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Original Synthetic Report

Origin of the G2019S mutation associated to Parkinson's disease in Europeans and in North Africans

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Abstract - ***Background***: The G2019S mutation in the LRRK2 gene is associated with 1-2% of sporadic Parkinson's disease (PD) cases. In Europe, the prevalence of G2019S in sporadic PD patients depends on the population, being relatively high in Spain and Portugal but low in northern Europe. ***Aim***: To drawn up a European frequency map of the G2019S mutation. ***Material and Methods***: A map of G2019S mutation isofrequences in Europe has been drawn up using the Spatial Analyst program, using the Kringing procedure. A total of 21 studies and publications on G2019S screening in European sporadic PD patients are taken in consideration in the present study. ***Results*:** This map shows a gradient of decreasing values from Iberia to peripheral countries. We have interpreted this geographic distribution of G2019S frequencies in Europe as the result of Berber and Arab invasions and expansions during the 8th century. An haplotype analysis, based on six microsatelliste markers, flanking on both sides of the 6055>A mutation, was performed in twenty G2019S carriers. A greater proportion of the short (SFH) and minimum–shared (MSH) haplotypes were found in Moroccan Berbers carriers. ***Conclusion***: The geographical origin of the G2019S mutation is located in North Africa; Moroccan Berbers could be the initial carriers of the mutation that they have early transmitted during history.

Key words - Parkinson's disease, G2019S *LRRK2* mutation, Gene map of G2019S frequencies in Europe, Dates and origins of G2019S, Berberian origin of the mutation.

Introduction

Parkinson's disease is a heterogeneous movement disorder characterized by the progressive degeneration of dopaminoergic neurons within the substancia nigra. PD is mainly considered as a sporadic disease, but various hereditary forms of parkinsonism have been recognized as well. In fact, approximately 90-95% of the patients have sporadic disease, and 5-10% represents family cases.

In the race to find the genetic key component of PD, mutations in the leucine-rich repeat kinase 2 (LRRK2) gene have come along as a major breakthrough. The LRRK2 gene was originally mapped (Funayama et al., 2002) in the PARK8 region located on chromosome 12p11.2-q13, in a large Japanese family with autosomal dominant (late-onset) PD (AdPD). The identification of pathogenic mutations in the LRRK2 gene in families with AdPD from various populations (Paisan-Ruiz et al., 2004; Zimprich et al., 2004) heralds an exciting time in the field of neurogenetics. Today, more than twenty LRRK2 mutations have been linked to AdPD, accounting for a significant fraction of sporadic PD cases, and for 6-7% of familial PD (Berg et al., 2005). So far the most common LRRK2 mutation is the G2019S mutation, which accounts for 2-5% of the AdPD cases, depending on the initial populations investigated (Nichols et al., 2005; Di Fonzo et al., 2005; Gilks et al., 2005; Kachergus et al., 2005).

Remarkably, the G2019S mutation is responsible for around 20% of the occurrence of PD cases in Ashkenazi Jewish patients, and up to 40% of PD cases in North African populations (Ozelius et al., 2006: Lesage et al., 2006). The frequency of G2019S LRRK2 is very high, at 37-41%, in familial and sporadic PD populations from North-African countries of Morocco, Algeria and Tunisia, if compared with European and American countries (Lesage et al., 2005a; Ishiara et al., 2006; Ishiara et al., 2007). In our own study on sporadic French PD (Funalot et al., 2006) one of the two patients bearing the G2019S mutation is of Berberian origin. In Europe, the frequency of G2019S appears to be relatively high in northern Spain (Infante et al., 2006; Gaig et al., 2006; Mata et al., 2006) and Portugal (Bras et al., 2005; Ferreira et al., 2007), but low in northern Europe (Kachergus et al., 2005).

This paper is reviewing twenty one studies on G2019S screening in European sporadic PD patients, in order to drawn up a frequency map of the mutation in Europe; our interpretation is that the European pattern observed for G2019S frequencies results from an influence of North African populations.

