Genetic Screening of the Mitochondrial Rho GTPases MIRO1 and MIRO2 in Parkinson's Disease

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Abstract: MIRO1 and MIRO2 (mitochondrial Ras homolog gene family, member T1 and T2) also referred to as RHOT1 and RHOT2, belong to the mitochondrial Rho GTPase family and are involved in axonal transport of mitochondria in neurons. Because mitochondrial dysfunction is strongly implicated in Parkinson's disease (PD), *MIRO1* and *MIRO2* can be considered as new candidate genes for PD. We analyzed two non-synonymous polymorphisms and one synonymous polymorphism in *MIRO1* and two non-synonymous polymorphisms in *MIRO2,* in a Swedish Parkinson case-control material consisting of 241 patients and 307 neurologically healthy controls. None of the analyzed polymorphisms in *MIRO1* and *MIRO2* were significantly associated with PD. Although we did not find a significant association with PD in our Swedish case-control material, we cannot exclude these Rho GTPases as candidate genes for PD or other neurodegenerative disorders.

Keywords: Association, mitochondria, single nucleotide polymorphism.

1. INTRODUCTION

Degeneration of dopamine (DA) neurons in substantia nigra (SN) pars compacta causes the typical motor symptoms seen in patients with Parkinson's disease (PD); resting tremor, rigidity, bradykinesia and postural instability [1,2]. However, neuropathology in PD is widespread, affecting neurons in areas from the gastrointestinal tract to cerebral cortex [3]. In accordance with the systemic nature of the disease, there is increasing evidence that mitochondrial dysfunction may underlie some forms of PD [4-6]. Mitochondria are essential in all eukaryotic cells for generating ATP, calcium buffering and involvement in programmed cell death [7-9]. To adapt to cellular demands mitochondria undergo fusion and fission, two opposing processes that exist in equilibrium [10]. The mitochondrial network is very dynamic in neurons [11,12] and the rate of mitochondrial fusion and fission is high [13]. Recruitment of mitochondria to specific neuronal compartments has been shown to be an active ATP consuming process [14]. In support of a mitochondrial involvement in PD, the metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is 1-methyl-4-phenylpyridinium (MPP^+), is a neurotoxin and inhibits the mitochondrial respiratory chain complex I, which causes degeneration of DA neurons in SN [15]. Another inhibitor of complex I is the pesticide rotenone. In rodents it causes selective degeneration of DA neurons, as well as other neurons to a lesser extent, thereby resembling the pathology of PD [16]. Complex I activity has been found to be reduced in SN and in platelets from PD patients [17].

Different polymorphisms in mtDNA have been reported to be associated with both increased and decreased risk of PD [18]. We and others have found associations between PD risk and two nuclear genes involved in mitochondrial maintenance, *MTIF3* (mitochondrial translation initiation factor 3) and *POLG1* (DNA polymerase gamma 1). *MTIF3* is part of the initiation complex formation on the mitochondrial 55S ribosome and regulates translation of proteins within mitochondria [19,20]. A synonymous single nucleotide polymorphism (SNP) in *MTIF3*, rs7669, has been reported to be associated with PD in cohorts with different geographical origin [21-23]. *POLG1* is important for replication and repair of the mitochondrial genome [24]. Variations in length of the polyglutamine tract of *POLG1* have been found to associate with PD by a number of groups in different geographical regions [25-27].

Several of the PARK genes identified by linkage studies have been reported to influence mitochondria in different ways. Mutations in PTEN induced putative kinase 1 (*PINK1*) at PARK6, reported to regulate mitochondrial fission, cause early-onset familial PD [28]. Mutations in *Parkin* at PARK2 have been reported to cause autosomal recessive early-onset Parkinsonism [29]. Parkin acts in a similar way as PINK1 [30] and is believed to be recruited from the cytoplasm by PINK1 to initiate autophagic degradation of impaired mitochondria [31]. *DJ-1* at PARK7 causes autosomal recessive early-onset Parkinsonism [32] and is suggested to operate in a parallel pathway to that of PINK1/Parkin to maintain mitochondrial function in oxidative environments [33]. Pink1 has

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been shown to be part of a mitochondrial multi-protein complex together with the atypical GTPases Miro1 and Miro2 (mitochondrial Ras homolog gene family, member T1 and T2) and the adaptor protein Milton [34]. This suggests that Pink1 also plays a role in mitochondrial trafficking.

Miro1 and Miro2, also referred to as Rhot1 and Rhot2, belong to the mitochondrial Rho GTPase family and are involved in axonal transport of mitochondria [35,36]. Miro1 and Miro2 were first identified in yeast [37] and later described to share similarities with Rho GTPases [38]. Miro proteins have a C-terminal domain locating them to the mitochondrial outer membrane, as well as two GTPase domains and two calcium binding EF-hands [36,37]. Calcium binding to the EF-hands regulates the trafficking of mitochondria along microtubules [39,40].

