# Large-scale assessment of polyglutamine repeat expansions in Parkinson disease

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## ABSTRACT

**Objectives:** We aim to clarify the pathogenic role of intermediate size repeat expansions of SCA2, SCA3, SCA6, and SCA17 as risk factors for idiopathic Parkinson disease (PD).

**Methods:** We invited researchers from the Genetic Epidemiology of Parkinson's Disease Consortium to participate in the study. There were 12,346 cases and 8,164 controls genotyped, for a total of 4 repeats within the SCA2, SCA3, SCA6, and SCA17 genes. Fixed- and random-effects models were used to estimate the summary risk estimates for the genes. We investigated between-study heterogeneity and heterogeneity between different ethnic populations.

**Results:** We did not observe any definite pathogenic repeat expansions for SCA2, SCA3, SCA6, and SCA17 genes in patients with idiopathic PD from Caucasian and Asian populations. Furthermore, overall analysis did not reveal any significant association between intermediate repeats and PD. The effect estimates (odds ratio) ranged from 0.93 to 1.01 in the overall cohort for the SCA2, SCA3, SCA6, and SCA17 loci.

**Conclusions:** Our study did not support a major role for definite pathogenic repeat expansions in SCA2, SCA3, SCA6, and SCA17 genes for idiopathic PD. Thus, results of this large study do not support diagnostic screening of SCA2, SCA3, SCA6, and SCA17 gene repeats in the common idiopathic form of PD. Likewise, this largest multicentered study performed to date excludes the role of intermediate repeats of these genes as a risk factor for PD. ***Neurology*®** **2015;85:1283–1292**

## GLOSSARY

**AAO** = age at onset; **CI** = confidence interval; **GEO-PD** = Genetic Epidemiology of Parkinson's Disease; **PD** = Parkinson disease; **SCA** = spinocerebellar ataxia.

Spinocerebellar ataxias (SCAs) represent a clinically and genetically diverse group of neurodegenerative diseases, which share degeneration of the cerebellum and its afferent and efferent connections, besides variable degeneration of multiple neurologic systems.[1] Expansions of trinucleotide repeats in the coding or untranslated regions of various genes cause several SCAs; these expansions also account for most of the clinical and genetic heterogeneity.[2] Emerging evidence provides tangible support to the growing consensus that clinically heterogeneous yet biologically overlapping late-onset neurodegenerative disorders may have common genetic risk factors that might change predisposition to the diseases.[2,3]

Whether polyglutamine repeat expansions in SCA genes such as SCA2, SCA3, SCA6, and SCA17 wield a similar effect in idiopathic Parkinson disease (PD) needs to be determined. Previous clinical and pathologic findings emphasize the need to evaluate the significance of polyglutamine repeat expansions of these genes in PD worldwide.[4–9] Most studies performed to date, including this study, are biased by case selection at specialist movement disorders clinics. However, to get a better estimate of the frequency of repeat expansions in such a setting, their relative contribution to disease worldwide, we performed a large multicenter study with members of the Genetic Epidemiology of Parkinson's Disease (GEO-PD) Consortium.

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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.

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**Supplemental data at Neurology.org**

## METHODS

**Participants and samples.** The GEO-PD Consortium includes researchers from 59 investigative sites, across 30 countries and 6 continents (http://www.geopd.org/about/); we invited all sites to participate in the study. Twenty-five sites from 20 countries and 4 continents contributed DNA samples and clinical data, resulting in 20,528 participants. Patients were diagnosed with PD by a movement disorders specialist using the standard criteria.[10–12] Controls at the date of examination were neurologically healthy, unrelated individuals free of PD or another associated movement disorder. Local sites collected demographically similar and sex-, age-matched neurologically healthy individuals as controls. Not all controls were given a detailed neurologic examination, but all were questioned about previous diagnoses or familial history of a neurologic disease. After quality control of data, a total of 20,510 samples were included (12,346 cases, 8,164 controls). The Caucasian series consisted of 16,819 (10,204 cases and 6,615 controls), and the Asian series consisted of 3,691 patients (2,142 cases and 1,549 controls). Patients with missing data were excluded from the relevant analysis. There were a total of 508 patients missing SCA2 genotype information, 445 missing SCA3, 861 missing SCA6, and 608 missing SCA17.