Subjects and localities

A total of 21 studies and publications on G2019S screening in European sporadic PD patients are taken into consideration into the present study (Table 1). To do it, we have searched the usual database such as PubMed and so on systematically with key words: LRRK2, G2019S, Europe, and every single name of the European countries. Studies realized and papers published before the end of 2007 have been included. Thirteen European countries (Figure 1) are concerned by our synthesis: Portugal (Bras et al., 2005; Ferreira et al., 2007), Spain (Infante et al., 2006; Gaig et al., 2006; Mata et al., 2006; Gao et al., 2009), Italy (Marongiu et al., 2006; Civitelli et al., 2007; Floris et al., 2009), France (Funalot et al., 2006), Austria (Haubenberger et al., 2007), Germany (Berg et al., 2005), Poland (Bialecka et al., 2005), England (Williams-Gray et al., 2006), Norway (Aasly et al., 2005), Sweden (Carmine Belin et al., 2006), Russia (Pchelina et al., 2006), Ukrainia (Illiarioshkin et al., 2007) and Greece (Spanaki et al., 2006; Kalinderi et al., 2007; Xiromerisiou et al., 2007)

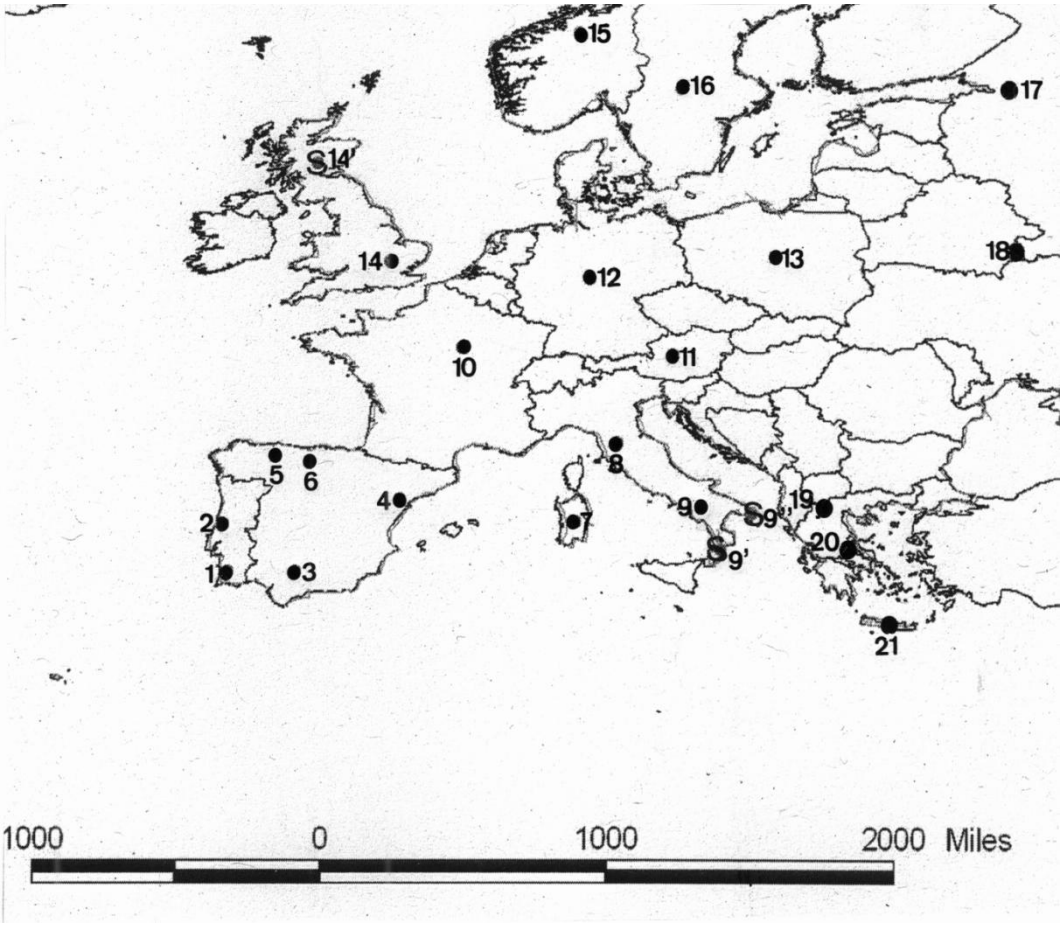
This synthesis totalizes a number of 5273 sporadic PD patients screened; seventy three (1.3%) of them are heterozygous for the mutation. Table 1 gives, for each location, 95% confidence intervals of the percentages according to the Poisson distribution.

Table 1. G2019S mutation carrier frequency (there are no homozygotes for the mutation in the samples) in twenty-one European populations of sporadic Parkinson's disease patients.

