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Global investigation and meta-analysis of the *C9orf72* $(G_4C_2)_n$ repeat in Parkinson disease

OPEN

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ABSTRACT

Objectives: The objective of this study is to clarify the role of $(G_4C_2)_n$ expansions in the etiology of Parkinson disease (PD) in the worldwide multicenter Genetic Epidemiology of Parkinson's Disease (GEO-PD) cohort.

Methods: *C9orf72* $(G_4C_2)_n$ repeats were assessed in a GEO-PD cohort of 7,494 patients diagnosed with PD and 5,886 neurologically healthy control individuals ascertained in Europe, Asia, North America, and Australia.

Results: A pathogenic $(G_4C_2)_{n>60}$ expansion was detected in only 4 patients with PD (4/7,232; 0.055%), all with a positive family history of neurodegenerative dementia, amyotrophic lateral sclerosis, or atypical parkinsonism, while no carriers were detected with typical sporadic or familial PD. Meta-analysis revealed a small increase in risk of PD with an increasing number of $(G_4C_2)_n$ repeats; however, we could not detect a robust association between the *C9orf72* $(G_4C_2)_n$ repeat and PD, and the population attributable risk was low.

Conclusions: Together, these findings indicate that expansions in *C9orf72* do not have a major role in the pathogenesis of PD. Testing for *C9orf72* repeat expansions should only be considered in patients with PD who have overt symptoms of frontotemporal lobar degeneration/amyotrophic lateral sclerosis or apparent family history of neurodegenerative dementia or motor neuron disease. ***Neurology*® 2014;83:1906–1913**

GLOSSARY

ALS = amyotrophic lateral sclerosis; **FTLD** = frontotemporal lobar degeneration; **GEO-PD** = Genetic Epidemiology of Parkinson's Disease; **PD** = Parkinson disease; **RP** = repeat-primed; **STR** = short tandem repeat.

A substantial number of patients with frontotemporal lobar degeneration (FTLD)/amyotrophic lateral sclerosis (ALS) (14%–35%) carrying *C9orf72* $(G_4C_2)_{>60}$ expansions[1–3] present with atypical parkinsonism in early disease stages and increased incidence of parkinsonism with or without features of the FTLD/ALS complex in their relatives.[4–9] Ten research groups have reported on *C9orf72* repeat expansions in Parkinson disease (PD) or atypical parkinsonism patients[10–19] but none of these investigated the *C9orf72* repeat in large-scale cohorts, and European and Australian populations were underrepresented in the published data. Apart from the pathogenicity of $(G_4C_2)_{>60}$ expansions, we provided in vitro evidence that the (G_4C_2) repeat size negatively correlated with the transcriptional activity of the *C9orf72* promoter.[20] Hence, it is conceivable that an increasing number of *C9orf72* repeats may affect transcription gradually and increase susceptibility to disease.[20] Three studies indicated a role of *C9orf72* repeats in PD susceptibility but associations were found using different dichotomizations of repeat length, muddling biological interpretation. In one study, a marginal increased risk of PD was observed for carriers of $(G_4C_2)_{10}$ repeats.[12] In the second, a significant increased frequency of $(G_4C_2)_{>20}$ repeats was observed in patients clinically diagnosed with PD.[15] In the third study, the authors

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GEO-PD Consortium coinvestigators are listed on the *Neurology*® Web site at Neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article. The Article Processing Charge was paid by research funding obtained by the principal investigator.

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Supplemental data at Neurology.org

reported association of $(G_4C_2)_{\geq 7}$ repeats with PD in the Chinese Han population.[16] All of these studies, however, were executed in ethnically distinct and medium scaled cohorts. We set out to clarify the role of the *C9orf72* $(G_4C_2)_n$ repeat in PD etiology in the first global multicenter study cohort of more than 7,000 patients with PD of 12 nationalities and 4 continents. First, we assess the global prevalence of pathogenic $(G_4C_2)_{>60}$ expansions. Second, the size of the combined study populations enables a detailed investigation of the specific *C9orf72* repeat allele or size threshold associated with increased risk of PD.