**Genotyping.** The SCA2, SCA3, SCA6, and SCA17 loci containing the CAG repeats were amplified with PCR using fluorescently labeled primers (primer sequences are available upon request). PCRs for SCA2, SCA3, and SCA17 were performed in one multiplex assay, SCA6 in a singleplex. All amplicons of one individual were pooled and separated by size using capillary electrophoresis on an ABI3730 sequencer. Data analysis was performed with GeneMapper 4.0 software. This included automatic sizing and allele calling. A total of 8 individuals (2 for each locus) were Sanger sequenced and the number of triplet repeats was counted. This information was used to convert amplicon lengths to repeat numbers.

**Standard protocol approvals, registrations, and patient consents.** The local ethics committee approved the study. All participants signed an informed consent.

**Statistical analysis.** We first generated distribution plots for SCA2, SCA3, SCA6, and SCA17 genes (see figure e-1 on the *Neurology*® Web site at Neurology.org) to estimate the repeats' cutoffs in our cohort. Based on our observation, expanding repeats for each gene were categorized into short, intermediate, and long repeats. Using the Monte Carlo simulation method (1,000 simulations) as implemented in the CLUMP, we compared the distribution of allele length of SCA genes to determine the significance of departure from the expected values between cases and controls.[13] Because CLUMP uses the Monte Carlo simulation method, all significances should be unbiased and robust to small expected values or continuity corrections.[13] We also assessed the correlation between age at onset (AAO) (5,310 cases) and polyglutamine repeats in our cohort. Likewise, in a subset of the data with the age at study available (14 sites, 4,400 controls, 5,310 cases), we analyzed the data with age at study as a covariate in the models. Finally, the association between SCA CAG expansion repeats and PD was evaluated using a logistic regression model with sex included as a covariate. Datasets from countries that included only cases were not included in the modeling because they lacked a proper control set, and thus could not be modeled using logistic regression. Fixed- and random-effects models estimated the odds ratios. Fixed-effect models assume that populations from different sites have the same risk effect from the repeat expansions and that observed differences are due to random chance. For datasets containing between-study heterogeneity, fixed-effect estimates provide smaller confidence intervals (CIs) and $p$ values, relative to random-effects models.[14–16] If, however, heterogeneity exists, the effects may diverge substantially across the populations. Random-effects models allow for random variation between the sites, therefore adjusting for genuine heterogeneity that may exist across different sites. We used the inverse variance method for fixed-effects models and the DerSimonian and Laird method for random-effects models.[17] To evaluate the between-site heterogeneity, we used the Cochran $Q$ test of homogeneity and the $I^2$ metric. The $I^2$ parameter is bounded by 0 and 1 and estimates the proportion of heterogeneity that is highly unlikely due to random variation. A larger $I^2$ value implies more heterogeneity, with $I^2$ more than 0.75 or 75% indicating large heterogeneity. However, given that there exists significant imprecision in the estimation of $I^2$, particularly for variants with low minor allele frequency, we also provided the 95% CI of $I^2$.[16] The overall analysis considered all sites and populations regardless of ancestry. We then separately modeled the Caucasian and Asian sites. All statistical analyses were performed using R version 3.0.2, with package "metafor" for the random-effects logistic regression models. The $p$ values are 2-tailed.

## RESULTS

A total of 25 sites contributed 12,346 patients with PD and 8,164 neurologically normal controls. Table 1 displays the characteristics of all participating sites. Nineteen sites contributed patients of Caucasian descent; 6 sites were from countries of Asian descent. The proportion of males ranged from 46% to 63% over the participating sites (table 1). The mean AAO of PD in this investigated population was 60 years. We excluded 2 sites that contributed only cases to avoid the influence of population substructuring (Japan and South Africa, 519 patients). Nevertheless, these 2 sites were analyzed independently to assess the expanded repeats. One German site contributed only cases, and allelic repeat density analysis did not show differences in repeat length between different German sites. Therefore, we decided to merge German sites into one data site titled "Germany" for further analyses, thus combining data from Deutschländer, Klein, and Gasser sites.

**Expanding repeats of SCA genes in PD.** Of 20,528 participants who were successfully genotyped, we did not observe any definite pathogenic repeat expansion for SCA2 (>32), SCA3 (>61), SCA6 (>19), and SCA17 (>47) genes in our cohort, thus excluding the role of definite pathogenic repeat expansion of these genes in PD.

