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RIT2 Polymorphisms: Is There a Differential Association?

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Abstract Neurological disorders include a wide variety of mostly multifactorial diseases related to the development, survival, and function of the neuron cells. Single-nucleotide polymorphisms (SNPs) have been extensively studied in neurological disorders, and in a number of instances have been reproducibly linked to disease as risk factors. The *RIT2* gene has been recently shown to be associated with a number of neurological disorders, such as Parkinson's disease (PD) and autism. In the study reported here, we investigated the association of the rs12456492 and rs16976358 SNPs of the *RIT2* gene with PD, essential tremor (ET), autism, schizophrenia (SCZ), and bipolar disorder (BPD; total of 2290 patients), and 1000 controls, by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. Significant association was observed between rs12456492 and two disorders, PD and ET, whereas rs16976358 was

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found to be associated with autism, SCZ, and BPD. Our findings are indicative of differential association between the *RIT2* SNPs and different neurological disorders.

Keywords Neurological disorders · Parkinson's disease · Essential tremor · Autism · Schizophrenia · Bipolar disorder · *RIT2* · Polymorphism

Introduction

Neurological disorders include a wide variety of diseases consisting of neurodevelopmental, neurodegenerative, and psychiatric disorders. In the majority of those disorders, a multifactorial pattern of etiology is influenced by both environmental and genetic factors, which may overlap in this group of disorders [1–7]. Similarly, from the phenotypic point of view, overlapping and distinct features are seen across different groups of neurological disorders, such as the brain regions involved, or alterations of specific neurotransmitters [8–11]. Parkinson's disease (PD), essential tremor (ET), autism, schizophrenia (SCZ), and bipolar disorder (BPD) are among the most common and severe neurological disorders, belonging to the neurodegenerative or psychiatric disorders. Several genes or genetic determinants have been identified to be risk factors for neurological disorders; only a minority of which are single-gene causes. The majority of the risk factors have small effects, which in an additive pattern, and in cooperation with environmental factors, make an overall great effect capable of altering the phenotype [12–14]. One of the recently identified genes associated with neurological disorders is *RIT2* [15]. This gene has an important role in neurodevelopment, neuron cell differentiation, and survival. *RIT2* is mainly expressed in the brain and preferentially in the dopaminergic neurons, and its protein product, Rin, is a member of the RAS GTPase superfamily, involved in many important cellular processes, either by directly interacting with other proteins or by indirectly affecting the downstream proteins in the pathway [16–18]. Two single-nucleotide polymorphisms (SNPs) in the *RIT2* gene have been recently linked to the pathophysiology of PD and autism; the rs12456492 SNP was identified to be associated with PD in a genome-wide association study (GWAS) [19] and consequently replicated in several studies and populations [20–23], and the rs16976358 SNP was found to be in significant association with autism disorder in another GWAS [24]. In the current study, we investigated the association of the two mentioned SNPs in several neurological disorders with overlapping clinical and pathophysiological features.

Materials and Methods

Subjects

This study was performed on a total of 3290 unrelated Iranian human subjects, consisting of patients, PD ($N=520$), ET ($N=350$), autism ($N=470$), SCZ ($N=510$), and BPD ($N=440$), and a total of 1000 healthy control subjects. For each disease group, the corresponding control group was selected based on the sex, age, and ethnicity of the patients (Table 1). Patients were diagnosed and confirmed by two neurologists. Written informed consent was taken from all participants. The study was approved by the ethic committee at Shahid Beheshti University of Medical Sciences, Tehran, Iran.

DNA Extraction and SNP Genotyping

Genomic DNA was extracted from peripheral blood of all subjects following a standard salting-out protocol. The rs12456492 and rs16976358 polymorphisms of the *RIT2* gene were genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method (Table 2). The PCR reactions were performed in a reaction containing 150–400 ng of genomic DNA, 0.3 mM of each primer, 0.2 mM dNTPs, 2 mM MgCl2, and 0.6 U Taq polymerase. Following digestion, PCR products were separated on a 3 % agarose gel to determine the genotypes. The accuracy of the genotyping method was confirmed by sequencing of 45 PCR products (15 sample of each genotype) for each disorder groups.