Population number	***Country***	***Heterozygous individuals/ N***[a]	***Frequency (range)***[b]	***References***
1	Portugal 1	5/102	4.90 (1.59-11.44)	Bras *et al.,* 2005
2	″	4/107	3.83 (1.02-9.57)	Ferreira *et al.,* 2007
3	Spain	6/175	3.43 (1.26-7.46)	Gao *et al.,* 2009
4	″	7/208	3.37 (1.35-6.93)	Gaig *et al.,* 2006
5	″	5/175	2.86 (0.93-6.67)	Mata *et al.,* 2006
6	″	5/82	6.09 (1.98-14.23)	Infante *et al.,* 2006
7	Italy	6/380	1.59 (0.58-3.44)	Floris *et al,* 2009
8	″	11/822	1.32 (0.67-2.39)	Marongiu *et al.,* 2007
9	″	11/449	2.44 (1.22-4.38)	Civitelli *et al.,* 2007
10	France	2/103	1.95 (0.24-7.01)	Funalot *et al.,* 2006
11	Austria	0/146	0 (0-2.53)	Haubenberger *et al.,* 2007
12	Germany	1/337	0.03 (0.01-1.65)	Berg *et al.,* 2005
13	Poland	0/153	0 (0.16-4.72)	Bialecka *et al.,* 2005
14	England	1/445	0.02 (0.01-1.25)	Williams-Gray *et al.,* 2006
15	Norway	1/368	0.03 (0.01-1.51)	Aasly *et al.,* 2005
16	Sweden	4/284	1.40 (0.38-3.61)	Carmine Belin *et al.,* 2006
17	Russia	1/157	0.64 (0.02-3.55)	Pchelina *et al.,* 2006
18	Ukrainia	2/191	0.73 (0.08-2.48)	Illiarioshkin *et al.,* 2007
19	Greece	0/180	0 (0-2.05)	Kalinderi *et al.,* 2007
20	″	1/235	0.42 (0.01-2.37)	Xiromerisiou *et al.,* 2007
21	″	0/174	0 (0-2.12)	Spanaki *et al.,* 2006

[a] *Numbers of patients in each population studied .*[b] *Confidence interval (0.05 level ; Poisson distribution).*

Figure 1.
Map of Europe, indicating the locations (Table 1) of the 21 populations studied. Locations S9', S9'' and S14' correspond to the added artificial points (see table 2).



Results and Discussion

A European frequency map of the G2019S mutation

The map of G2019S mutation isofrequencies in Europe has been drawn up with the Spatial Analyst program ("Arcview" software), by using the classical Kringing procedure. We have used the inverse distance weighting (IDW) method-which is well adapted to scarce data - with a power of 2 (so that the influence is greater at large distances). The grid has 250 rows and 355 columns; five neighbours are calculated for each quadrant.

Table 2 gives the geographic coordinates of the points used to drawn up the map. Twenty one points represent the towns or regions, in each country, where the patients were recruited for each study (the middle geographic points represent each country, when not subdivided). To equilibrate the map, three additional artificial points (two at the toe and heel –a "shoemaking" expression- of the Italian boot and one for Scotland) were added. Each geographic point is represented by an attributed mean frequency (one number after the first decimal) of the G2019S mutation percentages.

Figure 2 shows the European distribution of the G2019S frequencies. The map is divided into 10 artificial discontinuities, according to the mutation percentages. The most elevated value of G2019S frequencies (>5.4%) corresponds to the northern part of Iberia. In West Europe, mutation percentage values decrease in the peripheral countries from this focus. All the values in the remaining part of Iberia (except a little region in the north of Portugal) and in the south of France are comprised between 2.7 and 5.4%. In France the Pyrenean Mountains seem to constitute a natural barrier, as the frequencies in the great South-West of this country are comprised between 2 and 2.7%; a similar value has been found in the south of Italy. All the remaining parts in these last two countries, as well as in Sardinia and in Belgium, have lower values of the mutation frequencies (comprised between 1.3 and 2%). In Germany and Poland, the frequencies fall down to values comprised between 0.6 and 1.3%. Frequencies are very low in the central part of Germany, in Denmark, England, and the south of Scandinavia. Frequencies are also low, or very low, in Central Europe, West Russia and Greece.

Table 2. Geographic coordinates of the various populations (and artificial points) used for the drawing up of the map.