**Intermediate repeats and PD.** The distribution of the cutoff repeat length of SCA genes as observed in the density distribution plots in our study is in agreement with previously published studies.[2,18–20] Furthermore, the histogram plots showed that the distribution of intermediate repeat length are similar for SCA2, SCA3, SCA6, and SCA17 genes independent of ethnicities.[20]

Using CLUMP, we did not observe differences in allele length distribution between cases and controls

**Table 1** Characterization of sites and overall database

| Site | Country | Total | Cases | Controls | Male (%) | Mean AAO | Diagnostic criteria |
|---|---|---|---|---|---|---|---|
| Annesi | Italy | 394 | 197 | 197 | 204 (51.8) | 61.5 | UKPDBB |
| Bardien/Carr | South Africa | 398 | 398 | 0 | 246 (61.2) | | UKPDBB |
| Bozi | Greece | 218 | 114 | 104 | 105 (46.1) | 69.9 | UKPDBB |
| Brice | France | 504 | 272 | 232 | 301 (59.7) | 47.6 | UKPDBB |
| Chung | Korea | 1,900 | 1,200 | 700 | 876 (46.1) | | UKPDBB |
| Deutschländer | Germany | 140 | 70 | 70 | 80 (57.1) | 69.7 | UKPDBB |
| Garraux | Belgium | 77 | 64 | 13 | 40 (51.9) | 62.1 | UKPDBB |
| Goldwurm | Italy | 3,798 | 2,795 | 1,003 | 1,992 (52.4) | | UKPDBB |
| Hadjigeorgiou | Greece | 641 | 313 | 328 | 339 (52.9) | 63.4 | UKPDBB |
| Hattori | Japan | 121 | 121 | 0 | 62 (51.2) | | UKPDBB |
| Jeon | Korea | 737 | 397 | 340 | 427 (57.9) | | UKPDBB |
| Klein | Germany | 320 | 317 | 3 | 185 (59.3) | | UKPDBB |
| Krüger/Sharma/Gasser | Germany | 1,909 | 1,219 | 690 | 1,149 (60.4) | | UKPDBB |
| Lin | Taiwan | 320 | 160 | 160 | 160 (50.0) | 62.0 | UKPDBB |
| Lynch/Ross | Ireland | 700 | 339 | 361 | 322 (46.0) | 50.5 | UKPDBB |
| Mellick | Australia | 1,809 | 893 | 916 | 929 (51.4) | 59.0 | Bower |
| Mok | China | 390 | 214 | 176 | 232 (60.1) | | UKPDBB |
| Morrison | United Kingdom | 1,072 | 723 | 349 | 577 (53.9) | 66.1 | UKPDBB |
| Opala/Ross | Poland | 614 | 352 | 262 | 358 (58.3) | 50.2 | UKPDBB |
| Rogaeva | Canada | 562 | 391 | 171 | 296 (53.7) | 49.7 | UKPDBB |
| Tan | Singapore | 344 | 171 | 173 | 217 (63.1) | 59.7 | UKPDBB |
| Toft | Norway | 816 | 364 | 452 | 484 (59.3) | | UKPBDD |
| Van Broeckhoven | Belgium | 1,011 | 501 | 510 | 500 (49.6) | 60.5 | Pals/Gelb |
| Wirdefeldt | Sweden | 260 | 67 | 193 | 128 (49.2) | 65.8 | Gelb |
| Wszolek/Ross | United States | 1,455 | 69,4 | 761 | 764 (52.5) | 64.4 | UKPDBB |
| Total | | 20,510 | 12,346 | 8,164 | | | |

Abbreviations: AAO = age at onset; UKPDBB = United Kingdom Parkinson's Disease Brain Bank.

in the overall cohort (table e-1). Likewise, stratifying the analysis by ethnicity did not reveal associations; this suggests that intermediate repeats in SCA2, SCA3, SCA6, and SCA17 genes are not a major risk factor for PD (table e-2A).