METHODS

Standard protocol approvals, registrations, and patient consents. Genetic studies applied in this research were approved by the ethics committees of the ZNA (Hospital Network Antwerp), the Antwerp University Hospital, and University of Antwerp. Clinical protocols were approved by the ethics committees of the ZNA, the Antwerp University Hospital, and local ethical review boards of the participating research centers. All human biological samples were collected, fulfilling ethical approvals, and used in accordance with the terms of subjects' written informed consent.

Participants. The Genetic Epidemiology of Parkinson's Disease (GEO-PD) Consortium includes investigators from 60 sites from 30 countries and 6 continents (http://www.GEO-PD.org/about/). All sites were invited to participate in this study. A total of 18 sites representing 12 countries and 4 continents contributed either DNA or genotypic data, and clinical data of in total 15,123 individuals (tables 1 and 2). After thorough quality control as described in the procedures section below, 13,669 samples were included in this study. We excluded all duplicate samples, sex mismatches, and samples that failed in the DNA fingerprint analysis because of low quantity or quality of DNA or because of contamination of the sample. Demographics and diagnostic criteria of each series included in this study and the sample size breakdown from each site are provided in table 2. Controls were collected at the local sites as demographically matched neurologically healthy individuals.

Table 1 Synopsis of this global GEO-PD study

	Patients	Controls
$(G_4C_2)_{>60}$		
Total	4/7,232	1/5,478
Europe	4/4,252	0/3,172
US + CA	0/1,261	0/1,313
Asia	0/1,364	1/656
Australia	0/355	0/337
Risk associated with $(G_4C_2)_n$		
Total[a]	7,050	5,886
Europe	4,215	3,379
US + CA	1,118	1,313
Asia	1,190	660
Australia	527	534

Abbreviations: CA = Canada; GEO-PD = Genetic Epidemiology of Parkinson's Disease.
[a] For the meta-analyses, only the cohorts including both patients with Parkinson disease and geographically matched controls that were size-corrected using the reference panel were included.

Procedures. ***Sample quality control.*** Concentration and purity were checked spectrophotometrically using the Trinean DropSense96 UV/VIS droplet reader (Trinean, Gentbrugge, Belgium) for all consortium genomic DNA samples. Sex and DNA fingerprint were determined for all samples using an in-house–developed multiplex PCR panel composed of 13 short tandem repeat (STR) markers distributed over multiple autosomal locations: D20S480, D22S1174, D3S1287, D3S1744, D3S1764, D7S672, D7S2426, D8S1746, D14S1005, D20S866, D10S1237, D20S912, and D6S965. This panel also includes a marker specific for the X chromosome (DXS1187) and one for the *SRY* gene on the Y chromosome, and enables fast and accurate sample identification and sex determination in a single assay. After selective amplification of 20 ng genomic DNA, amplification products were size separated on an ABI 3730 automatic sequencer (Applied Biosystems, Foster City, CA) using GeneScan-600 LIZ (Applied Biosystems) as internal size standard and genotypes were assigned using in-house–developed TracI genotyping software (http://www.vibgeneticservicefacility.be).

Genetic analyses. To screen the GEO-PD cohorts for the pathogenic $(G_4C_2)_{>60}$ *C9orf72* repeat expansion, we designed a 2-step procedure: an STR fragment length assay with flanking PCR primers optimized for alleles with high GC content (STR-PCR) followed by 2 repeat-primed PCR assays (forward and reverse RP-PCR) as described earlier.[1,20]

Four participating research groups performed the genotyping in their local facilities according to previously published procedures.[2,17] For consistent allele scoring of repeat lengths between GEO-PD groups and accurate interpretation of the repeat length, we designed a reference DNA set of 14 samples covering a range of normal repeat sizes that was genotyped by each of these facilities. Furthermore, for 2 of the cohorts, a random set of samples homozygous for the STR-PCR assay were included in the RP-PCR analysis at the Antwerp site for independent validation of the absence of a pathogenic repeat expansion.