Based on the finding that mitochondrial dysfunction has been implicated in PD [4,41], the importance of Miro1 and Miro2 in mitochondrial transport [35,36] and the link between Miro and Pink1 [34], we analyzed SNPs in *MIRO1* and *MIRO2* with regard to PD. We hypothesized that genetic variations in functionally important regions of these two genes might lead to disturbed mitochondrial trafficking, fusion and/or fission disturbances in neurons and hence increase the risk of neurodegenerative events, such as those observed in PD. We therefore investigated the possible association of five SNPs located in functional regions of the proteins MIRO1 and MIRO2. The SNPs were selected from the NCBI database and screened in a Swedish Parkinson case-control material (see Table **1**). Three SNPs were selected in *MIRO1*, one synonymous SNP in the GTPase domain (rs16967164) and two non-synonymous SNPs in each of the two EF-hands (rs28630420, rs34538349). The other two SNPs were non-synonymous SNPs located in one of the EF-hand domains of *MIRO2* (rs1139897 and rs3743912).

2. MATERIALS AND METHODOLOGY

2.1. Subjects

A Swedish PD case-control material of Caucasian origin was genotyped for three SNPs in *MIRO1* and two in *MIRO2* (see Table **1**). The PD material consisted of 241 individuals from the Stockholm area (mean age 67.0 years, 60.9% men). The DNA was obtained after informed oral and written consent and approval of the local ethics committee, Regionala etikprövningsnämnden, Stockholm, Sweden. All PD subjects met the United Kingdom Parkinson's Disease Society Brain Bank Criteria for PD except that more than one affected first, second or third degree relative was allowed [42]. Control subjects consisted of 307 neurologically healthy spouses of PD patients and individuals from the SNAC-K project (The Swedish National Study on Aging and Care in Kungsholmen) from the Stockholm area (mean age 64.2 years, 40.4% men). DNA was extracted from blood according to standard protocols.

2.2. Genotyping

The SNPs were genotyped with predesigned TaqMan SNP Genotyping Assays: C_1630552_10 (rs16967164), C_60583023_10 (rs28630420), C_25937296_10 (rs3743912), C_2463996_1_ (rs1139897) and a custom designed assay (rs34538349) using a fast real-time PCR instrument (ABI 7500 FAST Real-Time PCR, Applied Biosystems, Foster City, CA, USA). The TaqMan assay contained primers and 5′ fluorescently labeled (FAM and VIC) minor groove binding probes (20×) for detection of the SNPs. Allelic discrimination was run with pre- and custom-designed primers and probes, genotyping master mix (TaqMan®, Applied Biosystems, Foster City, CA, USA) and 10-20 ng of genomic DNA in a total reaction volume of 10 µl mixed in transparent 96-well plates. The polymerase chain reaction (PCR) conditions followed the recommendations of default settings for the SNP assay, except that the number of cycles were set to 55 and run at 92°C for 15 s. The ramp speed was set to standard. A post-PCR read was done for allelic discrimination using appropriate software (SDS version 2.0.4) supplied with the instrument. To test for genotyping errors we used water as negative controls and re-genotyped randomly chosen samples to confirm the results. Case-control analysis between individual sequence variants in *MIRO1* and *MIRO2* were performed using a Chi-square (χ^2) test [43]. Three PD patients previously known to carry the pathogenic G2019S mutation in leucine-rich repeat kinase 2 (*LRRK2)* were excluded from the association analysis. Distribution of genotypes in controls was tested for consistency with the Hardy-Weinberg equilibrium. Statistical significance was defined as $p < 0.05$.

Table 1. Investigated Polymorphisms in *MIRO1* and *MIRO2,* their Nucleotide Position, Consequence, Genomic Location and Functional Protein Region

Reference Sequence	Nucleotide Position and Change	Amino Acid Change	Genomic Location	Protein Domain
MIRO1				
rs16967164	c.1458A>G	Glu486Glu	Exon 17	GTPase domain
rs28630420	c.766A>T	Thr256Ser	Exon 11	EF-hand
rs34538349	c.1048_1049insT	Cys350Leu	Exon 13	EF-hand
MIRO2				
rs1139897	c.734G>A	Arg245Gln	Exon 10	EF-hand
rs3743912	c.708C>T	Asn236Asn	Exon 10	EF-hand

3. RESULTS

The results from the TaqMan genotyping of the five SNPs in *MIRO1* and *MIRO2* are presented in Table **2**. We did not find any genotypic or allelic (data available upon request) association of the *MIRO1* or *MIRO2* SNPs screened in our Swedish Parkinson case-control material. The observed frequencies of the controls were in agreement with the Hardy-Weinberg equilibrium (data not shown). For two of the SNPs in *MIRO1 (*rs28630420, rs34538349) we only observed the wild-type genotype.

To investigate if any of the SNPs had a possible effect on age of onset we stratified the material into early disease onset (≤50 years) or late disease onset (>50 years) and compared genotype and allele frequencies. However, such stratification did not reveal any significant associations with disease at genotype or allele (data available upon request) levels, as shown in Table **3**.

