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Genealogical studies in *LRRK2*-associated Parkinson's disease in central Norway☆

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ABSTRACT

The most common mutation related to Parkinson's disease (PD) is the p.G2019S mutation in the *LRRK2* gene. Global population frequencies and crude estimates of haplotype conservation suggest most carriers are related. A total of 671 Norwegian PD patients and 215 of their family members were screened for the *LRRK2* p.G2019S mutation. Twenty-one PD cases and 44 family members were positive for the mutation and all could be traced back to 10 different families. A genealogical study employed data from the Norwegian National Family Record Centre, local parish registers and population censuses. A common ancestor couple (living between 1580 and 1650) was found in six families, and two other families were associated by intermarriage. The remaining two families could not be traced back to either of these ancestors, though chromosome 12q12 haplotype analysis showed p.G2019S carriers shared alleles for 15 markers in the *LRRK2* region.

The study provides support for a common ancestor in Norwegian families with *LRRK2* p.G2019S parkinsonism. The mutation was probably introduced to Norway through tradesmen from Europe. The extended pedigree that now links modern day carriers may help in mapping penetrance modifiers.

1. Introduction

The *LRRK2* p.G2019S mutation is the commonest known form of genetically-determined PD [1–3]. The majority of patients with p.G2019S parkinsonism have clinical features indistinguishable from sporadic PD, with asymmetric presentation, predominant resting tremor, bradykinesia, rigidity and a good response to dopaminergic therapy. The non-motor autonomic, psychiatric, and cognitive symptoms are usually reported to be mild [4,5], though not in all cases [6]. The most common neuropathology is Lewy body disease, although pleomorphic pathology has been described [7–9].

The frequency of the p.G2019S substitution varies, being highest in North African Arabs and Ashkenazi Jews [10,11], but is rare in Asia [12]. Across Europe the frequency of p.G2019S parkinsonism has not been rigorously evaluated (estimated 1–4%) [13–17]. Three different haplotypes have been described in various ethnic groups, suggesting common founders with at least three different founding events [6,10,11,18–21]. Haplotype 1, the most common, is a 143 kb segment, found in North African Arabs, Ashkenazi Jews and American Europeans [19]. Several groups have tried to identify the common founder in these populations [19,22–24]. Haplotypes 2 and 3 are distinct and rarer. Type 2 has been reported in cases from Western Europe, and type 3 was described in a Japanese population [20].

A considerable number of PD cases with the *LRRK2* p.G2019S mutation have been found in central Norway [5]. A high community-based incidence of 3.1% in a relatively small geographical area suggested a common founder effect [5]. In this report we provide genealogic ancestry for these PD patients.

2. Patients and methods

A total of 671 consecutive PD patients, all ethnic Norwegians, have been longitudinally followed from 1998 by a movement disorder specialist (JOA) at the outpatient clinic of the Department of Neurology, St Olav's University Hospital, Trondheim, and two other clinics within 200 miles of Trondheim. The diagnosis of PD was consistent with probable PD according to the Gelb criteria [25]. First degree family members of all PD patients were invited to participate in the study, and up to 2004 when *LRRK2*-associated PD was discovered, 117 had agreed to take part. Once *LRRK2*-PD was identified, family members, including children and siblings of *LRRK2*-affected families, were asked to participate ($n = 98$). All participants signed informed consent for genetic study, approved by the local ethical review board, and the demographic data are presented in Table 1.

Peripheral blood was drawn and screened for several pathogenic *LRRK2* mutations (p.R1441C, p.R1441G, p.R1441H, p.Y1699C, p.G2019S and p.I2020T) in the first 435 PD patients, as described previously [5]. The remaining 236 PD patients and all family members were tested specifically for p.G2019S. Patients who tested positive

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Table 1
Demographic data of study individuals.

	N	Sex (M/F)	Age	AAO (years)	Duration
Patients with PD	671	414/257	67.2 ± 11.0	59.4 ± 11.2	7.9 ± 6.8
Positive for p.G2019S	21 (16)	10/11	73.1 ± 10.0	61.2 ± 10.0	12.4 ± 7.8
Healthy family members	215[a]	116/99	54.8 ± 14.8	–	–
Positive for p.G2019S	44	30/14	52.0 ± 14.4	–	–

Five affected PD carriers are deceased, so "age" and "duration of disease" is applicable in 16 cases but "age at disease onset (AAO)" in 21 cases.
[a] 98 of these family members are from G2019S families.

were re-examined, using a standardized case-report form including extended family history and clinical evaluation. Nine patients from seven families and their 12 relatives have been described in an earlier study [5]. Genealogical studies were based on the self-report of family history from patients and family members, as well as additional data from the Norwegian National Registration Office, local parish registers and population censuses. Age-dependent penetrance was calculated by dividing the number of affected mutation carriers within each ten-year age-group by the total number of carriers. Haplotype analysis was performed in seven cases (cases 1, 2, 4, 8, 9, 12, 18) as described earlier [18].

