UCHL1 Is a Parkinson's Disease Susceptibility Gene

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The reported inverse association between the S18Y variant of the ubiquitin carboxy-terminal hydrolase L1 (*UCHL1*) gene and Parkinson's disease (PD) has strong biological plausibility. If confirmed, genetic association of this variant with PD may support molecular targeting of the *UCHL1* gene and its product as a therapeutic strategy for PD. In this light, we performed a collaborative pooled analysis of individual-level data from all 11 published studies of the *UCHL1* S18Y gene variant and PD. There were 1,970 cases and 2,224 unrelated controls. We found a statistically significant inverse association of S18Y with PD. Carriers of the variant allele (Y/Y plus Y/S vs S/S) had an odds ratio (OR) of 0.84 (95% confidence interval [CI], 0.73–0.95) and homozygotes for the variant allele (Y/Y vs S/S plus Y/S) had an OR of 0.71 (95% CI, 0.57–0.88). There was a linear trend in the log OR consistent with a gene dose effect ($p = 0.01$). The inverse association was most apparent for young cases compared with young controls. There was no evidence for publication bias and the associations remained significant after excluding the first published, hypothesis-generating study. These findings confirm that *UCHL1* is a susceptibility gene for PD and a potential target for disease-modifying therapies.

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To determine whether the ubiquitin carboxy-terminal hydrolase L1 (*UCHL1*) gene S18Y variant is associated with Parkinson's disease (PD), we performed a collaborative pooled analysis of 11 genetic association studies. Leroy and colleagues[1] originally reported a missense I93M mutation in the *UCHL1* gene at chromosome locus 4p14 in one of 72 probands with familial PD and her brother. Both siblings had clinically typical PD.[1] While sequencing this same gene in members of a family with chromosome 4p-linked parkinsonism and in additional autosomal dominant parkinsonism families, Lincoln and colleagues discovered a new polymorphic variant S18Y.[2] A first case–control study showed that S18Y carriers had a significantly lower risk of PD (odds ratio [OR], 0.53; $p = 0.03$), and the risk reduction was greater for young-onset cases.[3] Of note, 42% of controls were carriers of the variant.

The *UCHL1* gene is a biologically plausible susceptibility gene for PD. *UCHL1* expression is neuron specific and widespread throughout the brain, with regionally high in situ hybridization signals within the substantia nigra pars compacta.[4] *UCHL1* encodes a protein that represents 1 to 2% of total soluble brain protein and is present in Lewy bodies, the pathological hallmark of PD.[5] UCHL1 plays an important role in ubiquitin-dependent proteolysis by recycling polymeric chains of ubiquitin to monomeric ubiquitin. Ubiquitin is activated, conjugated, and ligated to damaged proteins for proteasomal degradation. Disruption of the

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ubiquitin proteasomal system and resultant cytoplasmic aggregation of α-synuclein (SNCA) have been implicated as a causal pathway for Parkinson's disease.[6] In rat mesencephalic cultures, inhibition of UCHL1 with ubiquitin aldehyde causes a dose-dependent degeneration of dopaminergic neurons and the formation of SNCA positive cytoplasmic inclusions.[7]

Despite this biological plausibility, three epidemiological studies reported no association for the *UCHL1* S18Y variant with PD,[8–10] four reported an association in subgroups only,[11–14] and only three studies replicated an inverse association of S18Y with PD overall.[15–17] Prompted by the potential protective effect of this common gene variant and by its strong biological plausibility, but also by the inconsistent findings across epidemiological studies, we performed a collaborative pooled analysis of the *UCHL1* S18Y variant in PD.

Materials and Methods

We conducted a collaborative analysis of pooled individual-level data from published genetic association studies of the *UCHL1* S18Y variant and PD. We included full papers and abstracts and used updated data sets, whenever available. The publications were identified via Web-based searches (PubMed, OMIM), review of publication references and meeting abstracts, and communications with experts. Web-based search terms included "Parkinson's disease," "UCHL1," "UCH-L1," "ubiquitin carboxy-terminal hydrolase L1," and "S18Y." These searches were performed in July 2002, just before the invitation of corresponding authors to participate. The lead author (D.M.M.) contacted all corresponding authors and invited them to submit available data for the collaborative pooled analysis. All authors submitted data using a standardized template and data were checked for potential inconsistencies that were resolved via communication with the investigators. Electronic searches were repeated in February 2004 and did not identify any additional studies.

We performed the Breslow–Day test for homogeneity of odds ratios from the studies, and assessed the goodness-of-fit of Hardy–Weinberg equilibrium for controls in each study. We performed analyses for all 11 studies combined and for strata defined by family history (one or more first-degree relatives with PD considered "positive"), age at examination (or at study; highly correlated with age at onset in cases, Pearson correlation coefficient = 0.86), sex, and ethnicity (white or Asian). To study the relation between the S18Y variant and PD, we first performed Mantel–Haenszel analyses including unadjusted data from all studies, because not all studies had data available for adjustment variables. We then used logistic regression models to estimate ORs, 95% confidence intervals (CIs), and p values adjusted for study and for age at examination and sex as appropriate. Studies were treated as fixed effects in the logistic regression models of our primary analyses, and as random effects[18] in secondary analyses. We considered autosomal recessive (Y/Y vs S/S plus Y/S), dominant (Y/Y plus Y/S vs S/S), dose effect (using a variable for linear trend in log OR), and unrestricted genetic models (with dummy variables for Y/Y vs S/S and Y/S vs S/S).

