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SGCE mutations cause psychiatric disorders: clinical and genetic characterization

Kathryn J. Peall[1], **Daniel J. Smith**[1], **Manju A. Kurian**[2], **Mark Wardle**[1], **Adrian J. Waite**[1], **Tammy Hedderly**[3], **Jean-Pierre Lin**[3], **Martin Smith**[4], **Alan Whone**[5], **Hardev Pall**[6], **Cathy White**[7], **Andrew Lux**[8], **Philip Jardine**[8], **Narinder Bajaj**[9], **Bryan Lynch**[10], **George Kirov**[1], **Sean O'Riordan**[11], **Michael Samuel**[12,13], **Timothy Lynch**[14], **Mary D. King**[10], **Patrick F. Chinnery**[15], **Thomas T. Warner**[16], **Derek J. Blake**[1], **Michael J. Owen**[1], and **Huw R. Morris**[1]

[1]MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, CF14 4XN, UK [2]ICH-Neurosciences Unit, Great Ormond Street Hospital, London, WC1N 3LU, UK [3]Paediatric Neurology, Evelina Children's Hospital, St Thomas' Hospital, London, SE1 7EH, UK [4]Paediatric Neurology, Birmingham Children's Hospital, Birmingham, B4 6NH, UK [5]Department of Neurology, Frenchay Hospital, Bristol, BS16 1LE, UK [6]School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, B15 2TT, UK [7]Department of Paediatrics, Singleton Hospital, Swansea, SA2 8QA, UK [8]Paediatric Neurology, Bristol Royal Hospital for Children, Bristol, BS2 8BJ, UK [9]Department of Neurology, Nottingham University Hospitals NHS Trust, Nottingham, NG7 2UH, UK [10]Paediatric Neurology, Children's University Hospital, Dublin 1, Ireland [11]Department of Neurology, St. Vincent's University Hospital, Dublin 4, Ireland [12]Department of Neurology, East Kent Hospitals NHS Foundation Trust, Ashford, Kent, TN24 0LZ, UK [13]Department of Neurology Kent and King's College Hospital, King's Health Partners, London, SE1 9RT, UK [14]Department of Neurology, Mater Misericordiae University Hospital, Dublin 7, Ireland [15]Institute of Genetic Medicine, Newcastle University, International Centre for Life, Central Parkway, Newcastle upon Tyne, NE1 3BZ, UK [16]Department of Clinical Neurosciences, UCL Institute of Neurology, London, WC1N 1PJ, UK

Abstract

Myoclonus dystonia syndrome is a childhood onset hyperkinetic movement disorder characterized by predominant alcohol responsive upper body myoclonus and dystonia. A proportion of cases are due to mutations in the maternally imprinted *SGCE* gene. Previous studies have suggested that patients with *SGCE* mutations may have an increased rate of psychiatric disorders. We established a cohort of patients with myoclonus dystonia syndrome and *SGCE* mutations to determine the extent to which psychiatric disorders form part of the disease phenotype. In all, 89 patients with clinically suspected myoclonus dystonia syndrome were recruited from the UK and Ireland. *SGCE* was analysed using direct sequencing and for copy number variants. In those patients where no mutation was found *TOR1A* (GAG deletion), *GCH1*, *THAP1* and *NKX2-1* were also sequenced.

Correspondence to: Dr Kathryn Peall, MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, Henry Wellcome Building, Heath Park, Cardiff, UK kathrynpeall@yahoo.co.uk.

SGCE mutation positive cases were systematically assessed using standardized psychiatric interviews and questionnaires and compared with a disability-matched control group of patients with alcohol responsive tremor. Nineteen (21%) probands had a *SGCE* mutation, five of which were novel. Recruitment of family members increased the affected *SGCE* mutation positive group to 27 of whom 21 (77%) had psychiatric symptoms. Obsessive–compulsive disorder was eight times more likely ($P < 0.001$) in mutation positive cases, compulsivity being the predominant feature ($P < 0.001$). Generalized anxiety disorder ($P = 0.003$) and alcohol dependence ($P = 0.02$) were five times more likely in mutation positive cases than tremor controls. *SGCE* mutations are associated with a specific psychiatric phenotype consisting of compulsivity, anxiety and alcoholism in addition to the characteristic motor phenotype. *SGCE* mutations are likely to have a pleiotropic effect in causing both motor and specific psychiatric symptoms.

Keywords

myoclonus dystonia; *SGCE*; psychiatric disorders

Introduction

Myoclonus dystonia syndrome is a rare movement disorder with onset in the first two decades of life. The clinical pattern is of alcohol responsive myoclonus of the trunk and upper limbs with cervical dystonia and/or writer's cramp, although the lower limbs may also be involved (Asmus *et al.*, 2002; Roze *et al.*, 2008). The disorder affects males and females equally (Raymond *et al.*, 2008) and is clinically consistent across ethnicities (Chung *et al.*, 2007; Chen *et al.*, 2008; Nardocci *et al.*, 2008).

