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Nonreplication of an Association of Apolipoprotein E2 With Sinistrality

Brian J. Piper^{a,b,*}, Alia L. Yassen^{b,#}, Amy E. Taylor^{c,#}, Jonatan R. Ruiz^d, J. William Gaynor^e, Catherine A. Dayger^a, Marcela Gonzalez-Gross^f, Oh D. Kwon^g, Lars-Göran Nilsson^h, Ian N. M. Day^c, Jacob Raber^a, and Jeremy K. Miller^b

^aDepartment of Behavioral Neuroscience, Oregon Health & Science University, Portland, Oregon, USA

^bDepartment of Psychology, Willamette University, Salem, Oregon, USA

^cSchool of Social and Community Medicine, University of Bristol, Bristol, United Kingdom

^dDepartment of Biosciences and Nutrition at NOVUM, Karolinska Institutet, Huddinge, Sweden

^eChildren's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

^fFacultad de Ciencias de la Actividad Física y del Deporte, INEF, Universidad Politécnica de Madrid, Spain

^gDepartment of Neurology, Catholic University of Daegu, Daegu, South Korea

^hDepartment of Psychology, Stockholm University, Stockholm, Sweden

Abstract

A recent report found that left-handed adolescents were over three-fold more likely to have an Apolipoprotein (*APOE*) 2 allele. This study was unable to replicate this association in young-adults (N=166). A meta-analysis of nine other datasets (N = 360 to 7,559, Power > 0.999) including that of National Alzheimer's Coordinating Center also failed to find an over-representation of 2 among left-handers indicating that this earlier outcome was most likely a statistical artifact.

Keywords

APOE; handedness; right

Introduction

The neurobiological origin of individual differences in handedness has been a long-standing enigma in the behavioral neurology field (Llaurens et al., 2009). Rife (1940) advocated for genetic factors when his pedigree analysis revealed that the likelihood of having a left-handed child increased over three-fold if at least one of the parents were themselves left-handed. The hand preference of adoptive children was independent of the handedness of their biologically unrelated parents which ruled out social-learning as the sole determinant of sinistrality (Carter-Saltzman, 1980). Although different mathematical approaches have been proposed to explain familial transmission patterns, most prominently by Annett (1964),

*Correspondence: Brian J. Piper, Ph.D., Department of Psychology, Willamette University, Salem, OR 97301, Phone: (413) 687-8729, Fax: (503) 370-6512, psy391@gmail.com or piperbj@husson.edu.

#Designated authors contributed equally.

the next logical step in this line of study is to move beyond modeling to empirically evaluating the prevalence of different genes in the general population.

The Apolipoprotein E (ApoE) gene is found on chromosome 19 and encodes a 299 amino acid protein. The Apo 3 isoform contains a cysteine and arginine at amino acid positions 112 and 158. In contrast, these positions are occupied by only cysteines in 2 and only arginines in 4. Apo 3 is typically found in the majority of the population, with 2 and 4 each being far less common. The 1 and 5 alleles have also been identified but in less than one out of every 500 people (Ordovas et al., 1987). ApoE, due to its involvement in specific diseases, is one of the few genes that have replicable consequences for human lifespan (Christensen et al., 2006). Importantly, over ninety percent of Alzheimer's disease cases develop after the age of sixty and 4 has been consistently identified as the predominant risk factor (Bekris et al., 2010; Raber et al., 2004). Further, 2 was protective against Alzheimer's in Caucasian sample (Genin et al. 2011). The ethnicity of the study population is a key factor because APOE exhibits tremendous variability (Cheung et al. 2000). For example, 2 is virtually non-existent among Native Americans while 4 ranges from five percent in European Sardinians to forty percent in African Pygmies (Corbo & Scacchi, 1999).

Several laboratories have examined whether there is also evidence of subtle neurocognitive differences that precede dementia in Apo 4 carriers (Acevedo et al., 2010; Berteau-Pavy et al., 2007; Ruiz, et al., 2010; Small et al., 2004). As part of this line of study, Bloss and colleagues (2010) found that visual-spatial skills on the Rey–Osterrieth Complex Figure Test were significantly lower in 2 children relative to either 3 or 4 carriers. A perhaps unintended finding from this same report was that left-handedness, as determined by self-reported writing hand, was three-fold more common in 2+ (7/24 or 29.2%) versus 2– individuals (10/113 or 8.8%, $p < .005$). Therefore, the primary objective of this report was to attempt to replicate the over-representation of the 2 allele among sinistrals. As this association was not found in an equivalent sized sample using similar methodology as Bloss et al., (2010), additional datasets from different aged participants (older and younger) as well as more homogenous ethnic groups were also evaluated. Utilization of geographically diverse samples may limit the potential of cultural suppression to attenuate any association between a single gene and handedness.

