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ISSN: 0976-3031

International Journal of Recent Scientific Research
Vol. 6, Issue, 6, pp.4894-4897, June, 2015

International Journal of Recent Scientific Research

RESEARCH ARTICLE

FREQUENCY OF G2019S LRRK2 MUTATION IN PARKINSON'S DISEASE AMONG DIVERSE POPULATIONS

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ARTICLE INFO

Article History:

Received 14th, May, 2015
Received in revised form 23th, May, 2015
Accepted 13th, June, 2015
Published online 28th, June, 2015

Key words:

Disorder, LRRK2, Mutation, Parkinson Disease

ABSTRACT

Parkinson's disease (PD) is a chronic and progressive movement disorder. The LRRK2 G2019S mutation is the most frequent known cause of familial and sporadic Parkinson's disease. Knowledge of its frequency distribution is essential for clinical and molecular research as well as genetic counseling. The objective of this review is to assess the frequency distribution of G2019S mutation causing Parkinson's disease in different populations including homogeneous ethnic groups or sub-groups of patients such as in Asia, Southern European such as Italy, Ashkenazi Jews, and North Africa. For comparison purposes, an article containing a critical analysis of this G2019S mutation distribution worldwide was reviewed. Results depicted a heterogeneous distribution with high frequencies in North African and Ashkenazi Jewish populations. Frequencies ranged from the no cases to 35.7% in sporadic and 42% in familial North-African Arab patients. Estimated frequencies were found to be variable, which may reflect ethnic differences and methodological inconsistencies. Hereby, it can be concluded that G2019S mutational frequency may vary amongst different ethnic races.

INTRODUCTION

Parkinson's disease is a progressive neurological condition (Pankratz *et al*., 2002). People with Parkinson's disease don't have enough of a chemical called dopamine because some nerve cells in their brain have died. Without dopamine people can find that their movements become slower so it takes longer to do things. The loss of nerve cells in the brain causes the symptoms of Parkinson's disease to appear (Parkinsons.org.uk, 2015). Trembling of feet and arms, stiffness of limbs, failure to move, disability in thinking are few symptoms of Parkinson's disease (Genetics Home Reference, 2015).

Most cases of Parkinson's disease probably result from a complex interaction of environmental and genetic factors. These cases are classified as sporadic and occur in people with no apparent history of the disorder in their families. The cause of these sporadic cases remains unclear (Genetics Home Reference, 2015). Approximately 15 percent of people with Parkinson disease have a family history of this disorder. Familial cases of Parkinson's disease can be caused by mutations in the LRRK2, PARK2, PARK7, PINK1, or SNCA gene, or by alterations in genes that have not been identified. Mutations in some of these genes may also play a role in cases that appear to be sporadic (not inherited) (Genetics Home Reference, 2015).

The role of genetic factors in the origin of Parkinson's disease (PD) has long been considered unimportant, but a series of recent discoveries are dramatically changing this view (Bonifati, 2006). Recent studies reported an astonishing high prevalence of a single mutation in leucine-rich repeat kinase 2 (LRRK2), G2019S, in North African Arabs and Ashkenazi Jews with PD (Bonifati, 2006). LRRK2 gene is located from base pair 40,225,010 to base pair 40,369,284 on chromosome 12 at position 12, donated as 12p12. (Figure 1) (Genetics Home Reference, 2015)

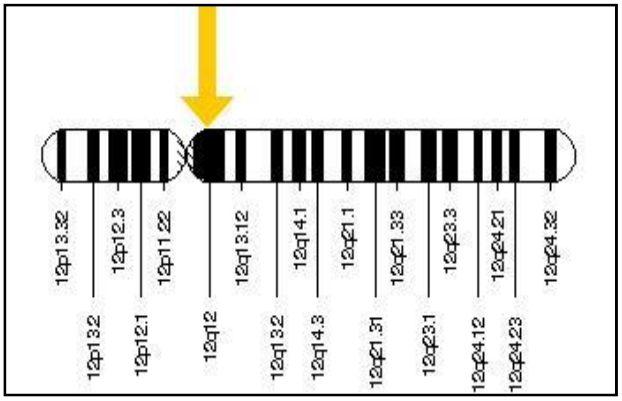

Figure 1 Location on the LRRK2 gene on the chromosome (Genetics Home Reference, 2015)