Mutations in the sarcoglycan, epsilon gene (*SGCE*) are responsible for a proportion of these cases (Zimprich *et al.*, 2001). *SGCE* mutations are inherited in an autosomal dominant manner with variable penetrance due to maternal imprinting (Muller *et al.*, 2002; Grabowski *et al.*, 2003). *SGCE* encodes the epsilon-sarcoglycan protein, a single pass transmembrane protein forming part of the dystrophin-associated glycoprotein complex in some tissues (Blake *et al.*, 2002; Esapa *et al.*, 2007; Waite *et al.*, 2009). *SGCE* mutation rates have varied amongst previously reported cohorts, some reporting no mutations (Valente *et al.*, 2003) and others reporting rates from 21 to 80% (Valente *et al.*, 2005; Gerrits *et al.*, 2006; Tezenas du Montcel *et al.*, 2006; Nardocci *et al.*, 2008; Ritz *et al.*, 2009). It is suggested that clinical classification, genetic heterogeneity (Grimes *et al.*, 2001, 2002) and copy number variants (DeBerardinis *et al.*, 2003; Asmus *et al.*, 2005, 2007; Dale *et al.*, 2011) may account for this observed variation in rates of mutation.

Co-morbid psychiatric disorders have been reported in a number of cases with myoclonus dystonia syndrome (Peall *et al.*, 2011), including obsessive–compulsive disorder (OCD) (Marechal *et al.*, 2003), depression (Doheny *et al.*, 2002), suicide (Misbahuddin *et al.*, 2007), psychosis (Dale *et al.*, 2011), anxiety (Nardocci *et al.*, 2008) and alcohol misuse (Saunders-Pullman *et al.*, 2002b). Systematic assessment using standardized questionnaires has supported an excess of OCD and alcohol misuse amongst mutation carriers (Saunders-Pullman *et al.*, 2002a; Hess *et al.*, 2007; Peall *et al.*, 2011), potentially indicating that *SGCE*

has pleiotropic roles. However, previous studies have not separated primary from secondary psychiatric disorders related to disability, and, to date, there has been no systematic comparison with an appropriate control group.

This study uses systematic and standardized methods to examine the rate and type of psychiatric disorders within a large cohort of patients with myoclonus dystonia syndrome caused by *SGCE* mutations. This is the first study to compare these patients systematically with a disability matched control group. We also performed intra-familial comparisons of mutation and non-mutation carriers.

Materials and methods

Patients with suspected myoclonus dystonia syndrome, some with previously confirmed *SGCE* mutations, were referred by adult and paediatric neurology centres throughout the UK and Ireland. The study was approved by the Multi-Centre Research Ethics Committee for Wales (MREC 09/MRE09/56 and 09/MRE09/35). Patients were recruited in two stages (Fig. 1) to allow separate assessment of motor and psychiatric co-morbidity.

Stage one recruitment

Patients in whom myoclonus dystonia syndrome was considered a potential diagnosis were recruited by movement disorder specialists, and where possible systematically assessed face-to-face by a single investigator. In those for whom this was not possible, a systematic *pro forma* was used for data collection.

Motor assessment—All cases were assessed using a systematic protocol, including videotaped clinical examination. Patients were classified as ‘definite’, ‘probable’ or ‘possible’ according to previously published clinical criteria (Supplementary Table 1, Grunewald *et al.*, 2008). Severity of motor symptoms in those with *SGCE* mutations was assessed using modified versions of the Unified Myoclonus Rating Scale (Frucht *et al.*, 2002) and Burke-Fahn Marsden Dystonia Rating Scale (Burke *et al.*, 1985).

Genetic analysis—Blood samples were collected from all cases after obtaining informed consent from the patient or assent from their parent/guardian. DNA was isolated from peripheral blood lymphocytes using standard protocols. All samples underwent direct sequencing of *SGCE* exons 1–12 (including alternatively spliced 1a and 11b). In those cases where no *SGCE* mutation was found, multiplex ligation-dependent probe amplification analysis was performed using the commercially available probe set P099B (MRC Holland) according to manufacturer’s instructions. Cases with whole gene deletions were analysed on a custom oligonucleotide Comparative Genomic Hybridization array platform (Roche) with 5900 probes covering chr7:88 000 000–98 000 000 (NCBI36/hg18 genome build). Data were analysed using the segment tool and visualized using SignalMap (Roche). To exclude other potential genetic diagnoses, all remaining samples were sequenced for the *TOR1A* (Torsin A) GAG deletion and mutations in *GCH1* (GTP cyclohydrolase 1), *THAP1* (THAP domain containing, apoptosis associated protein 1) and *NKX2-1* (NK2 homeobox 1) genes.