Statistical Analysis

Pearson's χ^2 test was applied to test the significance of genotype distribution and allele frequency between patient and control groups. Odds ratio with 95 % confidence interval (CI) was estimated, and P value of less than 0.05 (two-tailed) was considered to be significant. The Hardy–Weinberg equilibrium test was performed using Fisher's exact test. The distribution of genotype frequencies was analyzed under the following three different genetic models: additive (T/T = 0, C/T = 1, and C/C = 2 for rs16976358 and A/A = 0, G/A = 1, and G/G = 2 for rs12456492), recessive (T/T and C/T vs. CC for rs16976358 and A/A and G/A vs. G/G for rs12456492), and dominant (C/C and C/T vs. T/T for rs16976358 and G/G and G/A vs. A/A for rs12456492), using SNPassoc package of R version 3.2. The power calculations were performed using Quanto [25].

Table 1 Demographic data including age and sex distribution in study groups

Disorder	Age (mean ± SD)		*P* value	Gender				*P* value
	Case	Control		Case		Control		
				Male	Female	Male	Female	
Parkinson ($n = 520$)	59.5 ± 12.5	58.12 ± 12.22	0.07	278	242	268	252	0.38
Essential tremor ($n = 350$)	45.6 ± 8.3	46.8 ± 9.1	0.07	192	158	184	166	0.39
Autism ($n = 470$)	7.9 ± 2.7	8.2 ± 2.5	0.08	286	184	279	191	0.22
Schizophrenia ($n = 510$)	43.34 ± 7.21	44.11 ± 8.84	0.13	321	189	306	204	0.28
Bipolar ($n = 440$)	45.02 ± 9.38	44.81 ± 8.24	0.72	263	177	276	174	0.23

Results

There was no evidence of deviation from Hardy–Weinberg equilibrium in any of the studied groups for the two SNPs studied. Distribution of genotypes and allele frequencies of rs12456492 were significantly different in patients with PD and ET comparing with control groups (Table 3). Those differences were also significant under recessive and additive models (Table 4). The data for association analysis of rs12456492 with PD was retrieved from our previous article [20]. No association was observed between the rs12456492 genotypes or allele frequencies and autism, SCZ, and BPD (Table 3). The genotype distribution and allele frequencies were significantly different in rs16976358 between normal controls and patients with autism, SCZ, and BPD (Table 5). The association of rs16976358 with autism, SCZ, and BPD was also significant under additive and recessive models (Table 6). There was no association between rs16976358 and PD or ET (Table 5). Given the sample sizes available, we have 80 % power to detect an odds ratio of 1.45 for PD, 1.58 for ET, 1.48 for autism, 1.44 for schizophrenia, and 1.49 for bipolar disorder for rs16976358 using an additive model and OR of 1.28 for PD, 1.36 for ET, 1.3 for autism, 1.29 for schizophrenia, and 1.31 for bipolar disorder for rs12456492.

Discussion

Accumulating evidence suggests new genes, alterations, and variants, associated and related in various ways, to complex disorders. Each of those minor factors can contribute risk to disease susceptibility, importance of which, even small, is not negligible. The *RIT2* gene was recently identified as a new locus for both PD and autism, in two distinct GWAS reports [19, 24]. In each study, one SNP was identified to be significantly associated with its correlated disease, i.e., rs12456492 with PD and rs16976358 with autism. Later, the rs12456492 SNP was studied in the Taiwanese population and found not to be associated with PD [26]. We showed its significant association with PD in the Iranian population [20], and subsequently, three different studies in Chinese, Han Chinese, and mainland China populations replicated and confirmed our results [21–23]. Three meta-analysis studies also showed similar results and confirmed the overall association of the G-allele of this SNP with PD [27–29].

The rs16976358 polymorphism has been identified to be associated with autism in a recent GWAS report [24]. This SNP revealed the most significant association with autism in our study. In conclusion, we found differential association of the two SNPs with the spectrum of neurological disorders studied. The rs12456492 SNP was significantly associated

Table 2 The primer sequences and PCR and digestion conditions for studied polymorphisms

Polymorphisms	Primer sequences (5→3)	PCR conditions (°C/s)			Restriction enzyme digestion	Alleles	DNA fragment size (bp)
		Denature	Annealing	Extension			
rs12456492	F: CCTGAGTCTATTGGAGTGGG R: TCTCCCAACAACCTCCAGTT	95/30	55/30	72/30	*AluI* at 37 °C overnight	G A	60 + 189 60 + 69 + 120
rs16976358	F: TTCAAGATGAGATTTGGGTG R: TGGACTTCATTTCCAGATTCA	95/30	50/30	72/30	*HinfI* at 37 °C overnight	T C	213 104 + 109