To assess for potential bias, we analyzed funnel plots of the effect estimates against sample size for the individual studies and used Egger's test to detect possible publication bias.[19] We also conducted a meta-analysis of the published results from the studies contributing data to the pooled individual-level analyses. The meta-analyses provided random effects[20] estimates for unadjusted data. We further assessed potential bias by performing analyses excluding the data from the first published study that may be considered as hypothesis generating,[21] and using cumulative meta-analysis and recursive cumulative meta-analysis to estimate whether the summary OR changed over time as more data accumulated.[22]

Results

We identified 11 association studies of the *UCHL1* S18Y variant and PD (the original plus 10 replication studies).[3,8–17] There was full participation of all the corresponding authors. The pooled analyses included previously published data, as well as data from one study that had been published as an abstract only,[11] and extended data from the Mayo Clinic study[3] to include an additional 175 PD cases and 80 controls. Although the study by Zhang and colleagues published findings for both white and Asian subjects, data were available only for Asians for the pooled reanalysis.[12] There were 1,970 cases and 2,224 unrelated controls from seven white and four Asian studies. Table 1 summarizes the characteristics of the 11 studies. Only the study by Elbaz and colleagues used community-based cases and community-based controls.[14] Three other studies compared clinic-based cases to clinic-based controls, and the remaining seven studies compared referral-based cases (clinic or hospital) to controls from various sources. The S18Y allele carrier rate was 34% in white control subjects and 74% in Asian control subjects. Only the study by Satoh and Kuroda[16] showed significant departure from Hardy–Weinberg equilibrium in controls ($p = 0.02$). The 11 studies showed no significant heterogeneity (Breslow–Day test, $p = 0.21$ for Y/Y plus Y/S vs S/S and $p = 0.07$ for Y/Y vs S/S plus Y/S). The unadjusted analyses utilized the full set of 1,970 cases and 2,224 controls (4,194 total), whereas the logistic regressions included only 1,741 cases and 1,935 controls (3,587 total) because of missing values for sex and age at examination in some subjects.

All genetic models (autosomal recessive and dominant, dose effect, unrestricted) produced consistent results. Overall, we found an inverse association of S18Y with PD. Carriers of the variant allele (Y/Y plus Y/S vs S/S) had a Mantel–Haenszel estimate of the pooled OR of 0.84 (95% CI, 0.73–0.95), and homozygotes for the variant allele (Y/Y vs S/S plus Y/S) had a Mantel–Haenszel estimate of the pooled OR of 0.71 (95% CI, 0.57–0.88). The corresponding random effects estimates from the meta-analysis were 0.84 (0.71–0.98) and 0.72 (0.53–0.98), respectively. Figure 1A and B

Table 1. Characteristics of the 11 Studies Included in the Collaborative Reanalysis

	Cases								Controls				
Authors; country	Source	N	Age at Exam, yr (range)	Male Sex %	Age at Onset, yr (range)	Familial PD (%)	Ethnicity	Diagnostic Criteria	Source	N	Age at Exam, yr (range)	Male sex (%)	Ethnicity
Elbaz and colleagues, 2003; France[14]	Community	209	69 (37–76)	56.9	65 (35–75)	8.7	White	Bower[b]	Community	488	69 (36–79)	59.2	White
Gasser and colleagues, 2000; Germany[11]	Clinic	192	65 (40–88)	59.9	53 (32–78)	43.8	White	Gibb[c]	Spouses, clinic	254	64 (34–92)	47.2	White
Levecque and colleagues, 2001; France[9]	Clinic	114	67 (38–88)	47.4	60 (29–84)	100	White	Gibb[c]	Clinic, community	93	67 (44–89)	49.5	White
Maraganore and colleagues, 1999; US[3]	Clinic	307	70 (33–99)	61.9	64 (31–85)	12.7	White	Bower[b]	Spouses, community	190	72 (37–94)	37.9	White
Mellick and colleagues, 1999; Australia[8]	Clinic	142	66 (37–85)	48.6	59 (32–83)	14.1	White	Calne[d]	Spouses, volunteers	142	67 (39–86)	48.6	White
Momose and colleagues, 2002; Japan[17]	Hospital	230	63 (28–83)	49.1	55 (24–80)	5.7	Asian	Bower[b]	Volunteers	248	35 (20–90)	48.8	Asian
Satoh and colleagues, 2001; Japan[16]	Clinic	74	70 (46–86)	37.8	63 (39–79)	0	Asian	CAPIT[e]	Clinic	155	67 (40–88)	51.0	Asian
Savettieri and colleagues, 2001; Italy[10]	Clinic	169	67 (43–87)	58.6	59 (37–84)	0	White	Bower[b]	Aging study	165	73 (60–96)	45.5	White
Wang and colleagues, 2002; China[13]	Clinic	160	68 (34–86)	55.6	60 (30–82)	0	Asian	Gelb[f]	Clinic	160	69 (34–86)	55.6	Asian
Wintermeyer and colleagues, 2000; Germany[15]	Clinic	229	67 (29–91)	55	56 (22–87)	15.7	White	UK BB[g]	Aging study	200	?	52	White
Zhang and colleagues, 2000; Japan[12]	Clinic	144	63 (24–81)	46.5	57 (32–78)	0	Asian	Calne[d]	Clinic	129	56 (23–93)	58.9	Asian
Total		1,970	67 (24–99)	54.3	59 (22–87)	13.5				2,224	67 (20–96)	51.2	