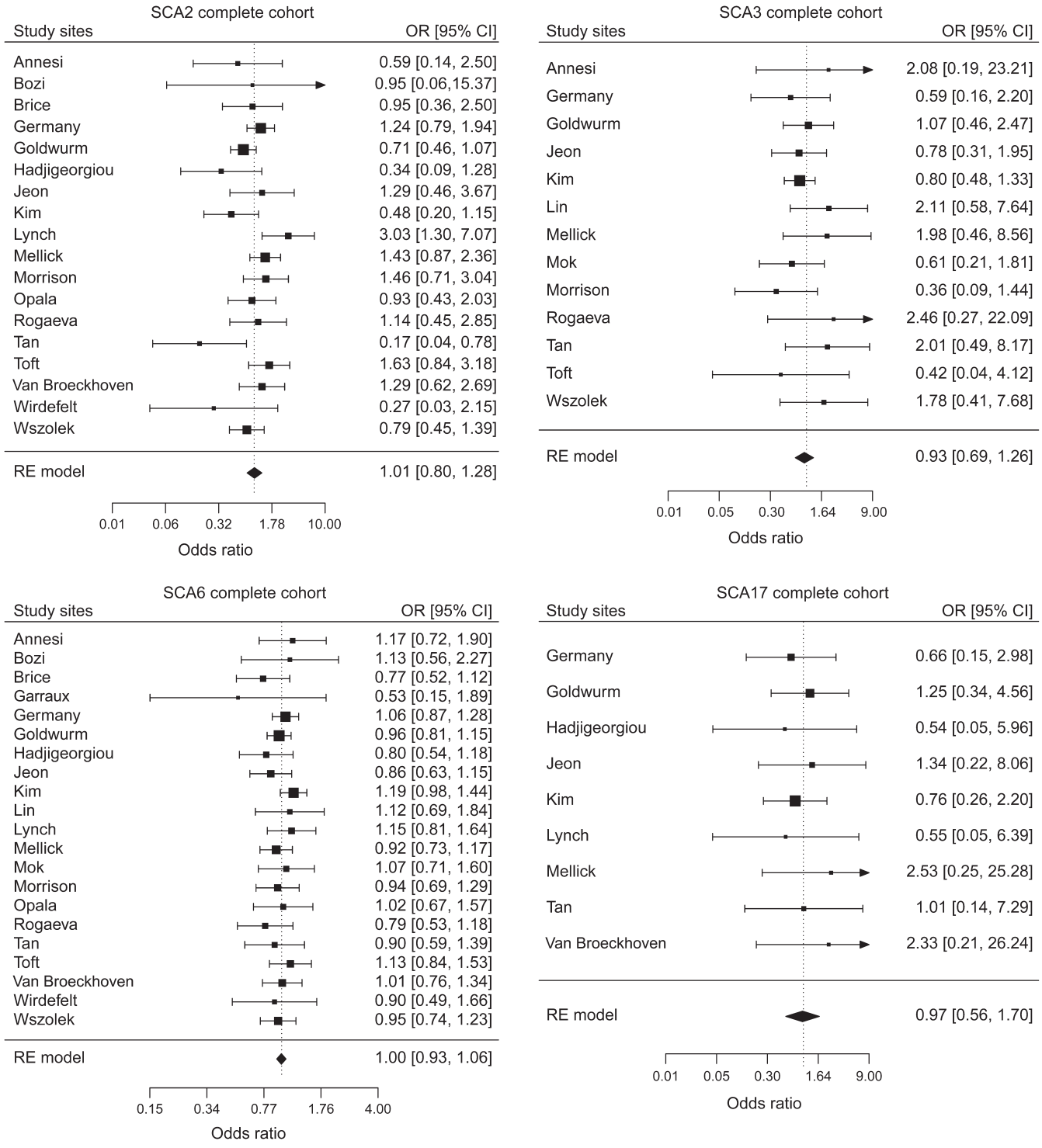
**Overall analysis.** In the overall cohort, we observed no statistically significant associations between PD and intermediate repeat length for the SCA2, SCA3, SCA6, and SCA17 genes. The odds ratio ranged from 0.93 to 1.01 in the overall cohort (table 2, figure 1). We observed no heterogeneity for SCA3, SCA6, and SCA17 loci in our cohort, while SCA2 showed moderate heterogeneity; however, all heterogeneity 95% CIs contained 0 (table 2). Of note, we observed a $p$ value of 0.013 (uncorrected) in our CLUMP

