SHORT REPORT

Co-occurrence of affective and schizophrenia spectrum disorders with *PINK1* mutations

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Objective: To investigate a possible association of mutations in the *PTEN-induced putative kinase 1* (*PINK1*) gene with psychiatric disorders in a large family with monogenic parkinsonism.

Method: 20 members of a family (4 homozygous, 11 heterozygous and 5 non-mutation carriers) were investigated for the presence of psychiatric disorders using the structured clinical interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV); information on three additional heterozygous mutation carriers was obtained according to the family history research diagnostic criteria.

Results: We found predominantly affective and schizophrenia spectrum disorders in 11 (61%) of the 18 mutation carriers and in 1 (20%) of the 5 mutation-negative cases.

Conclusions: First, affective and psychotic symptoms may be part of the phenotypic spectrum or even the sole manifestation of *PINK1* mutations. Second, patients with familial movement disorders associated with psychiatric conditions may serve as a valuable study population to explore (genetic) causes of neuropsychiatric disease.

In patients with Parkinson's disease (PD), a wide range of psychiatric disorders has been described including depression (20–50%),¹ psychosis (15–40%),^{2–3} anxiety disorder (20–40%) and cognitive impairment (20%).² Psychiatric disorders may be the first or even the only manifestation in carriers of *Parkin* gene mutations, the most-frequent known cause of early-onset parkinsonism (EOP).⁴ Likewise, psychiatric problems have been reported in patients and their motor-asymptomatic relatives with mutations in the recently detected *PTEN-induced kinase 1* (*PINK1*) gene, the second-commonest cause of EOP.^{5–9}

Two homozygous mutations in the *PINK1* gene were initially described in three consanguineous families with EOP.⁶ The frequency of *PINK1* mutations ranges from 1% to 8% in patients with PD of different ethnicities who are often selected for young age of onset and for family history (for review see Klein and Schlossmacher¹⁰). Most of the currently described mutations are localised near or within the functional serine/threonine kinase domain of *PINK1* and are expected to result in a loss-of-function effect in vivo. Wild-type *PINK1* functions as a protein kinase that is mainly located within the mitochondria.

Although *PINK1*-associated parkinsonism is generally considered an autosomal recessive condition, a growing body of evidence has been accumulating that supports the notion of a single heterozygous mutation conferring disease susceptibility in at least a subset of patients.^{6–8,9,11}

Currently, no studies have systematically assessed psychiatric symptoms in monogenic EOP. To investigate this possible association, we evaluated a large family with EOP with *PINK1* mutations for the presence of psychiatric disorders.

METHODS

After obtaining written informed consent from the participants and approval for the study by the local ethics committee, 20 family members were personally examined (4 homozygous and 11 heterozygous for the c.1366C>T mutation in *PINK1* and 5 non-mutation carriers). All members had also participated in a detailed neurological examination revealing a diagnosis of definite PD in all four homozygous mutation carriers.¹¹ Among the heterozygous mutation carriers, two showed signs of probable and four of possible PD but were unaware of it (asymptomatic).¹¹ Figure 1 provides further details. Table 1 lists the age and age of onset for PD and psychiatric disorders in the family members.

To assess axis I (clinical disorders) and II (personality disorders) psychiatric disorders and GAF, the latter referring to the last 4 weeks, two experienced psychiatrists (SS and RL) administered the structured clinical interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition,¹² and a consensus diagnosis was established. According to the definition of axis II diagnoses, the age of onset was set at 18 years. The GAF is a hypothetical continuum of mental health—illness ranging from 100% to 0% and considers social, occupational and psychological functioning. Impairment in functioning due to physical or environmental limitations is excluded. The psychiatrists were blinded with respect to the mutational status and the results of the detailed neurological examination although the diagnosis of definite parkinsonism, which was present in the homozygous mutation carriers was obvious to them. In addition, the Family History Research Diagnostic Criteria (FH-RDC) were applied to collect information on three heterozygous mutation carriers (I.1, I.2, and III.10) who were unable to participate.¹³ For family members I.1 and I.2, information was collected through individuals II.1, II.3, II.5, II.7 and II.11, whereas individuals II.5 and III.11 provided information about III.10.

The schizophrenia spectrum was defined according to Kendler and coworkers¹⁴ including schizophrenia, other non-affective psychosis, schizoaffective disorder, schizotypal personality disorder and psychotic affective illness (ie, bipolar disorders and major depression both with psychotic symptoms). A diagnosis of probable schizotypal personality disorder was given when three or four out of nine criteria for schizotypal personality disorder were fulfilled according to the SCID (Structured Clinical Interview for DSM-IV) II DSM-IV Axis II Disorders interview.