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Stage two recruitment

Related family members were recruited in *SGCE* kindreds. These cases were assessed face to face using the same protocol and a blood sample taken for genetic analysis. All *SGCE* mutation positive patients and family members were classified according to their motor and genetic status into three groups: (i) manifesting carriers: *SGCE* mutation and movement disorder (n = 27); (ii) non-manifesting carriers: *SGCE* mutation and no movement disorder (n = 10); and (iii) non-carriers: neither *SGCE* mutation nor movement disorder (n = 16). Patients with tremor who reported an improvement with alcohol were recruited from general neurology and movement disorder clinics, forming the control group for assessment of psychiatric co-morbidity and were examined using the same protocol. Manifesting carriers and the tremor control groups were matched for the effect of disease on quality of life, assessed by the Short Form Health Survey (SF-36).

Psychiatric and quality of life assessment—Lifetime psychiatric symptoms were assessed in a total of 98 participants (53 *SGCE*-positive patients and family members; 45 control subjects) using a modified version of the MINI International Neuropsychiatric Interview (M.I.N.I.) (Sheehan *et al.*, 1998), which allowed symptoms to be classified according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for major depressive episode, manic and hypomanic episode, panic disorder, agoraphobia, social phobia, OCD, alcohol dependence, alcohol abuse, psychotic and mood disorders and generalized anxiety disorder. For those aged <18 years, the M.I.N.I-Kid for Children and Adolescents (Parent version) was completed (nine of the total 27 manifesting carriers were under 18 years and underwent assessment with the MINI Kids). Further assessment was made using the Patient Health Questionnaire-9 (PHQ-9) (Kroenke *et al.*, 2001), Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), Yale–Brown Obsessive–Compulsive Scale (YBOCS) (Goodman *et al.*, 1989*a*, b) and the Alcohol Use Disorders Identification Test (AUDIT) (Saunders *et al.*, 1993). Quality of life was assessed using the Short Form Health Survey (SF-36) (Ware and Sherbourne, 1992). Population estimates for DSM-IV diagnoses were taken from the North American National Comorbidity Survey (Kessler *et al.*, 1994) and the Dunedin Longitudinal Birth Cohort Study (Douglass *et al.*, 1995), both large comprehensive epidemiological studies.

Statistical analysis

Results were analysed using the ‘R’ statistical software package. Chi-squared testing, Pearson correlation coefficient and binomial stepwise multiple logistic regression methods of analysis were used where appropriate. No correction for multiple testing was performed.

Results

Stage one

Eighty-nine probands were recruited to this study, 50 males and 39 females with a median age at onset of the movement disorder of 5 years (range 0–48 years).

***SGCE*-positive patients—**Nineteen (21%) of the 89 probands were found to have an *SGCE* mutation with a slight female predominance (8 male, 11 female). Median age at onset

was 3 years (range 1.5–18 years). Eight related affected family members of those with *SGCE* mutations were also assessed, increasing the number of clinically affected *SGCE* mutation positive patients to 27.

Motor symptoms—All probands had myoclonus and dystonia with 15/19 (79%) meeting criteria for clinically definite myoclonus dystonia syndrome. With the eight additional affected family members, upper limb myoclonus was evident in all 27 cases with head (66.7%) and truncal (66.7%) involvement also prominent. Dystonia was more widely distributed, although still predominantly affecting the upper body i.e. upper limbs (85.2%) and neck (77.8%).

Genetics—Seventy-nine per cent (15/19) of the mutation positive probands had a positive family history of myoclonus dystonia syndrome with mutated *SGCE* known to be paternally inherited in 74% of cases (14/19). In the remaining cases, we were unable to contact additional family members to confirm the presence or absence of motor symptoms and genetic mutations. Thirteen different types of mutation were identified, of which five are novel mutations. Four were nonsense, one missense, three splice-site mutations, three intra-exonic deletions, one single exon deletion (exon 5) and five whole gene deletions (Supplementary Table 2). The most prevalent was nonsense mutation c.289C>T p.Arg97X in exon 3, occurring in four unrelated Caucasian families.

***SGCE*-negative patients—**Seventy of 89 (78.7%) unrelated patients did not have an identified *SGCE* mutation with a male predominance (42 male, 28 female). No mutations were detected in the *GCH1* and *THAP1* genes, nor the GAG deletion in the TOR1A gene. Two cases were found to have *NKX2-1* mutations both having a low amplitude upper body tremor.

Stage two

Psychiatric analysis—Data were collected from 27 cases with myoclonus dystonia syndrome (manifesting carriers) from 11 families and 45 control cases with alcohol responsive tremor. A further 26 family members were recruited from the myoclonus dystonia syndrome families, 10 non-manifesting carriers and 16 non-carriers, the latter group including 10 married-in spouses. Manifesting carriers and tremor groups were matched for disability based on median Short Form Health Survey (SF-36) scores, sex, disease duration and alcohol use, although they differed significantly in age at onset and age at examination ($P < 0.001$) (Table 1).