**Table 2** Overall analysis irrespective of ethnicity and influence of between-study heterogeneity

| Locus | Gene name | Q test $p$ value | OR (95% CI) | $I^2$ | RE $p$ value | FE $p$ value |
|---|---|---|---|---|---|---|
| SCA2 | *ATXN2* | 0.03 | 1.01 (0.78, 1.28) | 37 (0, 82) | 0.93 | 0.76 |
| SCA3 | *ATXN3* | 0.66 | 0.93 (0.69, 1.26) | 0 (0, 63) | 0.64 | 0.64 |
| SCA6 | *CACNA1A* | 0.87 | 1.00 (0.93, 1.06) | 0 (0, 26) | 0.90 | 0.90 |
| SCA17 | *TBP* | 0.97 | 0.97 (0.56, 1.70) | 0 (0, 6) | 0.92 | 0.92 |

Abbreviations: *ATXN2* = ataxin 2; *ATXN3* = ataxin 3; *CACAN1A* = calcium channel, voltage dependent, P/Q type, alpha 1A subunit; CI = confidence interval; FE = fixed effects; OR = odds ratio; RE = random effects; *TBP* = TATA box binding protein.

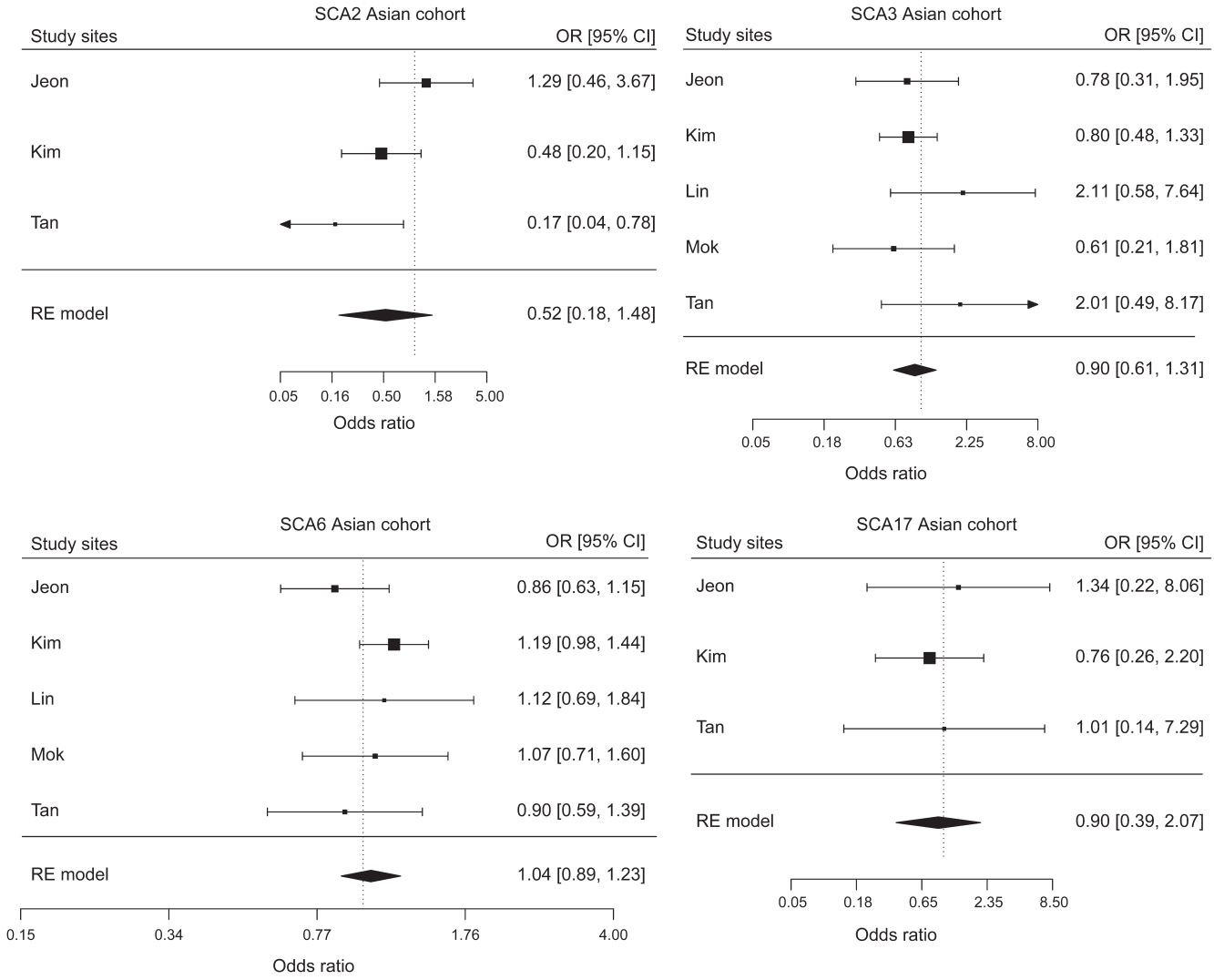
**Figure 1** **Forest plot of effect sizes of SCA2, SCA3, SCA6, and SCA17 loci in the overall cohort**