4. DISCUSSION

Dysfunctional mitochondria may be the cause or the consequence of DA neuron degeneration in PD. This is the first genetic study analyzing possible links between the two GTPases *MIRO1* and *MIRO2* and disease in general and neurodegenerative disease in particular. Two functionally important regions in the two Miro proteins are the two GTPase domains and two calcium binding EF-hands [36,37]. Another protein with a GTPase domain linked to PD is leucine-rich repeat kinase 2 (LRRK2), a large protein with multiple domains, including functional Roc GTPase and a protein kinase domain. Several mutations in the kinase domain of *LRRK2* are associated with both sporadic and familial PD [44]. Recently, a new mutation (N1437S) localized within the GTPase domain of LRRK2 (PARK8) was found to co-segregate with PD [45]. Furthermore, it has been suggested that the GTPase domain may contribute to the toxicity of LRRK2 [46]. Interestingly, knockdown of lrk-1, the ortholog of LRRK2 in *C. elegans*, has been reported to lead to reduced survival and is associated with dysfunctional mitochondria [47]. There are no reports on proteins with EF-hand domains being linked to PD today.

It has been shown that all domains of Gem1P (i.e. yeast Miro) are needed for proper mitochondrial morphology [37]. Loss-of-function mutations in the Miro GTPase in *Drosophila melanogaster* lead to impaired locomotion and premature death of the flies [48]. Based on these findings we selected polymorphisms that are located in functional regions in MIRO1 and MIRO2 to analyze possible association with risk for neurodegeneration. The three selected *MIRO1* SNPs are localized in one of the GTPase domains (rs16967164) and in each of the two EF-hands (rs28630420, rs34538349). The two SNPs in *MIRO2* (rs1139897 and rs3743912) are situated in one of the EF-hand domains. We did not find association with any of the selected SNPs in our Swedish case-control material. For two of the SNPs in *MIRO1* (rs28630420 and rs34538349) we only detected the wild-

Table 2. Genotype Frequencies of *MIRO1* and *MIRO2* Variants in Swedish Patients with Parkinson´s Disease (PD) Compared to Matched Neurologically Healthy Controls Analyzed using a Two-sided Chi-square (χ^2) test

	Genotype Frequency % (n)			χ^2	*P*-value
MIRO1					
rs16967164	**AA**	**AG**	**GG**		
PD	66.1 (152)	30.9 (71)	3 (7)	0.09	0.96
Control	66.3 (203)	31.1 (95)	2.6 (8)		
rs28630420	**AA**	**AT**	**TT**		
PD	100 (235)	0 (0)	0 (0)	-	-
Control	100 (300)	0 (0)	0 (0)		
rs34538349	**-/-**	**-/T**	**T/T**		
PD	100 (236)	0 (0)	0 (0)	-	-
Control	100 (306)	0 (0)	0 (0)		
MIRO2					
rs1139897	**GG**	**GA**	**AA**		
PD	57.3 (133)	34.9 (81)	7.8 (18)	2.03	0.36
Control	51.1 (155)	40.3 (122)	8.6 (26)		
rs3743912	**CC**	**CT**	**TT**		
PD	73.5 (169)	24.8 (57)	1.7 (4)	0.87	0.65
Control	76.9 (233)	21.8 (66)	1.3 (4)		

Table 3. Stratification of Parkinson's Disease (PD) Cases into Early (≤50 years) and Late Onset (>50 years), Comparing *MIRO1* and *MIRO2* Genotype Frequencies Analyzed using a Two-sided Chi-square (χ^2) Test

	Genotype Frequency % (n)			χ^2	*P*-value
MIRO1					
rs16967164	AA	AG	GG		
≤50 PD	62.3 (33)	40.0 (18)	3.8 (2)	0.45	0.80
>50 PD	66.7 (118)	31.1 (55)	2.2 (4)	0.06	0.97
Controls	66.3 (203)	31.1 (95)	2.6 (8)		
MIRO2					
rs1139897	GG	GA	AA		
≤50 PD	49.1 (26)	45.3 (24)	5.7 (3)	0.79	0.67
>50 PD	59.6 (106)	32.0 (57)	8.4 (15)	3.51	0.17
Controls	51.1 (155)	40.3 (122)	8.6 (26)		
rs3743912	CC	CT	TT		
≤50 PD	77.4 (41)	22.6 (12)	0	-	-
>50 PD	72.2 (127)	25.6 (45)	2.3 (4)	1.63	0.44
Controls	76.9 (233)	21.8 (66)	1.3 (4)		

type genotype in our material of cases and controls. Thus these two mutations tend to be very rare in the area from which our DNA samples have been collected. The results after stratification of the material regarding age of onset did not reveal any age-of-onset association with any of the detected polymorphisms. Further genetic analysis and functional studies in disease are however needed before one can exclude *MIRO1* and *MIRO2* as potential candidate genes for PD.

CONCLUSION

Genetic variation in *MIRO1* and *MIRO2* might influence transport of mitochondria along microtubules, leading to reduced local energy production which can lead to degeneration of DA neurons. Although we did not find a significant association with PD and the selected polymorphisms in *MIRO1* and *MIRO2* in our Swedish case-control material, we cannot exclude these Rho GTPases as candidate genes for PD or other neurodegenerative disorders.

CONFLICT OF INTEREST

None declared.

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