[a]Published only as an abstract.
[b]At least two of four cardinal signs; exclusion of other causes of parkinsonism; responsiveness to L-dopa, if tried with adequate dose (Neurology 1999;52:1214–1220).
[c]Criteria for probable PD (J Neurol Neurosurg Psychiatry 1988;51:745–752).
[d]At least three of four cardinal signs, or two of four cardinal signs with asymmetry in at least one of tremor, rigidity, or bradykinesia; exclusion of other causes of parkinsonism (Ann Neurol 1992:S125–127).
[e]CAPIT: Core Assessment Program for Intracerebral Transplantation criteria; at least two of four cardinal signs and exclusion of other causes of parkinsonism (Mov Disord 1992;7:2–13).
[f]Criteria for Parkinson's disease (Arch Neurol 1999;56:33–39).
[g]United Kingdom Parkinson's Disease Brain Bank criteria (J Neurol Neurosurg Psychiatry 1992;55:181–184).

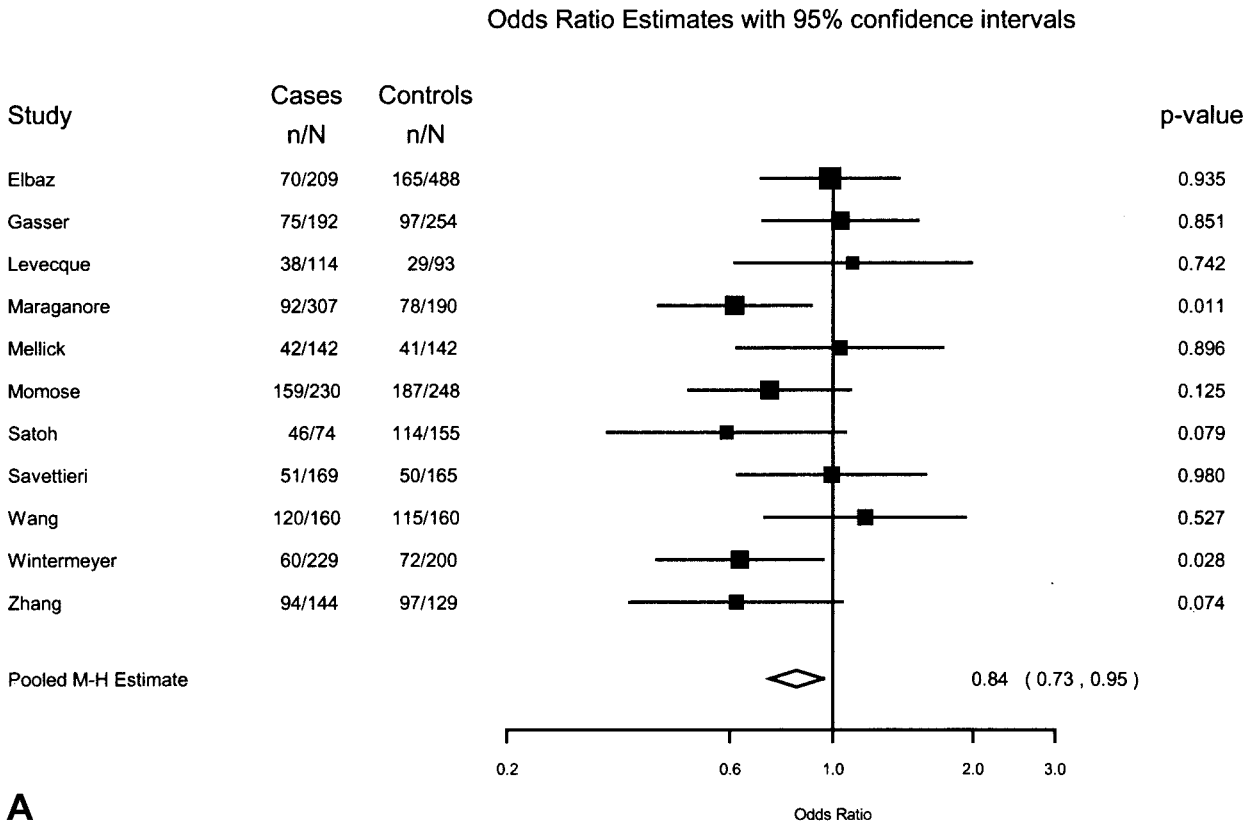
illustrates the pooled odds ratios for the studies (unadjusted). ORs from the logistic regression models adjusted for study, age, and sex were similar.