Boxes indicate the summary effect estimate. Germany site is a combination of Deutschländer, Klein, and Gasser sites. Axis scaled in relation to CIs. CI = confidence interval; OR = odds ratio; RE = random effects.

analysis for SCA6 in the overall cohort, but it was not significant after correcting for multiple testing (table e-1). The $I^2$ estimates ranged from 0% to 37% in the overall cohort. The $Q$ test was not statistically significant for all SCA loci (table 2). Restricting the analysis to the Caucasian and Asian populations did not reveal an association between PD and intermediate repeat length. The odds ratio ranged from 0.97 to 1.09 for the Caucasian population, while for the Asian population, effect estimates ranged from 0.52 to 1.04 for SCA loci (figures 2 and 3 and table e-2A). We observed a trend for association for the SCA2 locus

**Figure 2** Forest plot of SCA2, SCA3, SCA6, and SCA17 loci in the Asian population




Boxes indicate the summary effect estimate. Germany site is a combination of Deutschländer, Klein, and Gasser sites. Axis scaled in relation to CIs. CI = confidence interval; OR = odds ratio; RE = random effects.

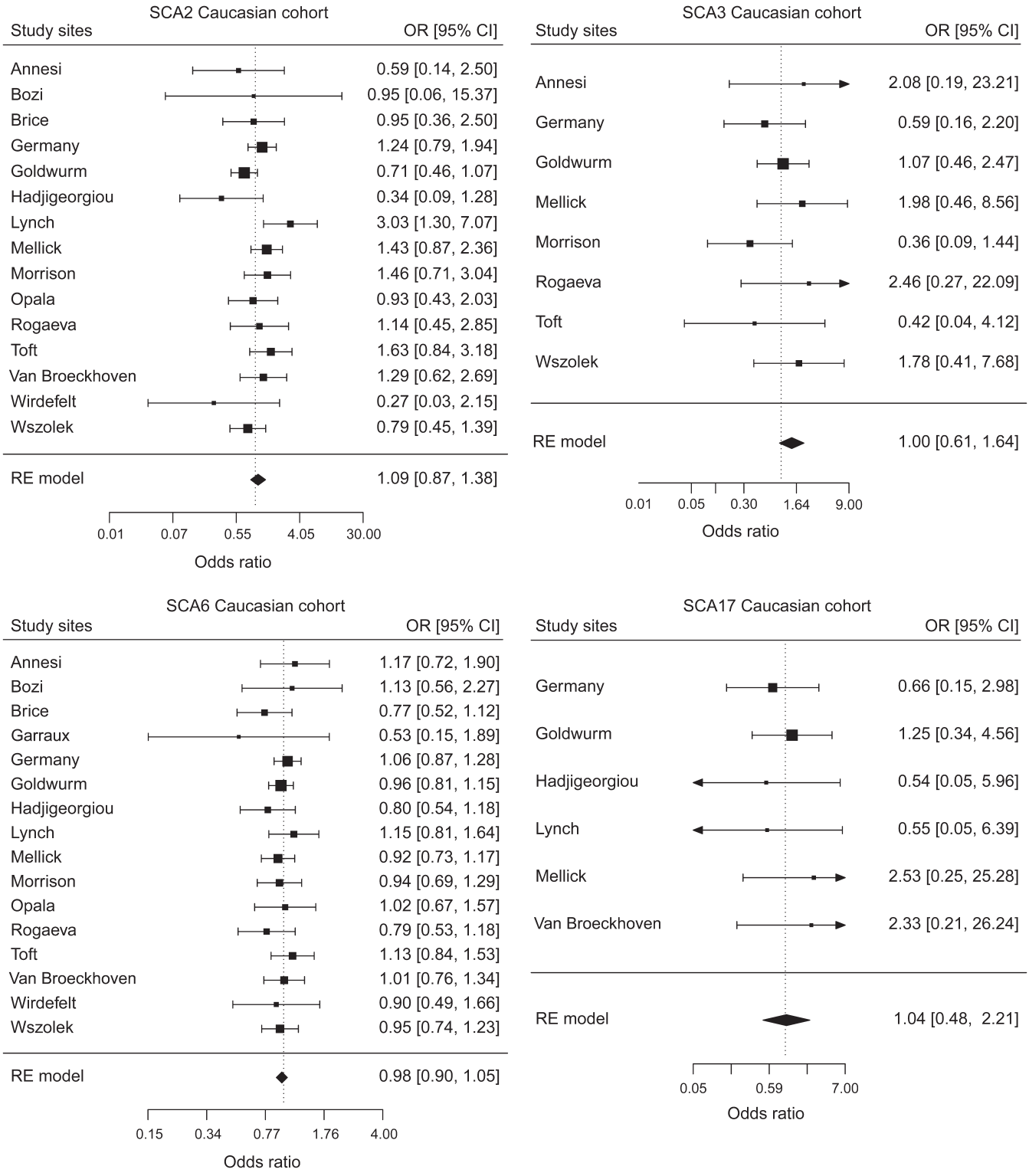
only in the Asian population with large heterogeneity, but this was not significant (table e-2A).