Statistical analyses. To investigate the association between repeat units and PD susceptibility, 3 explorative approaches were followed, based on (1) allele counts of the distinct repeat sizes, to determine whether one or more specific repeat sizes were associated with PD, (2) the total number of repeat units (sum of both alleles) per individual, and (3) the size of the longest repeat per individual (maximum allele). Summary statistics were computed in a random-effects meta-analysis (DerSimonian-Laird)[12,21] for each approach in the rmeta package implemented in the R environment version 2.15.3. Based on the results obtained in the above-mentioned analyses, we performed hypothesis-driven dichotomized genotypic meta-analyses. Details are provided in the e-Methods on the *Neurology*® Web site at Neurology.org.

To take into account the number of tests performed (n = 22), a Bonferroni-corrected 2-sided p value of ≤ 0.002 was considered statistically significant. Population attributable risk of $(G_4C_2)_{10}$, $(G_4C_2)_{\geq 10}$, and $(G_4C_2)_{\geq 17}$ was estimated using the epiR package in R. For the meta-analyses, only the cohorts including both the patients with PD and the controls that were

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Table 2 Characteristics of the GEO-PD cohorts included in the study

			Controls				Patients							
Site PI	Country	Ethnicity	In	QC OK	STR OK	2-step OK	In	QC OK	STR OK	2-step OK	% Males	% Familial	AAO ± SD	Diagnostic criteria for PD
C. Van Broeckhoven	Belgium	Caucasian	1,119	1,118	1,039	953	593	593	585	569	50	24	63.8 ± 13	Gelb[26]
G. Garraux	Belgium	Caucasian	0	0	0	0	139	126	125	116	59	NA	60.9 ± 10.5	Gelb[26]
C. Klein	Germany	Caucasian	706	697	679	581	433	410	396	396	55	33	52.0 ± 14.2	Hoehn and Yahr[27]
A. Deutschländer	Germany	Caucasian	87	81	79	79	87	81	79	79	57	22	61.5 ± 11.3	UKPDBB[28]
C. Ferrarese	Italy	Caucasian	92	89	86	86	87	84	68	68	58	20	65.5 ± 9.6	Gelb[26]
E.M. Valente	Italy	Caucasian	92	83	83	83	92	90	89	89	47	33	52.9 ± 5.0	UKPDBB[28]
G. Annesi	Italy	Caucasian	100	100	95	95	100	92	74	74	51	0	59.7 ± 9.0	Gelb[26]
G.M. Hadjigeorgiou	Greece	Caucasian	300	232	223	220	300	269	264	264	50	13	63.3 ± 10.4	Bower[29]
A. Puschmann	Sweden	Caucasian	43	43	43	43	119	115	111	111	56	49	61.7 ± 9.7	Ward and Gibb[30]
G.D. Mellick	Australia	Caucasian	920	571	534	337	920	535	527	355	46	27	62.0 ± 11.5	Gelb[26]
M.S. LeDoux	US	Caucasian	0	0	0	0	184	150	143	143	61	32	60.1 ± 11.8	Gelb[26]
S.J. Chung	Korea	Asian	650	568	562	558	1,200	1,113	1,088	1,088	46	9	59.0 ± 10.0	Gelb[26]
E.-K. Tan	Singapore	Asian	200	100	98	98	200	102	102	100	67	8	53.2 ± 7.0	UKPDBB[28]
N. Hattori	Japan	Asian	69	0	0	0	183	177	176	176	52	2	41.6 ± 11.9	Gelb[26]/Hoehn and Yahr[27]
R. Krüger/M. Sharma	Germany	Caucasian	647	625	625	605	1,386	1,367	1,367	1,304	62	NA	49.9 ± 17.1	UKPDBB[28]
S. Lesage	France	Caucasian	442	442	427	427	1,193	1,185	1,182	1,182	54	39	48.6 ± 12.0	UKPDBB[28]
Z.K. Wszolek	US	Caucasian	712	712	712	712	676	676	676	676	53	NA	69.2 ± 11.1	UKPDBB[28]
E. Rogaeva	Canada	Mixed	601	601	601	601	451	442	442	442	50	35	52.4 ± 13.7	UKPDBB[28]

Abbreviations: AAO = age at onset; GEO-PD = Genetic Epidemiology of Parkinson's Disease; NA = not available; PD = Parkinson disease; PI = principal investigator; QC = quality control; STR = short tandem repeat; UKPDBB = UK Parkinson's Disease Brain Bank.