Population number	*Country*	*Town/region*	*Mean frequency*	**Geographic coordinates**[b]	
				x	*y*
1	Portugal	Coimbra	4.9	37.7	-8.4
2	″	Lisboa	3.8	39.9	-8.6
3	Spain	Sevilla	3.4	37.7	-5
4	″	Catalogna	3.4	41	0.3
5	″	Asturias	2.9	43	-6
6	″	Cantabria	6.1	42.7	-4.3
7	Italy	Sardinia	1.6	40	9.2
8	″	Center	1.3	43.6	11.3
9	″	Napoli	2.4	40.6	15.5
9'[a]	″	(toe)	2.4	38.7	16.5
9"[a]	″	(heel)	2.4	40.3	18
10	France	Rheims	2	48	3.5
11	Austria		0	47.6	14.1
12	Germany		0	51.2	9.9
13	Poland		0	52.2	19.2
14	England		0	52	-0.2
14'[a]	″	(Scotland)	0	56.6	-3.9
15	Norway		0	62.5	9.4
16	Sweden		1.4	60	14.5
17	Russia	St Petersburg	0.6	60	31.1
18	Ukrainia		0.7	52.3	31.3
19	Greece	North	0	40.7	21.7
20	″	Thessaly	0.4	38.6	22.8
21	″	Crete	0	35.2	24.8

[a] *Artificial points: S9', the toe of the Italian boot; S 9", the heel of the boot; S14', Scotland.*
[b] *x: latitude; y: longitude north.*

Figure 2.
European distribution of the G2019S frequencies. The various nuances of grey correspond to artificial discontinuities, with density percentages as indicated.

Various ages and origins of G2019S

Most of the G2019S carriers, including Europeans, Ashkenazi Jews and North African Arabs and Berbers, share a common haplotype –a section of chromosome 12q12 that contains several microsatellite and single nucleotide polymorphisms flanking the LRRK2 6055G>A mutation- which is consistent with one ancestral founder (Kachergus et al., 2005; Lesage et al., 2005b; Lesage et al., 2006). As a general rule, the length of the haplotype and the carrier frequency of the genetic markers that it contains can indicate the age and origin of the associated mutation, as for example in the case of the triple-A syndrome (Génin et al., 2004).

The high prevalence of the 6055G>A mutation in Ashkenazi Jews and in North African Arabs has led to the hypothesis that the mutation originated in the Middle East (Ozelius et al., 2006). In a first study (Lesage et al., 2005b), based on only six families of North African or European origin carrying the mutation, it was estimated that the corresponding individuals had shared a common founder for ≈ 725 years. But, given the fact that the mutation is widely distributed across Europe and occurs at a high frequency among Ashkenazi Jews and North African Arabs, that relatively recent estimated date is difficult to reconcile with established patterns of human migration for Ashkenazims (Columbo, 2000; Niell et al., 2003).

This first estimate was tested in a second study (Zabetian et al., 2006), based on the frequencies of 25 microsatellite and single nucleotide polymorphism markers in 22 families with the mutation. Two distinct haplotypes were observed: haplotype 1, which is present in 19 families of Ashkenazi Jewish and European ancestry, and haplotype 2 which occurs in 3 European families; using a maximum-likelihood method, it was estimated in that study that families with haplotype 1 had shared a common ancestor for 2250 years ago (95%, CI 1650-3120), using a 30 years intergeneration interval, whereas those with haplotype 2 appeared to share a more recent founder.

If individuals with haplotype 1 alone are considered, those data are consistent with the hypothesis that European, Ashkenazi Jews and North African Arabs with the mutation arose from a common Middle Easter founder (Ozelius et al., 2006). That best estimate of a common ancestor living 2250 years ago better corresponds to a time when the ancestral Jewish population and some Arab communities existed in close proximity, during the period of the earlier Jewish Diaspora (586 BC to 70 AD).

Similar age estimates have been calculated for another mutation responsible for a disease at a high frequency among Ashkenazi and Sephardi Jews and Arabs, the mutation corresponding to one form of factor XI deficiency (Goldstein et al., 2003).

A third study, more recently published (Warren et al., 2008), concerned 39 European American PD families studied for 2 microsatellite and 39 single nucleotide polymorphisms flanking the LRRK2 gene. Haplotype 2 occurred in some of these families. In that study haplotype 1 was found in 21 Tunisian subjects (of Arab-Berber ethnicity) homozygous for the G2019S mutation. Using a 30-year intergeneration interval the common ancestor can be traced back to 3120 (95%, CI 2340-4620) years ago, an age estimates indicating that the variation occurred at a slightly (because the two confidence intervals overlap) earlier time than the one calculated in the second study.

Berbers, Arabs and Jews: comparisons between lengths of the founder haplotype

The common haplotype associated with the G2019S mutation is shorter (in the sense that the length of the haplotype determined by variants at microsatellite polymorphisms is smaller in this patient, compared to that of the founder haplotype of the other French patient) in our French PD patient of Berberian origin (Funalot et al., 2006).