Logistic regression models including random effects (secondary analyses; details not reported) produced results similar to the fixed-effects models (primary analyses). The primary logistic regression analyses indicated that carriers of the variant allele (Y/Y plus Y/S vs S/S) had an OR of 0.88 (95% CI, 0.76–1.01) and homozygotes for the variant allele (Y/Y vs S/S plus Y/S) had an OR of 0.75 (95% CI, 0.59–0.94). There was a significant decreasing linear trend in the log OR consistent with a gene dose effect ($p = 0.01$, data not shown). Contrasting heterozygotes and homozygotes for the variant allele separately with the homozygotes for the wild allele, there was evidence for a significant association between genotype and risk of PD ($p = 0.03$). The OR of 0.92 for Y/S versus S/S and OR of 0.71 for Y/Y vs S/S were also consistent with a gene dose effect. Because all four genetic models had very similar Akaike information criterion values, no single model could be considered clearly superior to the others.

We found a significant inverse association in the stratum of subjects below the median age at examination (≤67 years), in the stratum of cases without a family history of PD, and in the stratum of Asian subjects (Table 2, Fig 2). Logistic regressions with interaction terms for the stratification variables indicated that the associations were not significantly different in sporadic versus familial cases, men versus women, and white subjects versus subjects of Asian descent. However, the associations did differ significantly in younger subjects versus older subjects.

To assess the robustness of these results to deviations from Hardy–Weinberg equilibrium, we repeated the analyses excluding the study by Satoh and Kuroda.[16] The unadjusted summary OR estimate changed only from 0.84 to 0.85 for the dominant model and remained unchanged for the recessive model. Only the subgroup below the median age at examination (≤67 years) remained significantly associated in adjusted analyses.

Funnel plots of the effect estimates against sample size of the individual studies (Fig 3) and Egger's test showed no evidence for publication bias ($p = 0.94$ for Y/Y plus Y/S vs S/S and $p = 0.78$ for Y/Y vs S/S plus Y/S). The results were also robust in the meta-analyses when the data from the first hypothesis-generating study were excluded from the calculations (random effects OR, 0.86; 95% CI, 0.74–0.99 in the dominant model and OR, 0.72; 95% CI, 0.52–0.98 in the recessive model). The first study had suggested a some-