At the initial quality control step (QC), we excluded all duplicate samples, sex mismatches, and samples that failed in the DNA fingerprint analysis because of low quantity or quality of DNA or because of contamination of the sample. Additional samples did not pass the 2-step genetic analysis because of DNA shortage or limited concentration of the DNA sample.

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size-corrected based on the reference panel were included in the study.

RESULTS **Definite pathogenic *C9orf72* repeat expansions in PD.** A total of 12,710 samples, including 7,232 patients with PD and 5,478 control individuals, were successfully genotyped with the 2-step $(G_4C_2)_n$ repeat genotyping assay. RP-PCR analysis revealed the typical sawtooth tail pattern indicative of a pathogenic repeat expansion $(G_4C_2)_{>60}$ in one German (MS_RK cohort) (1/1,304; 0.08%) and 3 French (SL cohort) (3/1,182; 0.25%) patients but none in the other GEO-PD patient cohorts (table 1). Based on these results, we calculated a prevalence of pathogenic *C9orf72* repeat expansions in this global consortium cohort of 0.06%.

The German patient was diagnosed with idiopathic PD at the age of 57 years. One year after onset, clinical examination revealed hypomimia, hypokinesia, resting tremor of the right arm, minor postural instability, mild bilateral rigidity, and slowed shuffling gait but also short-term memory disturbances, social withdrawal, and minor apathy. The patient had a positive family history of neurodegenerative dementia. All 3 French patients were diagnosed with PD without cognitive dysfunction at disease onset, and a detailed clinical description has been reported previously.[17] Briefly, the first patient developed left hemiparkinsonism at age 29 years and symptoms worsened progressively while dopamine agonists were only partially effective. In the second patient, parkinsonism began at age 48 years and a cognitive decline was noted at age 56 years. The third patient developed parkinsonism at age 64 years and developed a mild cognitive deficit at age 69. Although these 3 patients were clinically diagnosed with PD, they all had family histories of atypical parkinsonism, degenerative dementias, or ALS. No expansions were detected in patients with sporadic PD or patients with a familial history of PD. Moreover, mutations in known PD genes had previously been excluded in these 4 pathogenic expansion carriers.

We identified one Asian control of Chinese origin with an age at inclusion of 52 years carrying a pathogenic $(G_4C_2)_{>60}$ expansion (table 1). Currently, there is no record of any symptoms related to PD, FTLD, or ALS in this individual. This brings the estimated prevalence of pathogenic repeat expansions in controls to 0.02% (1/5,478). Apart from the expansion mutations, the distribution of repeat lengths ranged from 0 to 32 in the Caucasian and from 7 to 14 in the Asian control persons.

***C9orf72* repeat and PD susceptibility.** We investigated the role of $(G_4C_2)_n$ repeats in risk of PD. First, we assessed the distribution of the alleles in patients with PD vs controls in the GEO-PD cohort (figure 1). The frequencies of the $(G_4C_2)_{10}$ allele and of $(G_4C_2)_{\geq 17}$ were nominally increased in PD vs the controls but the differences were not statistically significant after Bonferroni correction (figure 1, table 3, figure e-1, A and B). Genotypic frequencies for $(G_4C_2)_{10}$ (table 3, figure e-1, C) and $(G_4C_2)_{\geq 17}$ (table 3, figure e-1, D) were not significantly different between patients and controls after correction for multiple testing. The estimated attributable fractions in the population are very low (table 3). When considering the sum of the alleles and the size of the maximum allele as a quantitative variable, we observed a small but significant increase of disease risk with a rising number of repeat units (sum of alleles $p = 0.0012$, summary effect [β] = 0.0128 [0.00504–0.0205], figure e-2, A; maximum allele $p = 0.0010$, summary effect [β] = 0.0181 [0.00731–0.029], figure e-2, B). Together, these results suggested that the risk effect may not only be linked to the $(G_4C_2)_{10}$ repeat but may be increasing with length while the effect in the larger alleles is probably masked by the small number of carriers. Therefore, we decided to analyze the risk effect of *C9orf72* repeat expansions as a binary categorical value with a cutoff between 9 and 10. However, neither allelic nor genotypic meta-analysis of the GEO-PD cohorts revealed significant association with PD for $(G_4C_2)_{\geq 10}$ repeat alleles after Bonferroni correction (table 3, figure e-3, A and B). Furthermore, the estimated population attributable risk is low (table 3).