Results of psychiatric data analysis are shown in Tables 2 and 3 (M.I.N.I and M.I.N.I–Kids) and Table 4 (YBOCS, AUDIT, PHQ-9 and MADRS). All cases completed the M.I.N.I. questionnaires with the exception of two adult patients and one patient aged <18 years, where assent was declined. Both adult patients had recently been seen by consultant psychiatrists confirming diagnoses of depression and anxiety in one and schizophrenia in the other.

Overall rates of psychiatric disorders were higher in manifesting carriers and tremor cohorts than population estimates (77.8 and 62.2 versus 48%, respectively). The largest differences

were seen in rates of OCD and generalized anxiety disorder, OCD being three times higher in the manifesting carriers group than tremor controls, the largest contribution coming from compulsive symptoms, which were four times higher in the manifesting carriers group. Rates of generalized anxiety disorder were almost seven times greater amongst manifesting carrier patients with smaller excesses seen in social phobia (two times higher) and alcohol dependence/abuse (two times higher).

Comparison of manifesting carriers and tremor groups found no overall excess of psychiatric disorders amongst manifesting carriers patients [odds ratio (OR) 2.13, 95% confidence interval (CI) 0.64–7.31, $P = 0.20$]. However, large differences were seen in rates of OCD (OR 6.7, 95% CI 2.02–23.27, $P = 0.001$), generalized anxiety disorder (OR 3.71, 95% CI 1.16–12.22, $P = 0.02$) and social phobia (OR 3.7, 95% CI 1.12–12.56, $P = 0.03$). Alcohol excess/dependence was also more common amongst adult manifesting carriers (OR 4.3, 95% CI 1.08–18.06, $P = 0.02$). Attempts to discern a gene effect were made by comparing non-manifesting carriers cases with tremor and manifesting carrier cohorts. No overall or disorder-specific difference was seen between non-manifesting carrier and tremor groups. The same pattern of increased psychiatric morbidity was seen when the manifesting carrier group was compared with the non-manifesting carrier group, as had been seen when the manifesting carrier group had been compared with the tremor cohort (Table 3), although when the manifesting carrier and non-manifesting carrier groups were compared, the overall rate of psychiatric disorders was higher in the former (OR 5.25, 95% CI 0.88–34.12, $P = 0.05$).

Comparison of the manifesting carriers group with each of the other groups found a significantly higher total YBOCS score ($P < 0.001$). This largely reflected a significantly increased compulsivity score ($P < 0.001$) with no difference in obsessionality ($P = 0.16$). Alcohol use over the preceding year, measured with the AUDIT questionnaire, was higher amongst the manifesting carrier group compared with all other groups. Depression self-assessment in the form of the PHQ-9 found no statistical difference between the groups. However, clinician scoring of depressive symptoms using the MADRS found statistically significant differences between the manifesting carrier group and all other groups.

No association between presence of overall psychiatric disorders and motor severity scores was observed ($P = 0.08$). There was an association between motor severity and MADRS scores ($P = 0.05$, $r = 0.58$), but no link with overall YBOCS scores ($P = 0.83$, $r = 0.06$), obsessions ($P = 0.73$, $r = 0.095$), compulsions ($P = 0.98$, $r = 0.008$) and AUDIT scores ($P = 0.60$, $r = 0.14$). Stepwise multivariable logistic regression found duration of motor symptoms ($P = 0.04$) to impact on the incidence of psychiatric disorders, but with no effect when controlling for age at onset ($P = 0.20$). Results for OCD alone found no significant impact when controlling for age at onset ($P = 0.23$) or motor disease duration ($P = 0.05$).

Discussion

This study represents the largest single, multi-family cohort of patients with myoclonus dystonia syndrome systematically assessed using validated scales for rate and type of psychiatric disorders, and the first to compare psychopathology with a disability matched

control group. We have confirmed the hypothesis that patients with manifesting *SGCE* mutations have significantly higher rates of psychiatric illness as compared with control subjects with a significant movement disorder. Our findings point to a specific preponderance of OCD, generalized anxiety disorder and alcohol dependence and reveal that the association with OCD is specific to the compulsivity rather than the obsessional component of the disorder.