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Mutations in the LRRK2 gene were first identified in 2004 in families with autosomal-dominant PD; soon thereafter, the G2019S mutation was identified by several groups as a common cause of this disease, it has been found in approximately 5–6% of familial PD in addition to approximately 1–2% of sporadic PD in several European and US populations (Bonifati, 2006). This mutation leads to replacement of the amino acid glycine with the amino acid serine at protein position 2019 (written as Gly2019Ser or G2019S) (Genetics Home Reference, 2015)

The prevalence of the G1019S mutation was investigated in certain population group;

1. **Asian populations**
2. **Southern European populations such as Italy, Spain and Portugal**
3. **Ashkenazi Jewish**
4. **North African Mediterranean populations.**

METHODS AND MATERIALS

Asian populations such as Chinese & Indians

In 2005, E.K. Tan and his fellow colleagues from the Clinical Research and Health Screening, Singapore General Hospital performed analysis on a total of 1000 subjects to determine the presence of LRRK2 6055G > A (G2019S) (located in exon 41) (Tan *et al*., 2005).

Southern European populations such as Italy

In 2006, a total of 2976 unrelated consecutive Italian patients with degenerative Parkinson's disease were screened for mutations on exon 41 (G2019S, I2020T). Demographic and clinical features were compared between LRRK2-carriers and non-carriers. Family history in LRRK2-carriers was evaluated during formal genetic counseling (Goldwurm *et al*., 2006).

Ashkenazi Jewish

In Department of Neurology at the Beth Israel Medical Center in New York City, scientists screened 120 unrelated Ashkenazi Jewish patients with Parkinson's disease in 2006. Specialists in movement disorders performed clinical assessments, and all subjects met stringent diagnostic criteria for Parkinson's disease. Ancestry was determined according to the patients' self-descriptions, and all but one patient (who reported being 50 percent Sephardic) reported that both parents were Ashkenazic (Ozelius *et al*., 2006).

The Unified Parkinson's Disease Rating Scale, the Hoehn–Yahr scale, and a diagnostic checklist were completed, and peripheral blood or a cheek swab for DNA analysis was obtained with written informed consent. An Ashkenazi Jewish control group of 317 persons consisted of 113 parents from unrelated families with DYT1 dystonia and 16 from families with dysautonomia, and 188 unrelated Ashkenazi Jewish subjects from the Einstein Aging Study. All were of Ashkenazi Jewish ancestry according to self-report, were examined, and did not have Parkinson's disease at the time blood was drawn. The institutional review boards of both the Beth Israel Medical Center and the Albert Einstein College of Medicine approved this study (Ozelius *et al*., 2006).

DNA was extracted from white cells or buccal cells with the use of standard techniques. The G2019S mutation in LRRK2 (G6055A single-nucleotide polymorphism [SNP] in exon 41), two other coding SNPs, rs1427263 and rs11564148, and five microsatellite markers were genotyped (Ozelius *et al*., 2006).

North African Mediterranean populations

In 2006, the researchers in a study worked on 10 patients and 69 controls. They combined their results with the previous study in which the number of patients was 17 and number of controls was 82. Blood samples were drawn for genetic analysis (Lesage *et al*., 2006).

RESULTS

Asian population

Genetic analysis revealed none of the 1000 study subjects carried the G2019S mutation. There were 675 PD patients and 325 healthy controls. For PD patients, there were 570 (84.4%) ethnic Chinese, 51 Malays (7.6%), 40 (5.9%) Indians and 14 (2.1%) mixed ethnicity. 202 (29.5%) of them were young onset PD (age of onset < 55 years). In 58 (8.6 %) PD patients, there was a positive family history with one or more affected relatives (Tan *et al*., 2005).