DISCUSSION Molecular reclassification of complex brain diseases based on genetic etiology is of utmost importance to improve differential diagnosis and to rationalize drug development. Assessment of the contribution of novel disease genes to clinically and pathologically overlapping diseases is instrumental in this reclassification. In this global study, we assessed the prevalence of $(G_4C_2)_n$ repeat alleles and expansions in an extended PD cohort ascertained within the GEO-PD Consortium and excluded a major role for pathogenic $(G_4C_2)_{>60}$ repeat expansions in the causation of PD. The low frequency of these expansions (0.06%) in the GEO-PD cohort is in agreement with earlier findings in distinct patient groups[10–15,18,19] and falls in the range of frequencies observed in controls by us (0.02%) and others (0–0.6%).[1–4,22] Furthermore, 75% of the pathogenic expansion carriers in this global study showed a decline in cognitive functions within 1 to 8 years after onset. In the absence of autopsy diagnoses, we therefore cannot exclude that some if not all of these expansion carriers are primarily FTLD/ALS patients with pronounced early parkinsonian symptoms or comorbidity of PD and FTLD/ALS. This hypothesis is supported by the identification of only one pathogenic mutation carrier

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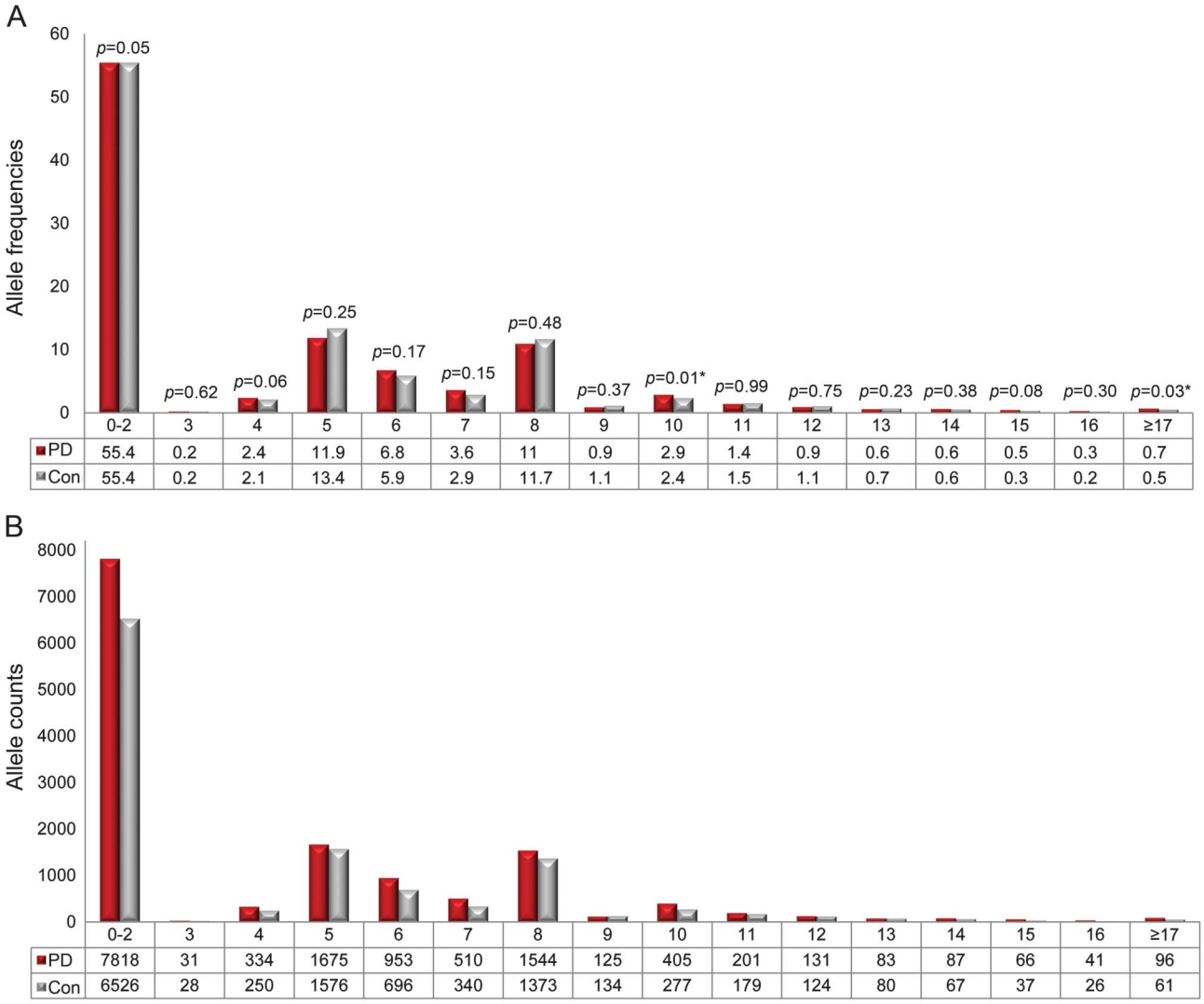
Figure 1 Overall distribution of *C9orf72* repeat alleles in the GEO-PD cohorts