**AAO analysis.** In a subset of data with AAO available, we did not find any significance correlation between the SCA2, SCA3, SCA6, or SCA17 repeats and the AAO of PD (table e-2D). Likewise, stratifying by ethnicity, we did not observe any association between intermediate repeats. The effect estimates of SCA loci on AAO ranged from −0.79 to 2.13 for the overall cohort, and for the Caucasian population, effect estimates ranged from −0.13 to 4.76 (table e-2D). In addition, the age-adjusted analysis did not yield any significant association between SCA repeats and PD (table e-2C). We also performed random-effects models with the Student *t* test comparing the mean repeat length between cases and controls, and logistic regression models using repeat length as a quantitative trait. We did not observe a significant association between disease and repeat length ($p > 0.05$).

**DISCUSSION** The expansion of trinucleotide repeats has provided mechanistic explanations for human disorders. Besides defining autosomal dominantly inherited disease genes, variability in the distribution of repeat length as well as composition has remarkable influence on the disease phenotype; the longer the expansion, the earlier the AAO and the more aggressive the disease course.[1] Therefore, we performed a large-scale multicenter evaluation to assess the role of SCA2, SCA3, SCA6, and SCA17 gene repeats in PD. Our study excluded a major role of poly-(Q) repeat expansions for these genes in the causation of PD, at least in typical PD.

So far, there is no clear consensus on the appropriate threshold to understand the influence of

**Figure 3** Forest plot showing the comparison of effect of SCA2, SCA3, SCA6, and SCA17 loci in the Caucasian population




Boxes indicate the summary effect estimate. Germany site is a combination of Deutschländer, Klein, and Gasser sites. Axis scaled in relation to CIs. CI = confidence interval; OR = odds ratio; RE = random effects.

intermediate repeat expansions in PD. We used our large cohort to estimate the global distribution of repeat length for SCA genes in PD. The allelic density as well as histogram distribution plots showed the threshold for intermediate repeats ranges from 24 to 32 for SCA2, 36 to 61 for SCA3, 11 to 19 for SCA6, and 42 to 47 for SCA17 in the PD cases. The intermediate range as observed in our study is in agreement with previously published studies.[21–26]

In contrast, a recently published study from a Japanese population suggested that a population-specific SCA2 intermediate repeat cutoff length could influence the PD outcome.[27] Using a cutoff of 25, the authors observed a significant association for the autosomal dominant form of PD in their population.[27] By using this repeat length cutoff, as suggested by Yamashita et al.,[27] we did not observe significant association for the SCA2 locus, and thus our study did not support the notion that variability in cutoff repeat length varies from population to population (table e-2B). Likewise, our study excluded the role of population-specific intermediate repeat length variability on the risk of PD, at least in sporadic forms of PD. Of note, using the cutoff as observed in our study, we observed a trend (nonsignificant) for SCA2 locus in the Asian population. The proportion of intermediate carriers for SCA2 in our Asian population cohort is small (1.5%) and thus these results need to be interpreted cautiously.

