Novel GCH1 variant in Dopa-responsive dystonia and Parkinson's disease


DOI: 10.1016/j.parkreldis.2015.01.004

License: Creative Commons: Attribution (CC BY)

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Link to publication on Research at Birmingham portal

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

• Users may freely distribute the URL that is used to identify this publication.
• Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
• Users may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
• Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Download date: 16. Jul. 2024
Novel GCH1 variant in Dopa-responsive dystonia and Parkinson's disease

A.J. Lewthwaite a, b, c, 1, T.D. Lambert a, 1, E.B. Rolfe d, S. Olgiati e, M. Quadri e, E.J. Simons e, K.E. Morrison a, c, V. Bonifati e, D.J. Nicholl a, d, f, *

a Department of Neurology, Queen Elizabeth Hospital, Birmingham, UK
b Department of Neurology, The Dudley Group NHS Foundation Trust, Dudley, UK
c School of Clinical and Experimental Medicine, College of Medicine and Dentistry, University of Birmingham, Birmingham, UK
d Department of Radiology, Queen Elizabeth Hospital, Birmingham, UK
e Department of Clinical Genetics, Erasmus MC, Rotterdam, The Netherlands
f Department of Neurology, Sandwell & West Birmingham Hospitals NHS Trust, Birmingham, UK

ARTICLE INFO

Article history:
Received 22 October 2014
Received in revised form 22 December 2014
Accepted 6 January 2015

Keywords:
Parkinson's disease
Dopa responsive dystonia
GCH1
SPECT DAT imaging

ABSTRACT

Background: GTP cyclohydrolase I (GCH1) mutations are the commonest cause of Dopa-responsive dystonia (DRD). Clinical phenotypes can be broad, even within a single family.

Methods: We present clinical, genetic and functional imaging data on a British kindred in which affected subjects display phenotypes ranging from DRD to Parkinson’s disease (PD). Twelve family members were studied. Clinical examination, dopamine transporter (DAT) imaging, and molecular genetic analysis of GCH1 and the commonest known familial PD-related genes were performed.

Results: We have identified a novel missense variant, c.5A>G, p.(Glu2Gly), within the GCH1 gene in affected family members displaying a range of phenotypes. Two affected subjects carrying this variant had abnormal DAT imaging. These two with abnormal DAT imaging had a PD phenotype, while the remaining three subjects with the novel GCH1 variant had normal DAT imaging and a DRD phenotype.

Conclusions: We propose that this GCH1 variant is pathogenic in this family and these findings suggest that similar mechanisms involving abnormal GTP cyclohydolase I may underlie both PD and DRD. GCH1 genetic testing should be considered in patients with PD and a family history of DRD.

© 2015 Published by Elsevier Ltd.

1. Introduction

Dopa-responsive dystonia (DRD) is an autosomal dominant dystonia, now classified as DYT5, with an estimated incidence of between 0.5 and 1 per million [1]. DRD typically manifests as lower limb dystonia in childhood, although the spectrum of symptoms can be broad, even within the same family. Patients typically have an excellent and sustained response to low dose levodopa. Women are more commonly affected with a lower penetrance of mutations in men [2,3].

Mutations in the GTP cyclohydrolase I gene (GCH1) are the most common cause of DRD. GCH1 is located on chromosome 14 (14q22.1-q22.2) and encodes the 32-kDa guanosine 5’-triphosphate cyclohydrolase 1 (GTPCH1) protein. GCH1 contains six exons, and more than 200 different mutations have been identified [1,2].

Single positron emission computerized tomography (SPECT) Dopamine Transporter (DAT) imaging is a demonstration of in vivo striatal dopamine activity. The DAT ligands for SPECT, including [123I]FP-CIT (DaTSCAN) have all shown significantly reduced striatal uptake in PD [4], whilst uptake has usually been normal in DRD [5].

We have studied a family with an inherited movement disorder, with phenotypes ranging from DRD to slowly progressive PD. We report results from clinical, genetic and imaging studies of this kindred.

