Alzheimer's disease *CD33* rs3865444 variant does not contribute to cognitive performance

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Alzheimer's disease (AD) is complex and one of the most common neurodegenerative diseases in the elderly (1). Three large-scale genome-wide association studies (GWAS) identified *CD33* rs3865444 polymorphism to be significantly associated with AD susceptibility in European ancestry with genome-wide significance ($P < 5.00E-08$). In our previous meta-analysis, we further confirmed the association between rs3865444 and AD susceptibility in Chinese and North American populations (1). In a recent study, Schwarz et al. analyze 13 SNPs, and identify that the human-specific–derived alleles of *CD33* (rs3865444) and other genes protect against postreproductive cognitive decline (2).

Until now, four large-scale GWAS have been conducted to investigate the common variants associated with childhood intelligence (general cognitive function in childhood, 17,989 individuals aged 6–18 y) (3), cognitive performance in a general population aged >30 y (106,736 individuals, 96.0% of the individuals were aged >30 y) (4), as well as educational attainment in a general population aged >30 y (101,069 individuals, 96.0% of the individuals were aged >30 y) (5). Two variables were used to measure the educational attainment, a quantitative variable for an individual's years of schooling (EduYears) and a binary variable for college completion (College) (5).

We acquired the summary association results from these three studies above (3–5), and investigated the association of these 13 variants with childhood intelligence, cognitive performance, and educational attainment, respectively (Table 1). We identified that 10 of these 13 variants were available in the four GWAS datasets. However, none of these variants shows significant association with childhood intelligence, cognitive performance, and educational attainment ($P > 0.05$).

In summary, Schwarz et al. (2) report the protective role of SNPs in *CD33* and other genes against postreproductive cognitive decline. Using the four large-scale GWAS datasets, we did not find any significant association between 10 of 13 SNPs and childhood intelligence, cognitive performance, and educational attainment. We believe that our findings provide important supplementary information about the role of *CD33* and other genes in cognitive decline.

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1 Li X, et al. (2015) CD33 rs3865444 polymorphism contributes to Alzheimer's disease susceptibility in Chinese, European, and North American populations. *Mol Neurobiol* 52(1):414–421.
2 Schwarz F, et al. (2016) Human-specific derived alleles of *CD33* and other genes protect against postreproductive cognitive decline. *Proc Natl Acad Sci USA* 113(1):74–79.
3 Benyamin B, et al.; Wellcome Trust Case Control Consortium 2 (WTCCC2) (2014) Childhood intelligence is heritable, highly polygenic and associated with FNBP1L. *Mol Psychiatry* 19(2):253–258.
4 Rietveld CA, et al. (2014) Common genetic variants associated with cognitive performance identified using the proxy-phenotype method. *Proc Natl Acad Sci USA* 111(38):13790–13794.
5 Rietveld CA, et al.; LifeLines Cohort Study (2013) GWAS of 126,559 individuals identifies genetic variants associated with educational attainment. *Science* 340(6139):1467–1471.

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Table 1. *CD33* and other genes with childhood intelligence (3), cognitive performance (4), and educational attainment (5)

				Childhood intelligence (3)		Cognitive performance (4)		College (5)		EduYears (5)	
Gene	SNP	EA	NEA	β	*P*	β	*P*	OR	*P*	β	*P*
PPARG	rs1801282	C	G	0.0358	0.07239	0.008793028	0.1697	1.011	0.4248	0.007	0.2028
COX-2	rs20417	C	G	−0.0418	0.01937	0.006811218	0.2852	0.998	0.8611	0.004	0.4291
EBF1	rs2149954	T	C	0.0172	0.1956	−0.005993436	0.1847	0.982	0.06918	−0.005	0.2409
PON1	rs2618516	T	C	0.0049	0.7088	−0.002542563	0.5677	1.006	0.5344	0.001	0.7542
CAPN10	rs2975760	T	C	NA	NA	−0.005909398	0.3185	0.997	0.7958	−0.005	0.3262
CD33	rs3865444	A	C	−0.0261	0.05591	0.002334702	0.6175	1.006	0.5284	0.004	0.9683
AGT	rs699	A	G	−0.0087	0.5064	0.003005322	0.5058	1	0.9952	0.004	0.28
CYP3A5	rs776746	T	C	−0.0082	0.7499	−0.004371438	0.6054	0.998	0.8997	−0.008	0.1766
TCF7L2	rs7903146	T	C	−0.0134	0.3487	0.003007023	0.5317	1.001	0.9588	0.003	0.4435
SCG2	rs1017448	T	C	0.0167	0.7019	NA	NA	NA	NA	NA	NA

β, Regression coefficient; College, a binary variable for college completion; EA, effect allele; EduYears, a quantitative variable for an individual's years of schooling; NA, not available; NEA, not effect allele; OR, odds ratio. For all the tests, the significance level is 0.05.