To obtain a precise estimate of G2019S frequencies in populations with elevated incidence of mutation carriers, we have tested for the presence of the mutation in the south Mediterranean countries (Change et al., 2008). Three thousand and one hundred healthy European subjects originating form 15 populations of southern Europe were compared for the G2019S incidence with 597 healthy Arab subjects originating from five populations in North Africa (Libya, Tunisia, Algeria, Berbers from Morocco and non-Berber Moroccans) and with 361 healthy Sephardi Jews subjects from five other populations. The main incidence of G2019S carriers is 1/46 in our sample of North African Arabs, the most elevated carrier incidence (1/30) being found in Moroccan Berbers; a relatively elevated incidence (1/72) has also been found in our sample of Sephardi Jews. That contrasts notably with the results we had found (incidence of 1/1550) in the European subjects.

An haplotype analysis, based on six microsatellite markers, flanking on both sides the 6055G>A mutation, was performed in the twenty G2019S carriers that were found in the above mentioned study. A greater proportion of the short (SFH) and minimum-shared (MSH) haplotypes were found in Moroccan Berber carriers, compared to Arab, Sephardi Jew and European subjects (Change et al., 2008): while the two European G2019S carriers are of the extended founder haplotype (EFH), two on eight of the North African non-Berbers carriers only are MSH versus three on the five Moroccan Berber carriers (the resting two being SFH); among Sephardi Jew carriers, one on the six only is MSH and another one is MSH. This result indicates that the mutation might have originated earlier in this ethnicity (Berber) and in this country (Morocco); Moroccan Berbers are also the population of the highest incidence of the G2019S mutation, compared to others.

Discussion about the Arab and Berber origins of G2019S

So, it appears that G2019S mutation in the LRRK² gene is consistently more frequent in North African Arabs than in Europeans with PD (Benamer et al., 2008), whether familial or sporadic, suggesting an important genetic contribution to the causation of PD in this group of peoples. The mutation is also at a relatively high frequency in unrelated normal Arab and Berber subjects in North Africa (Change et al., 2008); haplotypes associated to the mutation are shorter in Moroccan Berbers, indicating that they could be the earlier initial G2019S carriers.

North Africa and the Iberian Peninsula are separated by more an approximately 15 km-long Channel at the Gibraltar Strait, making the region a potential migration route between North Africa and Europe. We explain the elevated incidence of the G2019S mutation in Iberia by such a gene flow. Some admixture events took place in historical epochs that were reported to have left imprint in the Iberian background, namely of North African origin, resulting from the Moslem invasion during the 8th century. Historically documented contact began dramatically in 711 CE, when an Arab-Berber army, composed mainly from Berbers and led by the famous Berber Tariq Ibn Ziyad, crossed from Morocco, winning a key battle the following year.

Within only four years, the invaders had conquered the entire peninsula, with the exception of the northern Basque country, Cantabria, Galicia, Asturias, and most of the Pyrenees in the north of Spain and in the south west of France (which remained largely unoccupied). Arab and Berber occupied Iberia for more than five centuries, with a gradual withdrawal toward Andalusia in the south and a final expulsion in 1492 (Conrad, 1998).

The peculiarities of geographic distribution of G2019S frequencies are represented in figure 2, mainly: (i) the Iberian preponderance, (ii) decreasing frequencies from Iberia to southern France and other European countries, are in accordance to the explanation we proposed above.

However, when we look at the frequencies of the mutation in Spain, we can observe that the highest values (6.1%) are in the North of the country, and that values in the South (Sevilla, 3.4%) are lower than those observed in the North. This fact needs an explanation, because the North of Spain was, in terms of history, far from the North African influence as we state. We think that, probably, this bias represents an artefact due to the importance in ranges of calculated frequencies (table 1), inherent to those of low values percentages.

In conclusion, we have constructed a map of G2019S mutation frequencies in sporadic European Parkinson's disease patients. This map shows a gradient of decreasing G2019S frequencies from Iberia to peripheral Europeans countries. We have interpreted this geographic distribution of G2019S frequencies as the result of Berber and Arab expansions in Europe since the 8th century. That is based mainly on the fact that G2019S incidences in populations, very low in Europe (1/1550), attained much higher values in North Africa (1/64 in Tunisia, 1/51 in Morocco and 1/47 in Algeria). Haplotypes including the mutation are shorter in Moroccan Berbers compared to non-Berber Moroccans and Sephardi Jews; this indicates that the Moroccan Berbers could be the earliest G2019S carriers.

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