2. Methods

Twelve members of the kindred were studied. A diagnosis of PD was made according to United Kingdom Parkinson’s Disease Society (UKPDS) Brain Bank clinical...
diagnostic criteria. The Hoehn and Yahr PD rating scale and a Folstein MMSE (Mini Mental State Examination) were performed on each subject. Olfactory function was assessed by use of the University of Pennsylvania Smell Identification Test (UPSIT-40) (Sensornics, Haddon Heights, NJ) and data compared to normative values. Seven subjects (II:1-II:5, III:1 and III:11) underwent dopamine transporter SPECT scanning (DaTSCAN, Amersham Health) and images reviewed by ER, who was blinded to demographic and clinical data.

Molecular genetic screening of the six affected family members was performed by polymerase chain reaction (PCR) and sequencing of the entire coding sequence, and intron-exon boundaries, of the genes SNCA, Parkin, DJ-1, PINK1, LRRK2 and GCH1, using primers and PCR conditions available on request. Multiple ligation-dependent probe amplification (MLPA) was used to detect the presence or absence of copy number variation, using MLPA kits P051 and P052 (MRC Holland), details available on request. Subsequently, six unaffected family members (II:2 and III:4,5,7,9,13) and 150 UK control DNA samples from the PD GEN DNA databank were screened for the novel GCH1 variant.

All subjects gave informed written consent to take part in the study. The study had appropriate ethical approval from South Birmingham LREC and Sandwell and West Birmingham LREC.

3. Results

Twelve individuals in the pedigree (Fig. 1, those annotated with an age) were examined in detail. We noted features consistent with slowly progressive PD in individuals II:1 and II:4 (Supplementary video), with additional levodopa-induced dyskiniesias and dementia in subject II:1. Disease onset was at 58 and 50 years in II:1 and II:4 respectively. Subject II:3 had an isolated rest tremor (asymmetrical, right upper limb), with an older age of onset of 75 years, had not progressed over six years and did not meet diagnostic criteria for PD. Subjects II:5, III:1 and III:11 had features consistent with DRD, with median age of disease onset 17 years and median disease duration of 22 years. The remaining members of the family were unaffected. All the studied subjects are Caucasian and clinical symptoms and signs observed in subjects II:1 and II:4 met diagnostic criteria for PD. In both cases the disease was more slowly progressive than is usual in idiopathic PD. Subject II:3 had an isolated rest tremor (asymmetrical, right upper limb), with additional levodopa-induced dyskiniesias and dementia (Supplementary video), with additonal levodopa-induced dyskinesias and dementia due to atypical disease progression (ie only very slowly progressing which would be unexpected in idiopathic PD).

Novel or previously documented mutations were identified in the coding sequences of SNCA, Parkin, PINK1, DJ-1 and LRRK2. However, a novel heterozygous substitution was identified in the first exon of GCH1 affecting the fifth nucleotide of the open reading frame (c.5A > G) (Supplementary data). This change is predicted to replace a glutamic acid residue with glycine (p.(Glu2Gly)). This mutation (GenBank accession NM_000161.2, NP_000152.1.) is not listed as a known mutation or polymorphism in standard databases (dbSNP138 (http://www.ncbi.nlm.nih.gov/SNP/); 1000 genomes (release October 2013, http://browser.1000genomes.org/); Exome Variant Server (HLBI-EP56500, http://evs.gs.washington.edu/EVS/database accessed Sept, 2014). The novel GCH1 variant was identified in five of the affected members of the family, but not in subject II:3 or unaffected subjects II:2 and III:4,5,7,9,13, nor in 300 UK control chromosomes. MLPA did not reveal any copy number variation in SNCA, Parkin, PINK1, DJ-1 and LRRK2 or GCH1.