Although manifesting carrier and tremor groups are matched for disability, movement disorder duration, sex and alcohol use, a significant difference in age at onset and age at examination ($P < 0.001$) exists between the two groups (Table 1). However, multivariate analysis found neither the incidence of overall psychiatric pathology nor, more specifically, OCD to be influenced by age at onset of the motor disorder, and OCD alone appeared independent of the duration of movement disorder symptoms. In addition, our psychiatric interview involved lifetime assessment for each of these disorders rather than relating to a restricted time frame. These analyses suggest that the specific pattern of psychiatric morbidity seen in manifesting carriers compared with tremor controls was not due to differences in age at onset or age at examination between the two groups. In addition, alcohol-responsive tremor was considered the best disease match for a chronic disabling disorder that benefits therapeutically from alcohol in an attempt to separate therapeutic and addictive traits. Finally, we have not included a dystonia control group, and therefore we cannot exclude the possibility that the specific pattern of psychiatric morbidity seen in myoclonus dystonia syndrome is also associated with dystonia more widely.

The frequency of *SGCE* mutations within the primary cohort (21%) is in keeping with previously reported studies (Tezenas du Montcel *et al.*, 2006; Asmus *et al.*, 2009; Ritz *et al.*, 2009). A positive family history was an important factor when determining whether cases were ‘definite’, ‘probable’ or ‘possible’, being present in 95% of cases and paternally inherited in all cases where this information was available. Within this cohort, there were 17 definite, of which 15 had a *SGCE* mutation (88%), the highest reported rate to date. Eight ‘probable’ cases were identified, four of which had a *SGCE* mutation and had not been included in the ‘definite’ category owing to a lack of family history. This is likely due to maternal imprinting ‘silencing’ the mutation for several generations and therefore limiting the current diagnostic criteria.

Psychiatric assessment using the M.I.N.I. questionnaire found overall higher rates of psychiatric disorders amongst the manifesting carrier group compared with the tremor controls (77.8 versus 62.2%) and significantly higher than estimated within the general population (48%). Population estimates were taken from large cohort studies in Western populations similar to the one studied in this cohort (Kessler *et al.*, 1994; Douglass *et al.*, 1995). In addition, no association was seen between psychiatric disorders and motor severity, suggesting that the psychiatric phenotype may be independent of the motor disorder.

Obsessive-compulsive disorder

OCD was the most common disorder in manifesting carrier patients (59%), almost seven times more likely to occur compared with control subjects. OCD is generally not recognized

as a secondary psychiatric response to chronic disease (Fullana *et al.*, 2009), and therefore is an interesting finding in a chronically disabling and disfiguring disorder. Similar results were seen with the adult only manifesting carriers cohort (OR 5.65, 95% CI 1.53–21.69, $P = 0.006$) suggesting that despite population estimates that rates of OCD are higher amongst children (Douglass *et al.*, 1995), a significant difference remains between these groups. There were no differences in OCD rates between non-manifesting carrier and tremor groups and a significant difference between manifesting carrier and non-manifesting carrier cohorts. These results argue against a direct gene effect, although this is based on a small number of patients. YBOCS questionnaire scores further strengthened this association with the manifesting carriers median score being nine times higher and significantly different to all other groups. This effect was overwhelmingly owing to compulsivity scores, seven times greater than obsessive traits and did not relate to severity of the motor phenotype.

Rates of OCD have been assessed in other forms of dystonia with conflicting results. Mixed groups of focal dystonias have been compared with groups of other disfiguring disorders (Broocks *et al.*, 1998; Barahona-Correa *et al.*, 2011) and healthy individuals (Cavallaro *et al.*, 2002), finding increased rates of OCD or obsessive–compulsive symptoms amongst the dystonic group, although unable to relate this to a specific form of dystonia. Similarly elevated rates of OCD have been noted amongst first degree relatives of those with dystonia/OCD compared with those with dystonia alone. In contrast, others have found no association either amongst mixed dystonia types (Fabbrini *et al.*, 2010) or genetically defined *DYT1* cohorts (Heiman *et al.*, 2007).

Alcohol use disorders

Alcohol excess has also been frequently observed amongst DYT11 cohorts (Asmus *et al.*, 2002; Saunders-Pullman *et al.*, 2002b; Tezenas du Montcel *et al.*, 2006; Hess *et al.*, 2007; Misbahuddin *et al.*, 2007). Amongst the adult manifesting carriers cohort, alcohol excess was more than four times more likely than the tremor control group together with a significant difference in total AUDIT scores between the manifesting carriers and all other groups ($P < 0.001$). The median AUDIT score of non-manifesting carriers was also higher than that of the tremor participants, suggesting that alcohol use is higher amongst *SGCE* mutation carriers, irrespective of motor symptoms. This may reflect a functional role of the normally imprinted mutated maternal allele in certain brain regions (Guettard *et al.*, 2008; Beukers *et al.*, 2011*a*), causing failure of expression of the epsilon-sarcoglycan protein at the cell surface membrane.