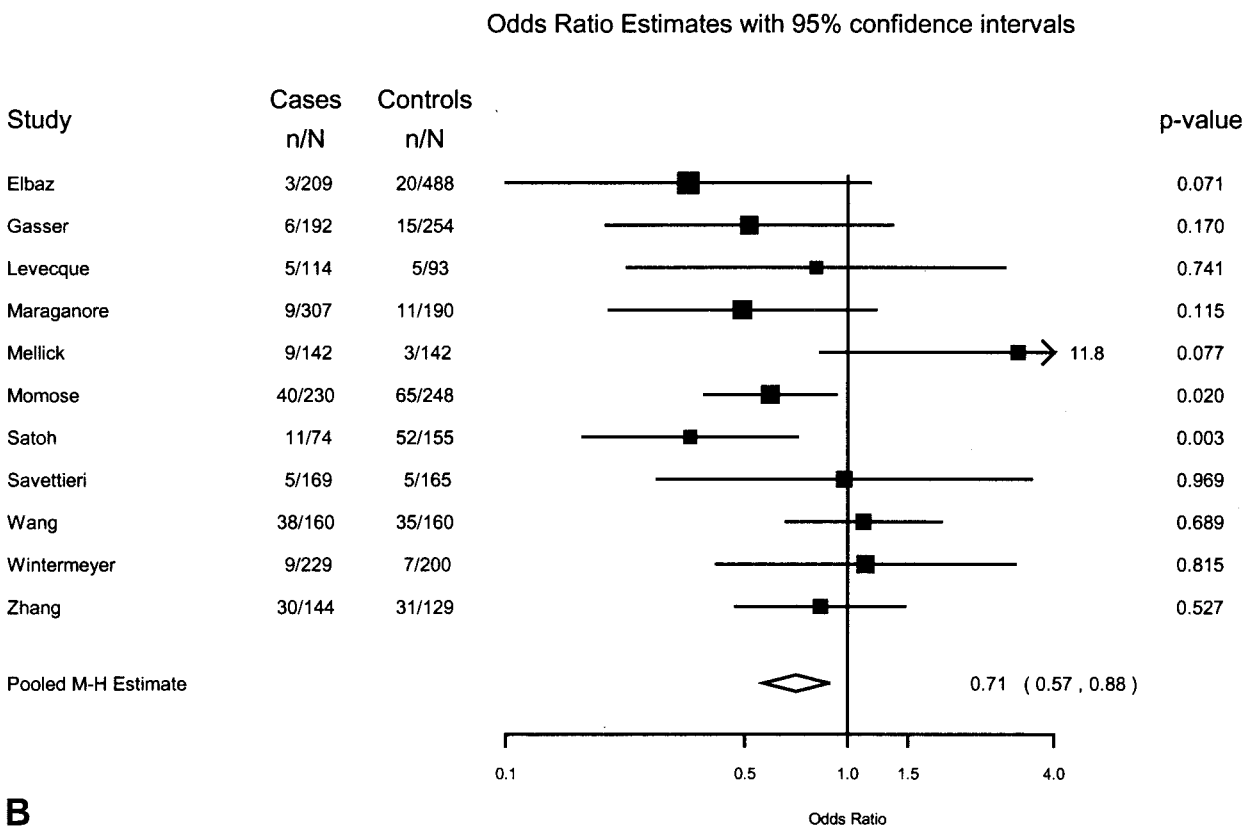


Fig 1. Odds ratios, 95% confidence intervals, and p *values for the UCHL1 S18Y variant and Parkinson's disease (unadjusted; not all studies had data for adjustment variables). (A) Assuming a dominant gene effect (Y/Y plus Y/S vs S/S); (B) assuming a recessive gene effect (Y/Y vs S/S plus S/Y). Individual studies and the pooled Mantel–Haenszel estimate are shown. Solid squares are proportional in area to the number of cases. The odds ratios are reported on a logarithmic scale.*

Table 2. Pooled Analyses of the Association between Parkinson's Disease and the UCHL1 Gene S18Y Variant

Sample or Stratum	No. of Studies	No. of Subjects	Unrestricted (genotype vs S/S)[a] OR (95% CI)	p[b]	Y/Y vs S/S + Y/S OR (95% CI)	p[b]	Y/Y + Y/S vs S/S OR (95% CI)	p[b]
Controls, all	11	2,224	Y/S: 0.92 (0.79–1.07)					
Cases, all	11	1,970	Y/Y: 0.71 (0.55–0.91)	0.03	0.75 (0.59–0.94)	0.01	0.88 (0.76–1.01)	0.07
Controls, neg fam hist[c]	8	1,636	Y/S: 0.85 (0.72–1.01)					
Cases, neg fam hist[c]	8	1,343	Y/Y: 0.71 (0.55–0.93)	0.02	0.78 (0.61–1.00)	0.05	0.82 (0.70–0.97)	0.02
Controls, pos fam hist[c]	5	394	Y/S: 0.90 (0.55–1.46)					
Cases, pos fam hist[c]	5	204	Y/Y: 1.29 (0.51–3.45)	0.35	1.35 (0.56–3.54)	0.51	0.95 (0.60–1.51)	0.83
Controls, age ≤67 yr	10	959	Y/S: 0.80 (0.65–0.99)					
Cases, age ≤67 yr	10	901	Y/Y: 0.49 (0.35–0.69)	0.0001	0.55 (0.40–0.76)	0.0002	0.73 (0.59–0.89)	0.002
Controls, age>67 yr	10	976	Y/S: 0.96 (0.78–1.20)					
Cases, age>67 yr	10	830	Y/Y: 0.92 (0.63–1.36)	0.90	0.94 (0.65–1.36)	0.75	0.96 (0.78–1.18)	0.67
Controls, women	10	988	Y/S: 0.94 (0.76–1.18)					
Cases, women	10	798	Y/Y: 0.71 (0.50–1.00)	0.15	0.73 (0.53–1.01)	0.06	0.89 (0.72–1.10)	0.30
Controls, men	10	1,036	Y/S: 0.89 (0.72–1.10)					
Cases, men	10	943	Y/Y: 0.68 (0.48–0.97)	0.10	0.72 (0.51–1.01)	0.06	0.85 (0.70–1.04)	0.12
Controls, white	6	1,531	Y/S: 0.97 (0.81–1.16)					
Cases, white	6	1,361	Y/Y: 0.70 (0.45–1.08)	0.26	0.71 (0.46–1.08)	0.11	0.93 (0.78–1.11)	0.43
Controls, Asian	5	693	Y/S: 0.76 (0.57–1.01)					
Cases, Asian	5	609	Y/Y: 0.67 (0.47–0.94)	0.05	0.80 (0.60–1.06)	0.12	0.73 (0.56–0.95)	0.02

[a]In dose-effect analyses, carriers of one Y variant were contrasted with subjects with the S/S genotype, and carriers of two Y variants were contrasted with subjects with the S/S genotype (no pooling of the Y/S individuals with either Y/Y or S/S).
[b]Odds ratios and likelihood ratio p values were adjusted for sex and age at examination in logistic regression models with study-specific intercepts (fixed effects). Analyses stratified by sex were adjusted for age at examination only.
[c]Cases with positive or negative family history were contrasted separately to the full group of controls in the contributing studies (with adjustment for sex and age at examination).

what larger effect size,[3] but the summary OR has not changed prominently since 2000.

Discussion

Considerations of Methods

There is growing interest in using quantitative syntheses of individual studies to clarify the impact of human genetic variation on health and disease.[21,23–25] Pooling or aggregation of studies increases the statistical power to detect associations, facilitates exploration of heterogeneities, and enables subgroup analyses.[26] In contrast with meta-analysis, collaborative pooled analyses maximize the use of existing databases.[27–29] Specifically, similar disease definitions and measurements, as well as uniform statistical analyses can be applied to all data from all studies. Collaborative pooled analyses also allow for the inclusion of unpublished studies and expanded data sets.