	0-2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	≥17
PD	55.4	0.2	2.4	11.9	6.8	3.6	11	0.9	2.9	1.4	0.9	0.6	0.6	0.5	0.3	0.7
Con	55.4	0.2	2.1	13.4	5.9	2.9	11.7	1.1	2.4	1.5	1.1	0.7	0.6	0.3	0.2	0.5

	0-2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	≥17
PD	7818	31	334	1675	953	510	1544	125	405	201	131	83	87	66	41	96
Con	6526	28	250	1576	696	340	1373	134	277	179	124	80	67	37	26	61

Only cohorts including both patients with PD and controls that were size-corrected based on the reference panel were included in the study. When the highest count for a specific allele was 5 or less across cohorts, the allele was clumped with the next allele for each cohort. (A) Allele frequencies. The *p* values for individual alleles were calculated using a Dersimonian-Laird random-effect meta-analysis. (B) Allele counts. *Nominally significant *p* values. Con = controls; GEO-PD = Genetic Epidemiology of Parkinson's Disease; PD = Parkinson disease.

in 826 (0.1%) autopsy-confirmed PD cases.[23,24] Of note, this carrier presented, in addition to Lewy body pathology, with frontotemporal degeneration and *C9orf72*-ALS/FTLD pathology with numerous p62-positive inclusions. Furthermore, although substantia nigra involvement is common in *C9orf72*-positive ALS, it can be clearly distinguished from PD-related mechanisms by the presence of p62-positive inclusion and absence of Lewy body pathology.[24]

Altogether, it is not advisable to include *C9orf72* $(G_4C_2)_n$ repeat expansion testing in a medical genetic diagnostic setting for typical PD patients. Exceptions can be made for patients with PD who have cognitive and/or behavioral deficits early in the disease process or in patients with a personal or familial history of FTLD/ALS.

Given differences in the existing literature on *C9orf72* $(G_4C_2)_n$ repeat length as risk factor for PD,[12,15,16] we used the size of this global cohort to estimate a PD-related threshold of *C9orf72* repeats. Calculation of the risk for each of the observed *C9orf72* $(G_4C_2)_n$ alleles in the GEO-PD cohorts suggested a role for the 10-units repeat and for the pooled alleles of 17 units or more in PD susceptibility. Genotypic meta-analysis supported a possible link between $(G_4C_2)_{10}$ and increased risk of PD but the association did not reach significance after correction for multiple testing. In addition, the number of carriers of these intermediate alleles is small and one should be cautious with the interpretation of these results. Furthermore, it is difficult to envisage the biological relevance of risk associated with a single