Previous literature has suggested a link between those traits that result in excess alcohol consumption and ritualistic OCD behaviour (Caetano, 1985). Assessment using the YBOCS questionnaire of a population diagnosed with alcohol dependence/abuse noted a positive correlation between alcohol craving and both individual obsession and compulsion scores (Modell *et al.*, 1992). Similarly, techniques traditionally used in the treatment of OCD have been found to reduce the desire to drink and to improve alcohol resistance. Collectively, this suggests that excess alcohol consumption in *SGCE*-positive individuals may not simply be a secondary therapeutic response as hitherto assumed, but rather that it is related to the compulsivity that we have demonstrated and forms part of the phenotype of the disorder.

Anxiety disorders and depressive symptoms

Other psychiatric disturbances that appeared to be influenced by genetic and motor status were social phobia and generalized anxiety disorder. Anxiety related co-morbidity has been noted during intrafamilial comparisons of myoclonus dystonia syndrome cohorts (Foncke *et al.*, 2009) and standardized testing of patients with cervical dystonia compared with the general population (Wenzel *et al.*, 1998; Gündel *et al.*, 2001). These features were also consistent when a similar cohort was compared with a control group of patients with alopecia areata, highlighting a potential dystonia-specific feature (Gündel *et al.*, 2003). Psychiatric features have also been known to predate the onset of dystonic symptoms, again suggesting that this psychopathology is a primary, rather than a secondary, reactive response (Lencer *et al.*, 2009).

Mood disorders differed between the groups when analysed using the self-completed PHQ-9 and assessor-completed MADRS, although under-reporting of symptoms with self-rated questionnaires is a well-recognized feature (Scheidt *et al.*, 1999). Despite this excess of affective symptoms likely being a secondary effect due to a chronic, disabling disorder, other genetically defined groups of dystonias have found an excess of depression (Duane, 2005), again suggesting a general increase of psychiatric co-morbidity amongst this group of disorders.

Other psychiatric disorders

Subtle differences were also observed when comparing psychiatric illness in the whole gene deletion cases to those with point mutations. The four cases with larger mutations (1.9–2.3 Mb) all had symptoms of OCD, depression and anxiety-related disorders similar to the population identified by Sanger sequencing. In contrast, the fifth whole gene deletion case initially presented to adult medical services with symptoms of schizophrenia requiring multiple inpatient admissions. Psychiatric features have not been observed in the majority of previous whole gene deletion case reports, the attention instead being focused on global cognitive impairment and learning difficulties (Asmus *et al.*, 2007; Saugier-Veber *et al.*, 2010). An Australian family was also reported to have symptoms of psychosis and, as in the case in this study, a much smaller deletion than those described above (Dale *et al.*, 2011). With the exception of a single member of a myoclonus dystonia syndrome family being reported to have schizoaffective disorder (Wong *et al.*, 2010), psychosis has not been reported previously in those with *SGCE* mutations, and none of the genes involved in these deletions (*PEG10, SGCE, CASD1* and *COL1A2*) are believed to contribute to the pathogenesis of psychosis.

Implications for the pathogenesis of dystonia and compulsivity

Comorbid OCD, dystonia and *SGCE* mutations reaffirm the likely role of the basal ganglia in the underlying pathogenesis of these disorders. PET and functional MRI studies of dystonias (Playford *et al.*, 1998) and OCD (Breiter and Rauch, 1996) have shown abnormal activation of the basal ganglia, thalamus, frontal and cingulate cortices, whereas an association has also been identified between dystonia severity and putaminal grey matter volume (Beukers *et al.*, 2011*b*). More recent functional MRI studies have also shown altered patterns of activation in the sensorimotor cortex and cerebellum, suggesting that additional

brain structures may also contribute (Beukers *et al.*, 2011*a*). Neurophysiological studies showing impaired saccadic adaptation in *SGCE* mutation positive cases also support this, suggesting involvement of the posterior cerebellum potentially in the generation of subcortical myoclonus (Hubsch *et al.*, 2011). Use of deep brain stimulation in the treatment of myoclonus dystonia syndrome has shown improvement of myoclonus and dystonia when stimulating the globus pallidus internus (Azoulay-Zyss *et al.*, 2011), compared with thalamic stiumulation (Gruber *et al.*, 2010), while lesions within the striatal-pallidal pathways are also associated with the development of OCD (Lauterbach *et al.*, 1994).

Conclusion

We have demonstrated an excess of specific psychiatric disorders among affected *SGCE* mutation carriers when compared with an external control group and to unaffected family members. OCD is the most strongly associated psychopathology, and this reflects compulsive rather than obsessive symptoms. Affected *SGCE* mutation carriers showed evidence of excess alcohol consumption even when compared with a control group with alcohol responsive tremor. Excess consumption in myoclonus dystonia syndrome is often attributed to the therapeutic effects of alcohol, but our findings suggest that this might have a more direct relationship to pathogenesis and may arise as a consequence of a primary disturbance of compulsive behaviour.