3. Results

A total of 65 individuals were heterozygous for *LRRK2* p.G2019S, whereof 21 had PD and 44 were asymptomatic carriers. The demographic data are presented in Table 1. The penetrance in this study was 14% at age 40–49 and 50% at age 70–79 years.

The 21 symptomatic carriers came from 10 distinct families living in small geographical areas along the coastline of central Norway. The north-south distance was about 500 km. Six of these families (H, D, C, J, F, G, Fig. 1), could be traced back 10 generations to a common Norwegian ancestor couple living between 1580 and 1650. Two families were associated with the same family-tree through intermarriage (E and I, Fig. 1), while two other families (A and B) could not be traced back to these ancestors, probably due to inadequate data. However, seven families including A and B were investigated by haplotype analysis, showing a shared region between markers D12S2514 to D12S1048 (Fig. 2). Five of the intragenic SNPs identified by Zabetian et al. [19] were not examined for the Norwegian patients.

The patients ($n = 21$) had a wide range of disease onset (mean 61.2 ± 10.0 years, range 43–77 years), but there was no apparent difference between the various family branches. There was no significant difference in age at disease onset between females and males (females: 59.4 ± 10.5, males 63.3 ± 9.7). However, from the data in Table 1 it is clear that of the total 40 male carriers of p.G2019S, only 10 had PD, while 11 of 25 female carriers had PD. Males therefore seemed to have a lower penetrance (25%) than females (44%).

The clinical data are presented in Table 2. The phenotype of the patients was heterogeneous with various initial symptoms, though tremor was most frequently reported. One patient had an atypical presentation with bilateral dystonia in both lower extremities. The clinical features were as expected for PD, including both tremor-dominant and akinetic types, the former being more common in cases under age 60, while patients with later onset had a predominantly akinetic form. Asymmetry and a good levodopa response were seen in all cases. Autonomic dysfunction was not a major problem and cognitive impairment was observed in only one case after 20 years of disease. Development of motor fluctuations with dyskinesias was not distinguishable from sporadic PD. It was not possible to distinguish the genealogical branches based on clinical features.

4. Discussion

Twenty-one PD patients from 10 different families living in small geographic areas in central Norway carried the *LRRK2* p.G2019S mutation, corresponding to 3.1% of the total PD population in this region. This is probably a greater percentage than in the total Norwegian population. Six families were traced back to a common ancestor, two were associated by intermarriage, and the two remaining families have not yet been linked to the same pedigree. It is not certain (though likely) that the Norwegian haplotype is type 1 as described by Zabetian et al. [19] for Europeans, North African Arabs and Ashkenazi Jews (Fig. 2).

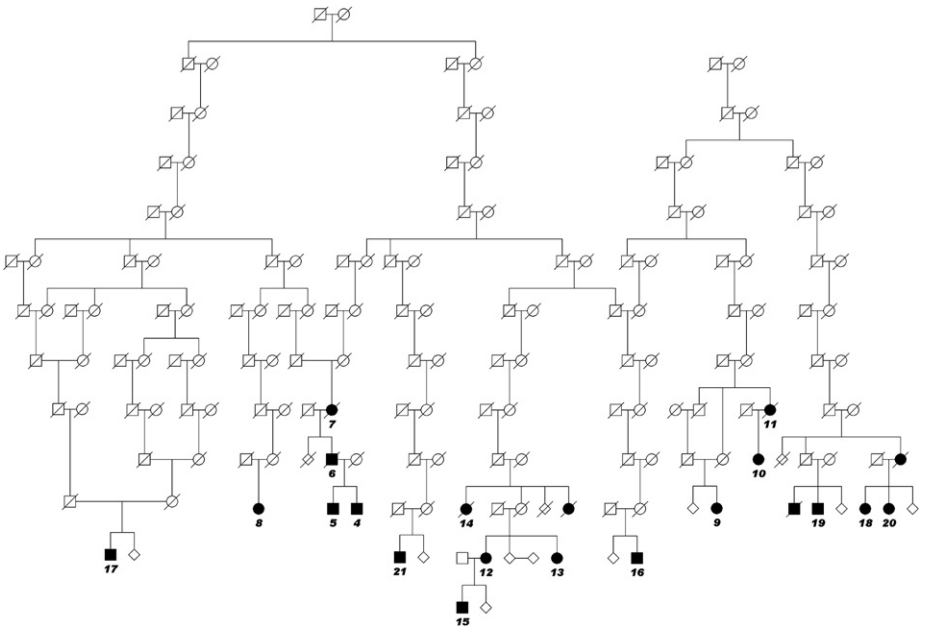

Fig. 1. Pedigree, presenting six kindreds traced back to a common founder couple, as well as two other families associated by intermarriage. (The youngest-affected generation is abridged to maintain confidentiality).