Table 3 Comparison of genotypes and allele frequencies of rs12456492

Subjects	Genotype frequencies (%)			*P* value	Allele frequencies (%)		*P* value	OR	95 % CI
	GG	GA	AA		G	A			
Parkinson ($n = 520$)	111 (21)	247 (47)	162 (32)	0.001*	469 (45)	571 (55)	0.007*	1.27	1.06–1.51
Control ($n = 520$)	72 (14)	265 (51)	183 (35)		409 (39)	631 (61)			
Essential tremor ($n = 350$)	81 (23)	156 (45)	113 (32)	0.0004*	318 (45)	382 (55)	0.003*	1.37	1.11–1.70
Control ($n = 350$)	42 (12)	180 (51)	128 (37)		264 (38)	436 (62)			
Autism ($n = 470$)	72 (15)	235 (50)	163 (35)	0.05	379 (40)	561 (60)	0.06	1.21	0.99–1.46
Control ($n = 470$)	52 (11)	236 (50)	182 (19)		340 (36)	600 (64)			
Schizophrenia ($n = 510$)	74 (15)	261 (51)	175 (34)	0.66	409 (40)	611 (60)	0.37	1.09	0.90–1.31
Control ($n = 510$)	66 (13)	258 (50)	186 (36)		390 (38)	630 (62)			
Bipolar ($n = 440$)	83 (19)	231 (52)	126 (29)	0.43	397 (45)	483 (55)	0.21	1.13	0.94–1.38
Control ($n = 440$)	75 (17)	222 (50)	143 (33)		372 (42)	508 (58)			

*Considered as significant

with PD and ET and showed no associations with autism, SCZ, or BPD. On the contrary, the second SNP, rs16976358, was significantly associated with autism, SCZ, and BPD and had no association with PD or ET. There are several studies showing similarities between PD and ET vs. autism, SCZ, and BPD [8, 9, 30]. PD and ET are grouped as neurodegenerative movement disorders, whereas autism, SCZ, and BPD are grouped as psychiatric disorders. Despite the differences, there are similarities between the two groups and among the disorders of each group, evidenced by shared etiology and co-incidence of those disorders [8, 31–35]. One of the remarkable examples of the shared etiology among the studied disorders is the imbalance of the dopamine neurotransmitter in the brain, which is a common feature in all the mentioned disorders, albeit in different patterns. It is well established that the dopamine levels are decreased in PD [36], and several studies have reported malfunction of the dopamine transporter (DAT) in ET [37]. Conversely, the dopamine levels are elevated in autism, SCZ, and BPD, and DAT is hyperactive, where dopamine antagonists are sometimes used for treatment [38–41]. From the molecular point of view, an important protein involved in the dopaminergic pathway is DAT, a membrane transporter of dopamine molecules [42], and found to have association with neurological disorders such as PD, SCZ, BPD, and autism spectrum disorder [43–46]. On the other hand, it has been found that the Rin protein, encoded by *RIT2*, is bound to DAT, at the cell membrane, so that they co-precipitate in immunohistochemistry assays [18]. Other direct physical interaction of Rin includes its attachment with calmodulin 1 [47], which is found to be linked to the

Table 4 Comparison of genotype frequencies of rs12456492 under three genetic models

Subjects		Additive (A/A = 0, G/A = 1, and G/G = 2)	Dominant (G/G and G/A vs. A/A)	Recessive (A/A and G/A vs. G/G)
Parkinson	*P* value	0.007*	0.166	0.001*
	OR	1.27	1.20	1.69
	95 % CI	1.07–1.52	0.93–1.55	1.22–2.34
Essential tremor	*P* value	0.003*	0.232	<0.0001*
	OR	1.37	1.21	2.21
	95 % CI	1.11–1.70	0.88–1.65	1.47–3.3
Autism	*P* value	0.055	0.198	0.053
	OR	1.21	1.19	1.45
	95 % CI	0.99–1.46	0.91–1.55	0.99–2.13
Schizophrenia	*P* value	0.372	0.471	0.466
	OR	1.09	1.10	1.14
	95 % CI	0.90–1.31	0.85–1.42	0.80–1.63
Bipolar	*P* value	0.218	0.213	0.482
	OR	1.13	1.20	1.13
	95 % CI	0.93–1.37	0.90–1.60	0.80–1.60