Our collaborative pooled analysis has several strengths. First, our study fulfills the methodologic recommendations of a recent systematic review of pooled molecular association studies.[26] Specifically, we described our search and selection criteria for studies; performed tests for heterogeneity of results across studies, for Hardy–Weinberg equilibrium among controls, and for publication bias; and considered multiple genetic models as well as "model-free" analyses. Second, our pooled sample had a large sample size, and the candidate gene has strong biological plausibility.[30] Third, in an effort to reduce the confounding effects of publication bias, our collaborative pooled analysis included one study that was published as an abstract only[11] and included unpublished data from the participating sites, whenever possible.[31] We also formally tested our series of studies for evidence of a publication bias.[19] Finally, our results remained significant when the first hypothesis-generating study was excluded.[3]

Our study also has some weaknesses. First, this is a retrospective reanalysis of several small studies. The cases and controls were recruited from multiple sources (community-based vs others), and this may have introduced some referral bias. A prospectively designed, large multicenter study might provide greater assurances against sampling and measurement biases resulting from within-study and between-study heterogeneities.[32] Large studies may tend to give more conservative results.[32] However, prospectively designed multicenter studies are costly. They also are not immune to sampling biases as a result of inherent demographic, genetic, and environmental differences across large study populations. In fact, the use of data from diverse settings, when appropriately adjusted for im-