In conclusion, this study shows that psychiatric co-morbidity forms a significant part of the clinical phenotype of myoclonus dystonia syndrome due to *SGCE* mutations. Clinicians need to be aware of this and of the need for psychiatric symptoms to be treated effectively and early. Further work is required to define and delineate the relationship between motor and psychiatric symptoms, which will enhance our understanding of the aetiology and pathophsyiology of both motor and psychiatric disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AUDIT	Alcohol Use Disorders Identification Test
MADRS	Montgomery–Asberg Depression Rating Scale
M.I.N.I.	MINI International Neuorpsychiatric Interview
OCD	obsessive–compulsive disorder

PHQ-9	Patient Health Questionnaire 9
YBOCS	Yale–Brown Obsessive–Compulsive Scale

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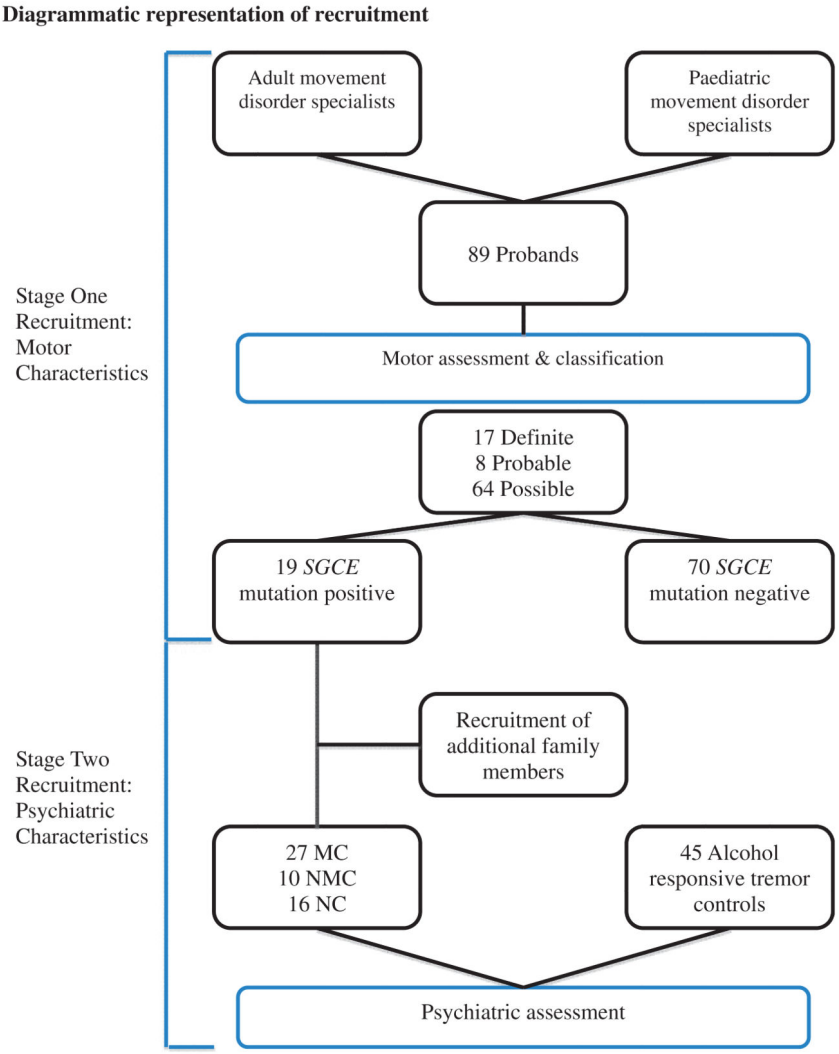

Figure 1. Clinical diagnostic criteria used for motor classification (Grunewald *et al.*, 2008)
MC = manifesting carrier; NMC = non-manifesting carrier; NC = non-carrier.

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Table 1
Demographics and analysis of variables

Demographics	MC	MC (>18 years)	NMC	NC	Tremor	MC versus tremor (total population)	MC versus tremor (adult only population)
Total (male:female)	27 (10:7)	18 (6:12)	10 (6:4)	16 (5:11)	45 (14:31)	0.62[a]	0.59[a]
Median age at examination (range)	28 (3–74)	42.5 (18–74)	38 (29–73)	40 (16–71)	62 (19–88)	<0.001[b]	<0.001[b]
Median age at onset of movement disorder (range)	3 (1.5–18)	4.5 (1.5–18)			26.5 (3–76)	<0.001[b]	<0.001[b]
Mean duration of movement disorder	25.57	31.93			30.78	0.27[b]	0.79[b]
Alcohol consumption (%)[c]	78	78	90	59	71	0.78[a]	0.78[a]
Median SF-36 scores (range)	92 (38–111)	92 (38–111)	104 (97–106)	101 (95–118)	99 (64–125)	0.09[a]	0.09[a]

[a] Calculated using chi-squared analysis.