*Considered as significant

Table 5 Comparison of genotypes and allele frequencies of rs16976358

Subjects	Genotype frequencies (%)			*P* value	Allele frequencies (%)		*P* value	OR	95 % CI
	CC	CT	TT		C	T			
Parkinson ($n = 520$)	11 (2)	99 (19)	410 (89)	0.49	121 (12)	919 (88)	0.25	1.16	0.89–1.52
Control ($n = 520$)	7 (1)	91 (18)	422 (81)		105 (10)	935 (90)			
Essential tremor ($n = 350$)	4 (1)	89 (26)	257 (73)	0.49	97 (14)	603 (86)	0.35	1.15	0.84–1.59
Control ($n = 350$)	5 (1)	76 (22)	269 (77)		86 (12)	614 (88)			
Autism ($n = 470$)	18 (4)	117 (25)	335 (71)	0.003*	153 (16)	787 (84)	0.010*	1.40	1.08–1.81
Control ($n = 470$)	4 (1)	106 (22)	360 (77)		114 (12)	826 (88)			
Schizophrenia ($n = 510$)	19 (4)	126 (25)	365 (71)	0.008*	164 (16)	856 (84)	0.024*	1.33	1.04–1.70
Control ($n = 510$)	5 (1)	118 (23)	387 (76)		128 (13)	892 (87)			
Bipolar ($n = 440$)	18 (4)	113 (26)	309 (70)	0.001*	149 (17)	731 (83)	0.007*	1.43	1.10–1.87
Control ($n = 440$)	3 (1)	103 (23)	334 (76)		109 (12)	771 (88)			

*Considered as significant

pathophysiology of SCZ in several studies [48]. The above may partially explain the mechanisms by which *RIT2* influences the risk of those disorders. The expression pattern of *RIT2* has been investigated in several studies, and results of the postmortem studies have shown its decreased expression in PD patients [49]. However, there is no expression data on other neural disorders in the literature.

SNPs can affect disease risk by altering gene expression or protein function [50]. The rs12456492 SNP is located in an intron of the *RIT2* gene, and no binding site for any regulatory protein has been found in this region, which implies that it does not alter the structure of the protein product. However, this SNP may affect the levels of the Rin protein by affecting gene expression [51]. Consistent with this hypothesis, it has been found that the G-allele of this SNP creates a CpG site, and at least theoretically, it may repress expression by being methylated [52]. The second SNP, rs16976358, is located relatively far from the *RIT2* gene and in its downstream region. There is no functional or sequence analysis available for this SNP, but overall, affecting gene expression levels by altering distant elements such as enhancers or silencers, or by means of changing the local chromatin structure, has been suggested for this type of polymorphisms [51]. Two studies have been performed in this regard, and neither of them found any significant association between the rs12456492 polymorphism and *RIT2* expression levels [29, 53]. However, both studies were confined by small sample sizes. Whereas conclusion of a lack of effect on gene expression warrants including more samples

Table 6 Comparison of genotype frequencies of rs16976358 under three genetic models

Subjects		Additive (T/T = 0, C/T = 1, and C/C = 2)	Dominant (C/C and C/T vs. T/T)	Recessive (T/T and C/T vs. CC)
Parkinson	*P* value	0.27	0.35	0.33
	OR	1.16	1.16	1.58
	95 % CI	0.89–1.52	0.85–1.57	0.61–4.12
Essential tremor	*P* value	0.37	0.29	0.73
	OR	1.15	1.20	0.80
	95 % CI	0.84–1.59	0.85–1.69	0.21–3.00
Autism	*P* value	0.010*	0.063	0.001*
	OR	1.40	1.32	4.64
	95 % CI	1.08–1.81	0.98–1.77	1.56–3.81
Schizophrenia	*P* value	0.024*	0.117	0.002*
	OR	1.09	1.25	3.91
	95 % CI	0.90–1.31	0.95–1.65	1.45–10.55
Bipolar	*P* value	0.007*	0.057	0.0004*
	OR	1.43	1.34	6.21
	95 % CI	1.10–1.87	0.99–1.80	1.82–21.24

*Considered as significant

and ideally of the brain tissue, other mechanisms should also be explored for the involvement of the two SNPs in the development of disease.

There are limitations to our study, such as inability to perform a principal component analysis for testing population stratification, due to lack of the necessary data. However, both the case and control samples were collected from same institutions and from several centers across Iran.

Because of the differential association observed in two different groups of disorders in our study, it can be suggested that rs12456492 and rs16976358 may have differential effects on the *RIT2* gene expression or function. More studies are warranted to identify the function of the two SNPs and their correlation with disease phenotypes.

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Compliance with Ethical Standards Written informed consent was taken from all participants. The study was approved by the ethic committee at Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Conflict of Interest The authors declare that they have no conflict of interest.

Competing Financial Interests The authors declare no competing financial interests.

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