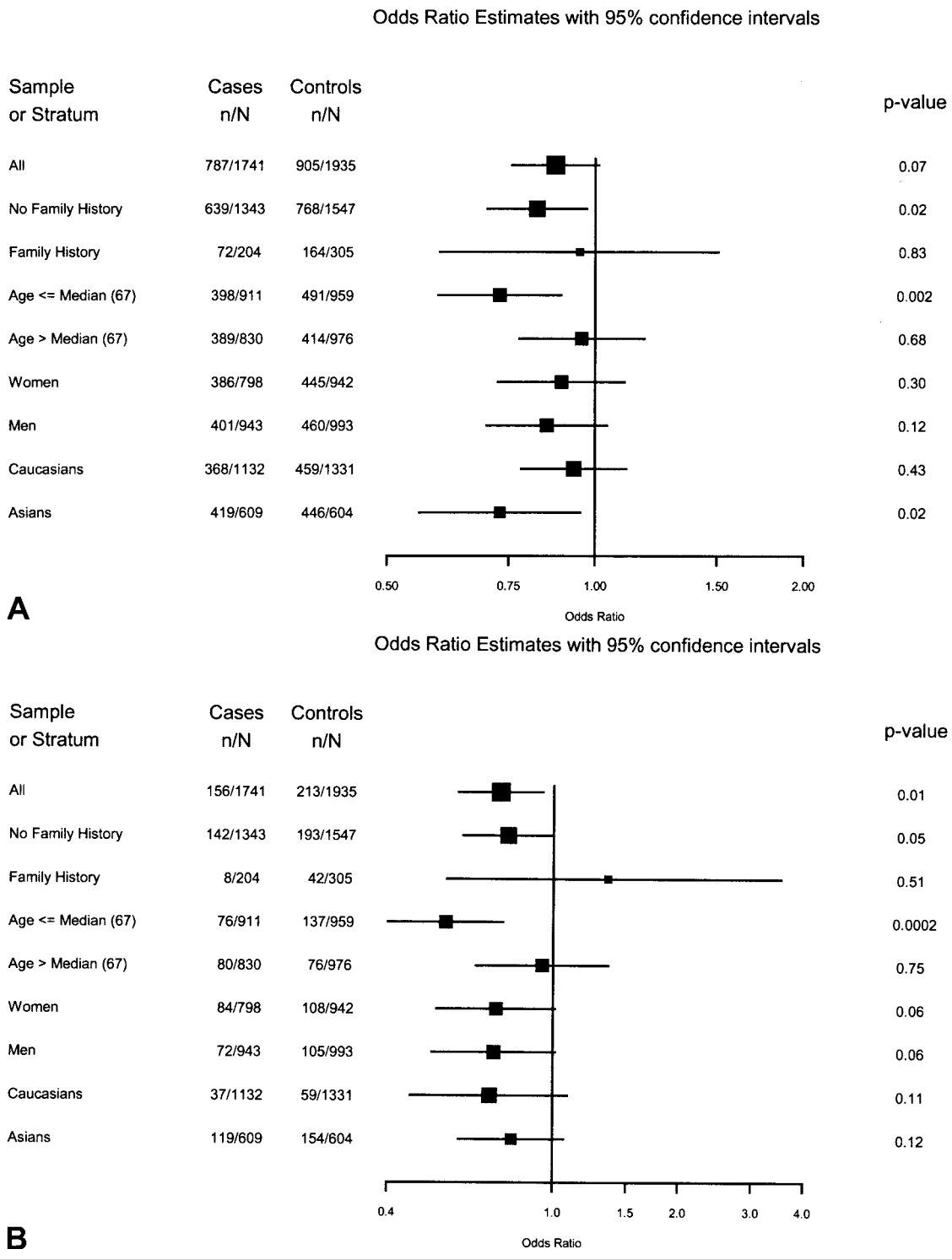


Fig 2. Odds ratios, 95% confidence intervals, and p *values for the UCHL1 and S18Y variant and Parkinson's disease in strata of the pooled sample. (A) Assuming a dominant gene effect (Y/Y plus Y/S vs S/S); (B) assuming a recessive gene effect (Y/Y vs S/S plus S/Y). Solid squares are proportional in area to the number of cases. The odds ratios are reported on a logarithmic scale. Family history for controls was unavailable for most studies. Not all studies provided family history information for cases. Some studies were restricted to familial or sporadic cases only. Hence, for studies in which family history information was available for cases, we contrasted subgroups of cases against controls from those studies with either the same or unknown family history. As a result, the sums of the number of cases (N) and controls (N) for the family history strata do not match those for the overall sample. Odds ratios and* p *values adjusted for study and for age at examination and sex whenever appropriate.*

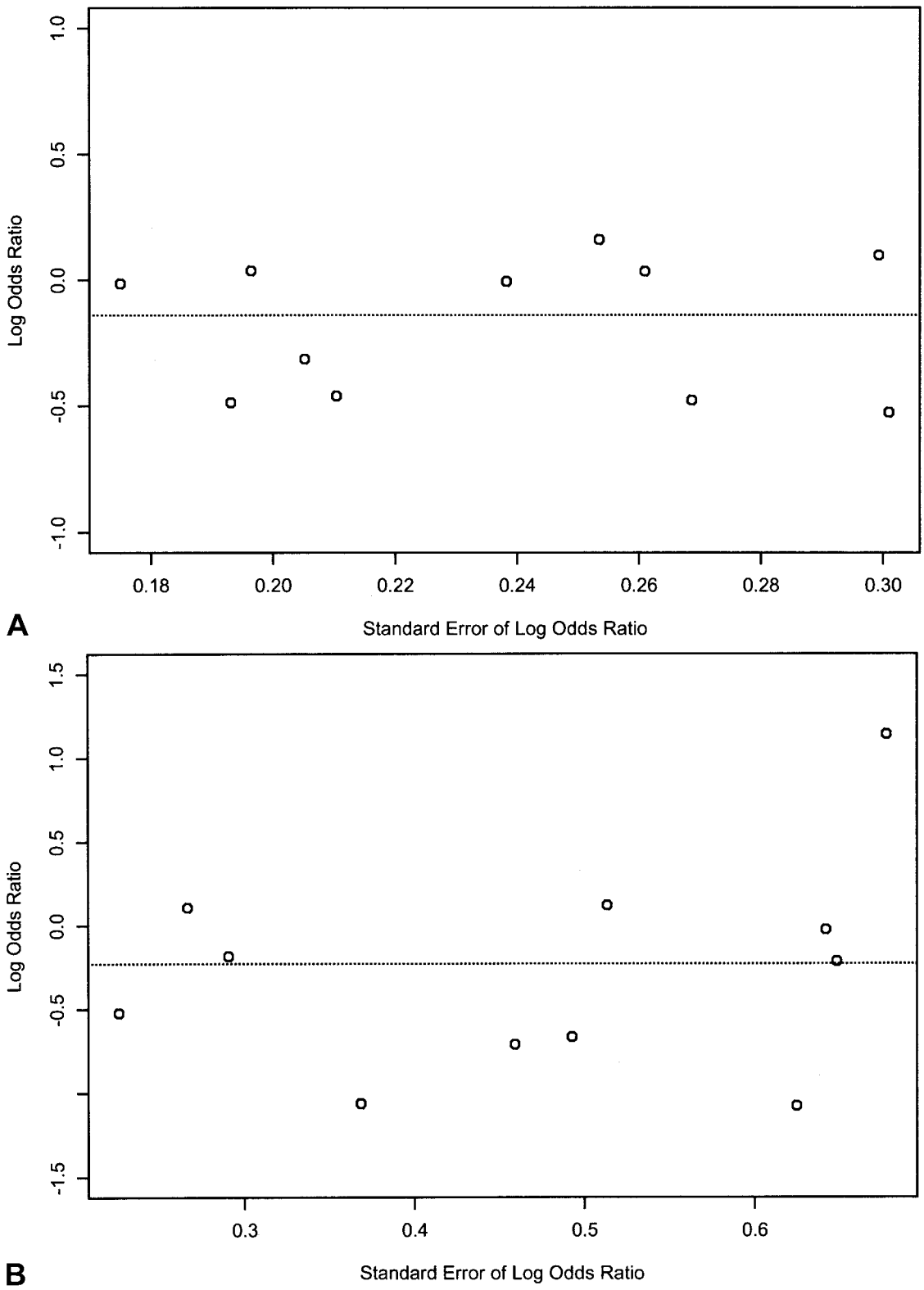


Fig 3. Funnel plots for assessing publication bias in relation to the UCHL1 S18Y variant and Parkinson's disease. (A) Assuming a dominant gene effect (Y/Y plus Y/S vs S/S); (B) assuming a recessive gene effect (Y/Y vs S/S plus S/Y). The horizontal line is the summary odds ratio. Circles represent individual studies. A slope indicating a bias in ORs between small and large studies was not apparent. Egger's tests for bias were not significant ($p = 0.94$ *for the dominant model and* $p = 0.78$ *for the recessive model).*