[b] Calculated using Student's *t*-test.

[c] Alcohol consumption refers to whether the participant drinks any alcohol at all.

MC = manifesting carrier; NMC = non-manifesting carrier; NC = non-carrier.

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Table 2
Rates of psychiatric disease in manifesting carriers and tremor cohorts

Lifetime disorder DSM-IV	MC *n* (%) (total = 27)	Tremor *n* (%) (total = 45)	Population estimates (%)
Any DSM-IV disorder	21 (77.8)	28 (62.2)	48[a]
Major depressive disorder	12 (44.4)	20 (44.4)	17.1[a]
Mania and hypomania	0 (0)	3 (6.7)	1.6[a]
Panic disorder	9 (33.3)	17 (37.8)	3.5[a]
Agoraphobia	6 (22.2)	7 (15.6)	5.3[a]
Social phobia	12 (44.4)	8 (17.8)	13.3[a]
OCD—overall	16 (59.2)	8 (17.8)	4[b]
Obsessions	4 (14.8)	8 (17.8)	
Compulsions	14 (51.9)	6 (13.3)	
Alcohol dependence/abuse	8 (29.6)	6 (13.3)	14.1[a]
Psychotic and mood disorders	1 (3.7)	9 (20)	0.7[a]
Generalized anxiety disorder	13 (48.1)	3 (6.7)	5.1[a]

[a]Values taken from National Comorbidity Survey (Kessler *et al.*, 1994).

[b]Values from Dunedin Longitudinal Birth Cohort Study (Douglass *et al.*, 1995).

MC = manifesting carrier; NMC = non-manifesting carrier; NC = non-carrier.

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Table 3

Comparison of rates of psychiatric disease between manifesting carrier, non-manifesting carrier and tremor groups

Psychiatric diagnosis (DSM-IV)	MC versus tremor	NMC versus tremor	MC versus NMC
Any	0.20 (2.13; 0.64, 7.31)	0.29 (0.41; 0.08, 1.96)	**0.05 (5.25; 0.88, 34.12)**
Major depressive disorder	1.0 (1.0; 0.34, 2.91)	1.0 (0.83; 0.17, 4.02)	1.0 (1.2; 0.22, 6.70)
Mania and hypomania	0.29 (0; 0, 3.8)	1.0 (0; 0, 11.37)	1.0 (unable to calculate)
Panic disorder	0.8 (0.82; 0.27, 2.51)	0.14 (0.18; 0.01, 1.67)	0.23 (4.5; 0.44, 109.94)
Agoraphobia	0.54 (1.55; 0.39, 6.08)	0.33 (0; 0, 3.63)	0.16 (∞; 0.40, ∞)
Social phobia	**0.03 (3.7; 1.12, 12.56)**	0.33 (0; 0, 3.03)	**0.02** (∞; **1.23,** ∞)
OCD	**0.001 (6.7; 2.02, 23.27)**	0.33 (0; 0, 3.03)	**0.002** (∞; **2.20,** ∞)
Alcohol dependence/abuse[a]	**0.02 (4.33; 1.08, 18.06)**	0.58 (0; 0, 4.46)	**0.03** (∞; **0.94,** ∞)
Psychotic and mood disorders	1.00 (0.54; 0.02, 6.36)	1.00 (0; 0, 11.37)	1 (∞; 0.02, ∞)
Generalized anxiety disorder	**0.02 (3.71; 1.16, 12.22)**	0.67 (0.44; 0.02, 4.36)	0.06 (8.36; 0.84, 201.48)

Results analysed using chi-squared testing.

Results expressed as: *P*-value (odds ratio, 95% confidence interval).

Statistically significant results highlighted in bold.

[a]Only participants aged >18 years included in analysis.

MC = manifesting carrier; NMC = non-manifesting carrier; OCD = obsessive-compulsive disorder.

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Table 4
Analysis of YBOCS, AUDIT, PHQ-9 and MADRS questionnaires

Questionnaire	Median score (range)				*P*-value
	MC	NMC	NC	Tremor	
YBOCS					
Total score	9 (0–26)	0 (0)	0 (0–8)	0 (0–33)	<0.001
Obsessions	0 (0–15)	0 (0)	0 (0–8)	0 (0–17)	0.16
Compulsions	7 (0–17)	0 (0)	0 (0)	0 (0–16)	<0.001
AUDIT					
Total score	4 (0–34)	4.5 (1–9)	1 (0–4)	2 (0–18)	<0.001
PHQ-9					
Total score	6 (0–18)	2 (0–12)	2 (0–12)	4 (0–25)	0.08
MADRS					
Total score	15 (0–32)	1 (0–22)	1 (0–22)	6 (0–30)	0.01

Statistical analysis using binomial stepwise multiple logistic regression.

MC = manifesting carrier; NMC = non-manifesting carrier; NC = non-carrier.