Southern European population such as Italy

Among the 2976 Italian patients included in the study, 2523 fulfilled the criteria for diagnosis of PD. LRRK2 mutations were identified in 40 of 2523 PD patients (1.6%) and not in other primary Parkinson's disease syndromes. Among which no major clinical differences were found between LRRK2-carriers and non-carriers. (Table 1) (Cilia *et al*., 2014)

Table 1 Distribution Table for Parkinson's disease for Italian Populations (Cilia et al., 2014)

LRRK2 mutations identified in PD patients.			
	Number of PD patients	**Mutation**	**N carriers (%)**
	2523	G2019S	**34 (1.35%)a**
I2020L	1 (0.04%)		
Exon 31	1088	R1441C	4 (0.37%)b
R1441H	1 (0.09%)		
Total	2523	All	40 (1.59%)

G2019S was the most frequent mutation (1.35%). No mutation was found in all the other patients with alternative clinical diagnoses (N = 453). LRRK2 mutations were significantly more frequent in familial than in sporadic PD cases (Cilia *et al*., 2014).

Ashkenazi Jewish

Among 120 Ashkenazi Jewish patients with Parkinson's disease, the LRRK2 G2019S mutation was detected in 22 (18.3%). The mutation was present in 11 of 37 subjects with a familial pattern (29.7 %) and 11 of 83 subjects with no family

history of Parkinson's disease (13.3 %). Among the 317 Ashkenazi Jewish control groups, only four people were identified as carrying the mutation (1.3 %) (Guedes *et al*., 2010).

Table 2 North African Population Distribution Table for Parkinson's Disease (Lesage et al., 2006)

Frequency of the G2019S Mutation in North African Arabs with Familial and Sporadic Parkinson's Disease and in Ethnically Matched controls.		
Types of Case and Study No. of mutation/total no. (%)	Patients	Control P Value
Familial	0/82	<0.001
Previous study 7/17 (41)	2/69 (3)	0.01
Present study 3/10 (30)	10/27 (37)	2/151 (1)
Combined studies		<0.001
Sporadic Present study20/49 (41)	2/151 (1)	<0.001
P values were calculated with the use of Fisher's exact test.		
Controls are from the present study (69) and the previous study (82).		

North African Mediterranean countries

Results depict that the frequency of the G2019S mutation was unusually high. It was around 37 percent among North African Arabs with familial Parkinson's disease and 41 percent in those without a family history of the disease (Table 2) (Lesage *et al*., 2006).

Although it is present at a low level in Arab controls, the G2019S mutation nevertheless constitutes a significant risk factor for Parkinson's disease in this population group (Lesage *et al*., 2006).

DISCUSSION

In 2010, an article was further evaluated for comparison purposes. This article highlights the frequency distribution of G2019S mutation globally.

Table 3 Worldwide Distribution Table for Parkinson's Disease (Guedes *et al*., 2010)

Table 3a Distribution of Parkinson Disease in Europe.

Table 3a	**Total PD**		**Familial cases**		**Sporadic cases**		**Controls**	
	N	**Mean% (95%Cl)**	**N**	**Mean% (95%Cl)**	**N**	**Mean% (95%Cl)**	**N**	**Mean% (95%Cl)**
Europe								
Norway	435	2.1	65	9.2	370	0.8	519	X
Swedan	284	1.4	84	X	200	2	305	0.3
Germany	1828	0.8	260	1.3	1346	0.6	1466	X
Holland	187	X	28	X	159	X		
Belgium	304	X	55	X	259	X	278	X
Poland	174	X	21	X	153	X	190	X
Russia	578	1.6	98	6.8	480	0.6	450	X
Austria	162	X	39	X	123	X	288	X
UK	1119	1.5	192	2	445	0.2	1951	X
Ireland	272	0.7	35	2.9	237	0.4	330	X
France	555	1.3	155	1.3	400	1.4		
Portugal	262	6.1	53	12.6	209	4.3	227	X
Spain	1110	5.1	391	7.9	719	3.9	616	0.4
Italy	2886	1.7	604	3.5	2282	1.2	605	X
Sardinia	454	1.4	78	0.8	376	1.5	263	0.9
Greece	604	0.1	100	X	504	0.1	395	X