portant parameters, as in this pooled analysis, may provide a prime opportunity for addressing sources of genuine heterogeneity in the genetic effects. We performed a statistical test for heterogeneity of the OR, which was not significant. We also adjusted for study in our statistical analyses.

Second, for one of the 11 studies included, the allele frequencies in controls were not in Hardy–Weinberg equilibrium. This lack of equilibrium may have been caused by several causes: (1) the alleles were not segregating independently; (2) there was nonrandom mating; (3) the alleles reflected recent mutation that had not yet reached equilibrium; (4) there was a selection bias; (5) there was population stratification; or finally (6) a genotyping error occurred in the laboratory. As suggested by Attia and colleagues, we performed a sensitivity analysis excluding the unusual study, and the results were reassuringly very similar.[26]

Third, we cannot exclude population admixture as a confounder of our findings, particularly because our pooled sample included outbred populations.[33,34] To account for possible population heterogeneities, we stratified our statistical analyses for ethnicity. We observed a statistically significant inverse association of the *UCHL1* S18Y variant with PD for Asian but not white study populations. This difference may simply reflect the greater allele frequency of the S18Y variant in Asian control subjects (greater statistical power), or it may be caused by chance. Although we were unable to reaccess white subject data from the study of Zhang and colleagues as required for adjusted analyses,[12] inclusion of the published data in unadjusted analyses did not change the results considerably (data not shown).

Consideration of Results

Our collaborative pooled analysis confirms an inverse association between the *UCHL1* gene S18Y variant and PD, particularly in younger subjects. Although our association findings were positive overall, we only considered one polymorphism. It is possible that this variant is only a marker for genetic association of PD with another *UCHL1* variant or a variant within another gene (in linkage disequilibrium with *UCHL1*). Lincoln and colleagues sequenced all exons of the *UCHL1* gene and 50bp 5′ and 3′ of the flanking introns (to detect splicing variants).[2] The S18Y variant was the only amino acid substitution identified. However, they did not sequence the promoter regions.[3] Sequencing of the *UCHL1* gene in French families with PD subsequently identified a rare A371C polymorphism in exon 5, leading to a M124L amino acid change.[35] This variant did not segregate with PD, and its functional effects are not known.

Although the S18Y variant produces an amino acid change in the encoded protein, this change is distal to the binding site. Position 18 is not conserved between humans and other species, suggesting that this residue is not involved in normal biological activity of UCHL1 (hydrolysis). On the other hand, Liu and colleagues recently demonstrated that UCHL1 and α-synuclein colocalize with synaptic vesicles and can be coimmunoprecipitated from human brain.[36] Their cell culture and in vitro experiments suggested that the *UCHL1* gene encodes two opposing enzymatic activities. In its monomeric form, UCHL1 hydrolyses polymeric K48 ubiquitin and ubiquitin conjugates to monomeric ubiquitin; while in its dimeric form it acts as a K63 ubiquitin ligase.[36] By resisting dimerization and thus reducing ligase activity in a dose-dependent fashion, the S18Y encoded variant may inhibit cytosolic aggregation of the endogenously toxic protein SNCA and thus may have a neuroprotectant effect.

Extending these experimental findings, Maraganore and colleagues recently reported an interaction for genotypes defined by *UCHL1* S18Y and *SNCA* REP1 variants.[37] Sizing variants of the *SNCA* promoter (REP1) and haplotypes defined by these alleles previously were associated with an increased risk for PD.[38] Study subjects carrying one or two copies of the *UCHL1* S18Y variant had a greater likelihood of being a control (reduced PD case likelihood). Persons who were *UCHL1* S18Y carriers required two copies of the *SNCA* REP1 allele to have a greater case likelihood, whereas persons who were not *UCHL1* S18Y carriers required only one copy of the *SNCA* REP1 variant to have a greater case likelihood.[37] Unfortunately, *SNCA* REP1 genotypes were not available for the other studies included in this collaborative reanalysis; therefore, we were unable to test for interactions with *UCHL1* genotypes in the pooled sample.

In summary, our collaborative reanalysis confirms that the *UCHL1* gene S18Y variant is inversely associated with PD overall, and, in particular, for younger subjects. We detected a gene dose effect, consistent with functional studies.[36] These genetic association data, in combination with experimental data, suggest that the *UCHL1* S18Y variant protects against PD. Our findings also encourage initiatives to target the *UCHL1* gene and its product for new drug development.

Appendix

The UCHL1 Global Genetics Consortium includes 30 investigators, who are all contributors to this manuscript. They are listed by contribution and in alphabetic order, below.

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