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Table 3 Overview of DerSimonian-Laird meta-analyses

	Allelic			Genotypic		
	OR (95% CI)	*p*	AF (95% CI)	OR (95% CI)	*p*	AF (95% CI)
$(G_4C_2)_{10}$[a]	1.3 (1.06–1.60)	0.01	0.53% (0.13–0.93)	1.31 (1.06–1.62)	0.012	1.05% (0.26–1.84)
$(G_4C_2)_{\geq 17}$[a]	1.44 (1.03–2.01)	0.03	0.16% (−0.03 to 0.35)	1.47 (1.05–2.05)	0.025	0.35% (−0.03 to 0.72)
$(G_4C_2)_{\geq 10}$[b]	1.16 (1.04–1.3)	0.009	0.69% (0–1.39)	1.18 (1.03–1.35)	0.02	1.47% (0.07–2.85)

Abbreviations: AF = attributable fraction; CI = confidence interval; OR = odds ratio.
For the meta-analyses, only the cohorts including both patients with Parkinson disease and geographically matched controls that were size-corrected using the reference panel were included. The *p* values were calculated using DerSimonian-Laird meta-analysis; $p = 0.002$ is considered statistically significant (22 tests).
[a] Allele count approach.
[b] Dichotomized approach.

allele. Of note, we observed a small but significant increase in risk with an accumulative number of repeats supporting the idea of a threshold size rather than a single allele as the culprit of increased risk. We therefore decided to study the combined effect of (G_4C_2) alleles of 10 units and larger in the global GEO-PD cohort. Although meta-analyses implicated a potential role for these intermediate-sized repeats in PD risk, none of the associations survived Bonferroni correction suggesting that if *C9orf72* repeats of 10 units or larger have a role in PD susceptibility, the effect is small. This is supported by the fact that none of the published genome-wide association studies revealed the *C9orf72* locus as a risk factor for PD.[25] A limitation of this study is that we did not yet include all published association studies of *C9orf72* in PD; however, we chose to include only those studies that were corrected for allele scoring bias based on a reference panel.

Altogether, these data support the current hypothesis that pathogenic $(G_4C_2)_n$ repeat expansions in *C9orf72* appear to be specific for the FTLD/ALS spectrum with little or no contribution to the wider spectrum of movement disorders. It will be of interest to study the role of intermediate repeats ≥10 units in other neurodegenerative disorders, however, to obtain a more profound knowledge on their role in neurodegenerative diseases and a better understanding of the underlying mechanism.