Table 3b Distribution of Parkinson Disease in Middle East and North Africa

Table 3b	**Total PD**		**Familial cases**		**Sporadic cases**		**Controls**	
	N	**Mean% (95%Cl)**	**N**	**Mean% (95%Cl)**	**N**	**Mean% (95%Cl)**	**N**	**Mean% (95%Cl)**
Middle East and North Africa								
Israel (AJ)	344	14.8	96	26	246	11.8	841	2.4
Israel (non-AJ)	112	2.7					957	0.4
North African Arabs (ATM)	538	39	132	40.3	406	33	588	1.5
Nigeria	57	X	9	X			51	X

Table 3c Distribution of Parkinson Disease in North America and South America

Table 3c	**Total PD**		**Familial cases**		**Sporadic cases**		**Controls**	
	N	**Mean% (95%Cl)**	**N**	**Mean% (95%Cl)**	**N**	**Mean% (95%Cl)**	**N**	**Mean% (95%Cl)**
North America								
Canada	476	0.6	157	2	319	X	474	X
USA (C)	3930	1.9	805	3.5	1096	0.4	6345	X
USA (H)	20	5	6	16.7	14	X	54	X
USA (J)	329	13	67	23.4	259	10.2	415	1.7
South America								
Brazil	237	2.8	62	6.9	175	1.6	125	X
Chile	166	3	29	3.4	137	2.9	153	X
Peru	240	0.4	4	X	236	0.4		
Uruguay	125	4	29	0.3	96	4.2		

Table 3d Distribution of Parkinson Disease inAsia and Australia

Table 3d	Total PD		Familial cases		Sporadic cases		Controls	
	N	Mean% (95%CI)	N	Mean% (95%CI)	N	Mean% (95%CI)	N	Mean% (95%CI)
Asia								
India	778	0.1	58	X	718	0.1	212	X
Taiwan	994	X	27	X	967	X	213	X
Singapore	570	X					325	X
South Korea	525	X	29	X	436	X	100	X
Japan	586	0.3	32	X	554	0.4	317	X
Australia								
Australia	904	1.9	282	4.6	622	0.2		

The frequency data of each country were grouped by six main world regions: Europe, Africa and the Middle East, North America, South America, Asia and Australia. (Table 3) (Guedes *et al*., 2010) According to worldwide distribution of this mutation, Tunisian Arab–Berber patients had the highest frequency for G2019S in familial cases (42%). Arab sporadic patients from North Africa had the mutation in 35.7% of the cases (Guedes *et al*., 2010). Furthermore, the highest frequency of the mutation in controls was found in Middle Eastern and North African populations. In Europe, a study from Cantabria, in Spain, reported the greatest frequency, with the mutation occurring in 18.7% of the familial cases and 6.1% of sporadic cases. These values were closely followed by those from Portugal and Italy. In the United States, Jewish and Hispanic communities were the most prevalent carrier sub-groups. However, Asian countries, as a group, presented with the lowest frequency of G2019S (Guedes *et al*., 2010). Comparing these results with studies reviewed in this article, similar outcomes are observed.

CONCLUSION

Based on the results, G2019S mutation is rare (at least < 0.1%) in Asian cohort. As a growing number of studies is reported, Arab–Berber North-African patients, Middle East Mediterranean countries and other studied Ashkenazi Jewish populations have been confirmed as leaders in frequency for G2019S, not only in familial, but also in sporadic PD, followed by the Southern European countries Spain, Portugal and Italy.
Based on the studies analyzed in this review, LRRK2 G2019S mutation is confirmed highly in North-African patients and Ashkenazi Jewish populations and lowest in Asia. However, this mutation is one of a small number of LRRK2 mutations proven to cause Parkinson's disease. Therefore, the frequency of G2019S can be highly heterogeneous between populations of different genetic backgrounds.

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