4. Discussion

We have identified a novel heterozygous missense variant within GCH1 (c.5A > G) in five family members affected by PD or DRD. Several arguments support the contention that this variant is pathogenic. The variant cosegregates with disease state in the family; it is absent from 300 UK control chromosomes tested here, and from all the large public databases; furthermore, it is almost completely conserved among species (Supplementary Fig. 2), and it is predicted to replace one of the larger hydrophilic amino acids with a small hydrophobic glycine within the N-terminal region of the protein. It is well known that in-silico prediction tools possess limited accuracy [6]. This mutation is predicted as pathogenic by SIFT and SNP&GO, but not by PolyPhen-2 and Mutation Taster. The clinical symptoms and signs observed in subjects II:1 and II:4 met diagnostic criteria for PD. In both cases the disease was more slowly progressive than is usual in idiopathic PD. Subject II:3 had an isolated rest tremor and subjects II:5, III:1 and III:11 were diagnosed.

Fig. 1. Pedigree of study family. Numbers refer to the age (in years) at clinical evaluation and blood sampling of the twelve family members studied.
with DRD. The symptoms in subjects III:1 and III:11 started at a young age and in the case of subject III:11 were more severe than those seen in subject II:5, illustrating the extreme phenotypic heterogeneity in this kindred and possibly reflecting the increased penetrance of GCH1 mutations in females.

DaTSCAN data supported the clinical diagnoses in most cases. The clinical phenotypes of DRD and PD and correspondingly normal and abnormal scans were found in subjects carrying the same GCH1 mutation. DAT imaging is typically normal in DRD. Indeed DAT imaging has been proposed as a diagnostic tool to help differentiate between DRD and early onset PD [5]. There have been case reports of individuals with adult onset dystonia-parkinsonism [7] or PD without any dystonia [8] carrying a GCH1 mutation and an abnormal DaTSCAN.

Recently, Mencacci and colleagues reported 4 unrelated individuals with adult onset parkinsonism, presumed pathogenic GCH1 mutations and abnormal DaTSCANS [9].

These cases, and the two in our family (subjects III:1 and III:4), raise the question as to whether PD, in patients with presumed pathogenic GCH1 mutations, is in fact a rare phenotype of DRD. Certainly the phenotype of DRD is suggested to be broad, as illustrated by a recently reported family with classical DRD, adult onset PD and an MSA-like phenotype associated with a GCH1 two exon deletion [3]. As recently speculated by Mencacci and colleagues [9], chronic dopamine deficiency resulting from GCH1 deficiency could directly predispose to nigral cell death (rather than classical Lewy body associated neurodegeneration as typically seen in PD). Although earlier studies screening for a GCH1 mutations in PD cohorts did not identify a significant role for genetic variation in GCH1, recent studies have implicated GCH1 as a risk locus for PD [9,10].

An alternative, but less plausible, explanation in our family is the functional effects of the novel variant described here. We anticipate that future post-mortem histological data on affected individuals, particularly those with the PD phenotype will shed more light on disease mechanisms in this interesting family.

**Author roles**

The study was designed by AJL, with support and advice by DJN, VB, and KEM. AJL and TDL carried out the clinical assessments and the LRRK2 sequencing work. SO, MQ, EJS, and VB carried out the further genetic analyses (sequencing and MLPA). EBR assessed the DaT Scans. AJL and TDL drafted the manuscript. All the co-Authors contributed to revising the manuscript for intellectual content and approved the final version for publication.

**Conflict of interest**

None of the authors has any conflict of interest to disclose.

**Acknowledgments**

Funding agencies: The Parkinson’s Disease Society of the UK, Sandwell and West Birmingham Hospital NHS Trust and the Midland Neuroscience Teaching and Research Fund. Stichting ParkinsonFonds, The Netherlands (research grant to VB).
We thank the participating family for all their cooperation with this work. A subset of DNA samples from subjects with PD, and controls, was supplied from the PD GEN DNA databank (Prof C.E. Clarke, Prof K.E. Morrison & Prof K. Wheatley, funded by the Medical Research Council of the UK). We gratefully acknowledge our funding sources The Parkinson's Disease Society of the UK, Sandwell and West Birmingham Hospital NHS Trust and the Midland Neuroscience Teaching and Research Fund, and the Stichting ParkinsonFonds, The Netherlands (research grant to VB).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2015.01.004.

References