Most, if not all, studies that have been published so far screened the SCA2, SCA3, SCA6, and SCA17 genes only in cohorts of autosomal dominant forms of PD,[21–26] and identified carriers for SCA2, SCA3, SCA6, and SCA17 repeats in different ethnic populations, which suggests that intermediate repeat structure influenced the clinical variability in autosomal dominant forms of PD and autosomal dominant cerebellar ataxia. For example, a previous French study identified 9 patients with PD who are carriers for SCA2 repeats.[28] They observed interrupted repeats for SCA2 as compared to the patients with autosomal dominant cerebellar ataxia who carry pure CAG repeats suggesting that differences in the repeat structure may lead to different phenotypes. Likewise, a study in Asian patients identified 7 SCA2 carriers that showed overlapping phenotype with ataxia such as dysarthria and postural instability.[7] However, such patients would not have been included in this study because the inclusion criterion was diagnosis of PD. Our study also did not investigate the role of interruptions in the repeats on PD, thus we cannot draw any conclusions for this subcategory of patients. It is worthwhile to mention that most of the participants in our cohort showed intermediate repeats in the normal range, and hence it will be unlikely that intermediate repeats will have an important role in PD. Nevertheless, deep sequencing of intermediate repeats should be pursued to resolve the role of intermediate repeats in PD, as emerging evidence has shown that genetic variations in these regions have an important role in explaining the missing heritability.[29,30]

Taken together, we examined the role of poly-(Q) repeats in PD using the largest sample size until now, and our results unequivocally show that polyglutamine repeats in SCA2, SCA3, SCA6, and SCA17 are unlikely to be clinically important risk factors for typical, idiopathic PD, without evidence of a family history of neurodegenerative disease (parkinsonism) or atypical signs (e.g., ataxia). Nevertheless, emerging genetic and functional evidence suggest that further studies of these genes in the context of other neurodegenerative diseases are justified.

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## Comment: CAG repeats in idiopathic Parkinson disease—To screen or not to screen

In this large study within the Genetic Epidemiology of Parkinson's Disease Consortium, Wang et al.[1] examined the relationship between idiopathic Parkinson disease (PD) and CAG repeat expansions in ataxia genes. They examined, on a larger scale, an issue that has been examined by several authors. The rationale for the study is that parkinsonian phenotypes, and even L-dopa–responsive PD, occur in carriers of SCA mutations, mainly in Asians, and that intermediate poly-Q expansions are predisposing factors for dominant PD.[2,3] The authors studied 12,346 patients with PD from Caucasian and Asian populations and 8,164 controls, seeking CAG expansions in SCA2, SCA3, SCA6, and SCA17 genes. The study is "negative" since they did not identify causative mutations or increased risk of PD attributable to long normal repeat alleles.

The major strength of the study is that this is the largest screening of ataxia loci in idiopathic PD and takes advantage of large samples of cases and controls from multiple international sites. The study is technically well executed: all samples were tested in one facility; quality monitored; internal standards run; and some samples were sequenced to confirm repeat length. Limitations of the study are that a similar number of patients and controls from the different centers would have been advisable, and that the full range of disease-associated CAG expansions (i.e., Huntington disease and SCA1) was not investigated.

These results suggest that the previously reported association between these loci and parkinsonism probably refers to familial or atypical forms and not to typical idiopathic PD.[3,4] The study therefore does not support genetic screening of SCA2, SCA3, SCA6, and SCA17 in idiopathic PD and excludes the role of intermediate alleles of these genes as risk factors for PD; this may redirect the field away from association studies of CAG repeats in ataxia genes and PD, a valuable contribution in and of itself.

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