RESULTS

Figure 1 summarises clinical information including psychiatric and neurological diagnosis. Three of the four homozygous carriers with definite PD had a lifetime diagnosis of major depression (II.1, II.5 and II.7) manifesting at 4, 8 and 13 years,

Abbreviations: EOP, early-onset parkinsonism; PD, Parkinson's disease

Figure 1 Pedigree of the family with *PINK1* mutations. The quadrants symbolise different categories of psychiatric disorders as detailed in the upper left corner of the figure. Black and grey quadrants represent definitely (def.) or probably (prob.) affected members, respectively. Furthermore, the individual global assessment of functioning (GAF) scores and neurological status are shown. Individuals represented by empty symbols are unaffected (unaff), or deceased (slashed symbol). Asterisks indicate whether information was obtained by the Structured Clinical Interview for DSM-IV (SCID) or the Family History Research Diagnostic Criteria (FH-RDC) interview. Mutational status is given as homozygous (Hom), heterozygous (Het) or wild type (WT).

respectively, before the onset of PD. Six of the 11 heterozygous carriers had a lifetime diagnosis of affective or schizophrenia spectrum disorder, antedating the diagnosis of probable or possible parkinsonism at 23 years (range 17–26 years) in four of them: bipolar I disorder with psychotic symptoms (III.1,

III.2), non-psychotic major depression (III.12), schizotypal personality disorder (III.4) and probable schizotypal personality disorder (III.3, III.5) with an additional diagnosis of non-psychotic major depression in one of them (III.3). One homozygous (II.7) and one heterozygous (III.12) carrier

Table 1 Psychiatric and neurological diagnoses with ages of onset and the mutational status for all family members included in the study

Pedigree code	Age (years)	Parkinson consensus diagnosis	Age when parkinsonism was first diagnosed (years)	Psychiatric diagnosis according to DSM IV	Age of onset for psychiatric disorders (years)	Mutational status (c.1366C>T)
I.1	Deceased	Unknown	–	–	–	Heterozygous
I.2	Deceased	Unknown	–	–	–	Heterozygous
II.1	71	Definite	47	Major depressive disorder, recurrent, with psychotic symptoms	43	Homozygous
II.3	69	Definite	39	Major depressive disorder, single episode	–	Homozygous
II.5	67	Definite	61	Major depressive disorder, single episode	53	Homozygous
				Obsessive-compulsive personality disorder	18	
II.7	60	Definite	53	Major depressive disorder, single episode	40	Homozygous
				Panic disorder with agoraphobia	50	
II.11	57	Secondary	–	–	–	Negative
III.1	49	Probable	49	Bipolar I disorder, most-recent episode manic, with psychotic symptoms	23	Heterozygous
III.2	47	Possible	47	Bipolar I disorder, current episode depressed, with psychotic symptoms	21	Heterozygous
III.3	46	Possible	46	Major depressive disorder, recurrent	29	Heterozygous
				Probable schizotypal personality disorder	18	
III.4	44	Unaffected	–	Schizotypal personality disorder,	18	Heterozygous
				Adjustment disorder, with depressed mood	21	
III.5	42	Probable	42	Probable schizotypal personality disorder	18	Heterozygous
III.6	44	Unaffected	–	Adjustment disorder, with depressed mood	44	Heterozygous
III.7	43	Unaffected	–	–	–	Heterozygous
III.8	39	Possible	39	Obsessive-compulsive personality disorder	18	Heterozygous
III.9	34	Unaffected	–	–	–	Heterozygous
III.10	42	Unknown	–	Schizophrenia, continuous	37	Heterozygous
III.11	47	Possible	47	–	–	Heterozygous
III.12	31	Unaffected	–	Major depressive disorder, single episode with atypical features	27	Heterozygous
				Panic disorder		
III.13	43	Unaffected	–	Adjustment disorder, with depressed mood,	35	Negative
				Agoraphobia without history of panic disorder	18	
III.14	38	Unaffected	–	–	–	Negative
III.15	35	Unaffected	–	Major depressive disorder, single episode	32	Negative
III.16	31	Unaffected	–	Adjustment disorder, with depressed mood	25	Negative

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition
For more details see Hedrich *et al.*¹¹

additionally had an anxiety disorder. Another two heterozygous carriers (III.6, III.8) had other psychiatric disorders (ie, adjustment disorder and obsessive-compulsive personality disorder; fig 1), one of them having possible PD (III.8). In two of the three obligate but not personally examined heterozygous carriers, the family history interview revealed schizophrenia preventing participation in the interview (III.10) and a recurrent major depression with psychotic symptoms leading to suicide (I.2). The third obligate carrier was reportedly unaffected. In all homozygous or heterozygous *PINK1* mutation carriers, we found evidence for a total rate of 72% (13/18) psychiatric disorders with affective and/or schizophrenia spectrum disorders in 11 of them (61%). Among the five non-mutation carriers, there was one case of non-psychotic major depression (III.15) and two cases (III.13, III.16) with adjustment disorder or agoraphobia, but no one had a schizophrenia spectrum disorder (fig 1 and table1).

