recruitment for an ongoing TS genetic study, the authors reported on the effectiveness of the TIQue, showing that 631 participants completed the online questionnaires and also provided a DNA sample compared to only 238 TS participants recruited through a standard methods at six TS specialty clinics over the same time period (Egan et al., 2012). The authors also reported a concordance rate of 100% between eligibility criteria for genetic studies of TS determined by the web-based screen and eligibility based on in-depth diagnostic interviews conducted in a subset of participants.

Since this initial report, over 1400 additional individuals have completed the TIQue; thus, we now have the ability to expand our previous validation of the TIQue for TS and to extend analyses to OCD and ADHD. Therefore, the goals of this study were 1) to examine the concordance rates for TS diagnoses between the TIQue and gold standard diagnoses in a larger, potentially more heterogeneous sample, and 2) to analyze the reliability of OCD and ADHD diagnoses provided by the TIQue, and 3) to identify the best method of assigning DSM-IV diagnoses using TIQue variables.

2. Methods

2.1. Procedures and participants

The data used in the current study were part of a larger data collection effort for ongoing TS genetic studies (Egan et al., 2012; Scharf et al., 2013). Detailed procedures, including the development and implementation of the TIQue, have been described in Egan et al. (2012). Current analyses consist of TIQue data collected between April 2010 and January 2014, and include the preliminary sample evaluated in the initial report. In addition to letters emailed and mailed to Tourette Syndrome Association (TSA) members, patients identified as likely having TS were referred to the website by clinicians at multiple collaborating sites. Individuals accessed the TIQue through an open link. Approval was obtained from the Institutional Review Board at each site. Participants, or their parents, in the case of minors, provided informed consent before completing the TIQue.

As the main study aimed to collect TS-affected individuals for genetic research, exclusion criteria included the following: known intellectual disability, seizure disorder or epilepsy, other known genetic or neurological conditions, individuals whose family members had previously completed the TIQue, or completion of a TS genetic study in the previous five years by an individual or family member. Since its launch, a total of 3251 individuals initiated the TIQue and 2643 individuals completed it (81.3%). A random sample of those with complete data ($n=614$) was invited to undergo in-depth clinical interviews for the current validation study; 257 (41.9%) agreed.

A semi-structured clinical interview (the TSAICG Tic and Comorbid Symptom (TICS) inventory described in Section 2.2.2) was conducted in-person or using an online video-calling service to enable observation and documentation of tics or by telephone when other options were not available. Interviews were administered by a PhD level interviewer or a senior medical student with clinical research experience (CI, CE, ME, MH), specifically trained in TS and related disorders and in the standardized administration and scoring of the TICS inventory. Additionally, interviewers were asked to provide narrative information documenting their observations of psychiatric symptoms.

2.2. Assessments

2.2.1. The TIQue

The TIQue (Egan et al., 2012) is a web-based screen and assessment tool adapted from the comprehensive diagnostic Tourette Syndrome Association International Consortium for Genetics (TSAICG) TICS Inventory (Tourette Syndrome Association International Consortium for Genetics, 2007). The TIQue collects demographic, medical history and disorder-specific symptom information corresponding to the diagnoses of TS, OCD and ADHD. The TIQue also asks participants whether they had been previously diagnosed with TS, OCD, or ADHD by a clinician.

The Tic section of the TIQue is comprised of a checklist of tic symptoms grouped into 12 categories of simple and complex motor tics and 6 categories of simple and complex phonic tics. Each category contains examples of several related tics. For example, the Eye Movements category includes eye blinking, squinting, eye rolling, or opening eyes wide briefly, looking surprised or quizzical, looking to one side for a brief period of time. Respondents indicated their lifetime experience of each tic category (i.e., whether the tics occurred in the past month, sometime in the past, or never). Subsequent questions assessed the participant's age at tic onset, duration of tics, and characteristics such as suppressibility, premonitory urges, and fluctuating severity and course.

The TIQue OCD symptom checklist is based on the Florida Obsessive Compulsive Inventory (FOCI; Storch et al., 2007) and includes 10 obsessions and 10 compulsions that participants rated for lifetime occurrence (i.e., current, past, never). Severity ratings for time, distress, control, avoidance and interference for both current and worst ever periods were also collected. These dimensions were rated on the 5 point scale adapted from the Yale Brown Obsessive–Compulsive Scale ratings (Goodman et al., 1989), generally corresponding to "0-none", "1-mild", "2-moderate", "3-severe" and "4-extreme".

The ADHD section was adapted from the Swanson, Nolan, and Pelham Questionnaire (SNAP-IV; Swanson et al., 1992) and consists of 10 inattentive and 10 hyperactive–impulsive symptoms (e.g., "often had difficulty sustaining attention in tasks or play activities"). ADHD symptoms were rated on a 4 point scale, depending

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