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REFERENCES

1. Gijselinck I, Van Langenhove T, van der Zee J, et al. A C9orf72 promoter repeat expansion in a Flanders-Belgian cohort with disorders of the frontotemporal lobar degeneration–amyotrophic lateral sclerosis spectrum: a gene identification study. Lancet Neurol 2012;11:54–65.
2. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron 2011;72:245–256.
3. Renton AE, Majounie E, Waite A, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron 2011;72:257–268.
4. Cruts M, Gijselinck I, Van Langenhove T, van der Zee J, Van Broeckhoven C. Current insights into the C9orf72 repeat expansion diseases of the FTLD/ALS spectrum. Trends Neurosci 2013;36:450–459.
5. Takada LT, Pimentel ML, DeJesus-Hernandez M, et al. Frontotemporal dementia in a Brazilian kindred with the C9orf72 mutation. Arch Neurol 2012;69:1149–1153.
6. Savica R, Adeli A, Vemuri P, et al. Characterization of a family with c9FTD/ALS associated with the GGGGCC repeat expansion in C9ORF72. Arch Neurol 2012;69:1164–1169.
7. Luigetti M, Quaranta D, Conte A, et al. Frontotemporal dementia, parkinsonism and lower motor neuron involvement in a patient with C9ORF72 expansion. Amyotroph Lateral Scler Frontotemporal Degener 2013;14:66–69.
8. Hsiung GY, DeJesus-Hernandez M, Feldman HH, et al. Clinical and pathological features of familial frontotemporal dementia caused by C9ORF72 mutation on chromosome 9p. Brain 2012;135:709–722.
9. Van Langenhove T, van der Zee J, Gijselinck I, et al. Distinct clinical characteristics of C9orf72 expansion carriers compared with GRN, MAPT, and nonmutation carriers in a Flanders-Belgian FTLD cohort. JAMA Neurol 2013;70:1–9.
10. Harms MB, Neumann D, Benitez BA, et al. Parkinson disease is not associated with C9ORF72 repeat expansions. Neurobiol Aging 2013;34:1519.e1–1519.e2.
11. DeJesus-Hernandez M, Rayaprolu S, Soto-Ortolaza AI, et al. Analysis of the C9orf72 repeat in Parkinson's disease, essential tremor and restless legs syndrome. Parkinsonism Relat Disord 2013;19:198–201.
12. Xi Z, Zinman L, Grinberg Y, et al. Investigation of C9orf72 in 4 neurodegenerative disorders. Arch Neurol 2012;69:1583–1590.
13. Majounie E, Abramzon Y, Renton AE, Keller MF, Traynor BJ, Singleton AB. Large C9orf72 repeat expansions are not a common cause of Parkinson's disease. Neurobiol Aging 2012;33:2527.e1–2527.e2.
14. Daoud H, Noreau A, Rochefort D, et al. Investigation of C9orf72 repeat expansions in Parkinson's disease. Neurobiol Aging 2013;34:1710–1719.
15. Nuytemans K, Bademci G, Kohli MM, et al. C9ORF72 intermediate repeat copies are a significant risk factor for Parkinson disease. Ann Hum Genet 2013;77:351–363.
16. Jiao B, Guo JF, Wang YQ, et al. C9orf72 mutation is rare in Alzheimer's disease, Parkinson's disease, and essential tremor in China. Front Cell Neurosci 2013;7:164.
17. Lesage S, Le Ber I, Condroyer C, et al. C9orf72 repeat expansions are a rare genetic cause of parkinsonism. Brain 2013;136:385–391.
18. Yeh TH, Lai SC, Weng YH, et al. Screening for C9orf72 repeat expansions in parkinsonian syndromes. Neurobiol Aging 2013;34:1311–1314.
19. Akimoto C, Forsgren L, Linder J, et al. No GGGGCC-hexanucleotide repeat expansion in C9ORF72 in parkinsonism patients in Sweden. Amyotroph Lateral Scler Frontotemporal Degener 2013;14:26–29.
20. van der Zee J, Gijselinck I, Dillen L, et al. A pan-European study of the C9orf72 repeat associated with FTLD: geographic prevalence, genomic instability, and intermediate repeats. Hum Mutat 2013;34:363–373.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.
22. Beck J, Poulter M, Hensman D, et al. Large C9orf72 hexanucleotide repeat expansions are seen in multiple neurodegenerative syndromes and are more frequent than expected in the UK population. Am J Hum Genet 2013;92:345–353.
23. Nuytemans K, Inchausti V, Beecham GW, et al. Absence of C9ORF72 expanded or intermediate repeats in autopsy-confirmed Parkinson's disease. Mov Disord 2014;29:827–830.
24. Cooper-Knock J, Frolov A, Highley JR, et al. C9ORF72 expansions, parkinsonism, and Parkinson disease: a clinicopathologic study. Neurology 2013;81:808–811.
25. Lill CM, Roehr JT, McQueen MB, et al. Comprehensive research synopsis and systematic meta-analyses in Parkinson's disease genetics: the PDGene database. PLoS Genet 2012;8:e1002548.
26. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. Arch Neurol 1999;56:33–39.
27. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427–442.
28. Hughes AJ, Daniel SE, Lees AJ. Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. Neurology 2001;57:1497–1499.
29. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976–1990. Neurology 1999;52:1214–1220.
30. Ward CD, Gibb WR. Research diagnostic criteria for Parkinson's disease. Adv Neurol 1990;53:245–249.

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Global investigation and meta-analysis of the *C9orf72* $(G_4C_2)_n$ repeat in Parkinson disease

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