DISCUSSION

In this first report of a systematic and standardised evaluation of psychiatric disorders in a family with monogenic *PINK1*-associated parkinsonism, we detected a high rate of psychiatric disorders predominantly consisting of affective and schizophrenia spectrum disorders (61%) in both homozygous and heterozygous mutation carriers. Our findings are in line with reports of increased rates of depressive and psychotic symptoms both in *Parkin* mutation carriers with symptoms and also in asymptomatic *Parkin* mutation carriers.⁴ This is in keeping with recent descriptions of unrelated patients with parkinsonism being heterozygous *PINK1* mutation carriers and displaying psychiatric symptomatology, predominantly consisting of symptoms of depression and anxiety.⁷⁻⁹ In four of these, parkinsonism was confirmed by autopsy.⁸

Supporting the hypothesis that heterozygous mutations may act as a susceptibility factor,¹¹ we found evidence of a neurological or a psychiatric manifestation or both in 10 (71%) of the 14 heterozygous family members. In two of the personally examined heterozygous carriers, the psychiatric disorder was, in fact, the only disease manifestation (III.4 and III.12). In five of the six heterozygous carriers with possible or probable PD, it occurred several years before the diagnosis of neurological signs. In three of the homozygous mutation carriers with definite PD, the affective disorder occurred many years prior to the onset of PD. Correspondingly, in 25% of the studied *Parkin* mutation carriers, the psychiatric disorder also manifested before the onset of EOP.⁴ Thus, the psychiatric disorders may be part of the clinical spectrum and may even be the initial or sole manifestation of *PINK1* mutations, as was previously shown in carriers of *SGCE* mutations (ϵ -sarcoglycan gene) that are associated with both myoclonus dystonia and psychiatric disorders.¹⁵

It should be noted that the mutational and clinical status do not entirely correspond in three family members (III.13, III.15 and III.16) who had psychiatric disorders in the absence of *PINK1* mutations, including one with non-psychotic major depression. Similarly, we identified one family member with signs of probable secondary parkinsonism (II.11).¹¹ Given the high prevalence of these psychiatric conditions and of PD, these individuals may represent phenocopies. While the association of *PINK1* mutations with PD has been well established, we cannot currently prove that the *PINK1* mutations are indeed causal of the psychiatric disorders in this family.

The importance of the psychiatric manifestation may be underestimated as patients can achieve high GAF scores during phases of remission as was the case in this family. This indicates that, despite the severity of the psychiatric illness, psychological, social and occupational functioning can be

relatively unimpaired in between episodes due to effective medication and psychotherapy.

One possible explanation for a relatively high frequency of affective and psychotic disorders in patients with movement disorders is shared neurotransmitters. Note, we observed an especially high rate of schizophrenia-spectrum disorders (7/18, 38%) in the mutation carriers of this family with *PINK1* mutations. Psychotic symptoms occur in up to 40% of patients with PD,² sometimes even without dopaminergic treatment.¹⁶ Pathophysiologically, they may arise from an imbalance within the dopaminergic and the serotonergic transmitter systems. Dopa-responsive dystonia may serve as another example of a monogenic disorder with both psychiatric and motor involvement.¹⁷ The majority of dopa-responsive dystonia is caused by mutations in the guanosine triphosphate-cyclohydrolase (*GTP cyclohydrolase*) 1 gene encoding the rate-limiting enzyme in tetrahydrobiopterin production, which is an essential cofactor in the synthesis of both dopamine and serotonin linking both neurotransmitter systems. Alternatively, clues as to the increased vulnerability to both psychiatric and motor signs may be derived from the putative function of the *PINK1* protein as a mitochondrial kinase. It remains to be studied whether certain types of psychiatric disorders are associated with mutations in specific genes, and the data of our pilot study need to be interpreted with caution and replicated in larger patient samples.

Mutations in single genes following a mendelian pattern of inheritance are likely to explain a few psychiatric disorders at best. However, PD has long been considered another "textbook example" of a complex genetic or even non-genetic disorder, a view that has recently been challenged by the identification of at least five PD genes.¹⁰ In the absence of known genetic causes of psychiatric disorders, patients with familial movement disorders associated with psychiatric conditions may serve as a valuable study population to aid in the identification of (genetic) causes of neuropsychiatric disease.

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