Methods

Saliva samples from young-adult participants ($N = 169$, 52.3% female, Age = 18.9 ± 0.1) were stored at -20°C , thawed and transferred to Whatman FTA Classic Cards and *ApoE* genotypes were subsequently determined at the General Clinical Research Center of OHSU by polymerase chain reaction (PCR) with two SNP haplotype of rs429358 and rs7412. Genomic DNA containing apoE sequences with amino acid positions 112 and 158 were amplified using standard PCR procedures (Hixson & Vernier, 1990), and the SNP's were identified by DNA sequencing using an Applied Biosystems (Carlsbad, CA) 3130 XL genetic analyzer. More detailed information is available elsewhere (Berteau-Pavy et al. 2007). Participants also filled out a standard handedness inventory regarding hand usage for common activities (Oldfield, 1971) with the Laterality Index calculated as $[(R-L)/(R+L)]*100$. All procedures were approved by the IRB of Willamette University. Hardy-Weinberger equilibrium was tested using the program described in Rodriguez, Gaunt, and Day (2009). A χ^2 compared handedness by 2– (3 3, 3 4, or 4 4) versus 2+ (2 2 or 2 3). The 2 4 participants were excluded from this analysis as was also done previously (Bloss et al., 2010).

As each laboratory may use slightly different categorizations in determining handedness (described below), Table 1 results are presented with the left-handed and ambidextrous subjects collapsed into a single non-right-handed group. Statistics were conducted with the SPSS version 16.0 with parametric data presented as mean $\pm$ the standard error or the mean. A post-hoc power analysis conducted for the goodness of fit contingency table within G*Power 3 (Faul et al. 2007) using an alpha of .05 and an effect size of 0.197 (calculated from Bloss et al. 2010), revealed that 166 participants would result in only moderate power (0.72), 271 would be needed to for a very high power (0.90), and 831 would be required for maximal power (0.9999).

The sources of the datasets contained in Table 1 are:

1. Children's Hospital of Philadelphia (CHoP): This data comes from a prospective trial examining the consequences of APOE polymorphisms on neurodevelopmental function in preschoolers that received cardiac surgery during infancy. Handedness (left, right, or ambidextrous) was based on parental report which occurred twice (test-retest agreement of 93%) between ages 4 and 5. Additional details regarding the participants and genotyping procedures for the blood and buccal samples are available elsewhere (Gaynor et al. 2009;).
2. Alimentación y Valoración del Estado Nutricional en Adolescentes (AVENA), or, in English, the Food and Assessment of the Nutritional Status of Spanish Adolescents: This cross-sectional investigation was designed to evaluate the nutritional status of a sample of urban Spanish teenagers. Handedness was based on self-report. Further information about his cohort may be found in Ruiz et al. 2010. APOE (rs7412 and rs429358) genotypes were determined from blood samples by PCR and allele-specific restriction digestion of the amplified products with the restriction enzyme HhaI (Hixson & Vernier, 1990).
3. Lothian Birth Cohort of 1936 (LBC1936): The LBC is a cohort of residents of Scotland, born in 1936, who also completed standardized mental testing at ages 11 and 70 (Deary et al. 2002, 2007). Handedness (left, right, or ambidextrous) classification was based on self-report. APOE was genotyped from DNA extracted from white-blood cells (SNPs rs7412 and rs429358) using TaqManŽ technology (Applied Biosystems) by the Wellcome Trust Clinical Research Facility Genetics Core, Western General Hospital, Edinburgh.
4. Betula Prospective Cohort Study (BPCS): The BPCS sample is from Umea, a small city in northeastern Sweden. Participants (ages 40, 45, 50, 55, 60, 65, 70, 75, 80, or 85) completed extensive health and memory examinations described elsewhere (Nilsson et al., 1997). During the second wave of testing (1993–1995), participants were asked “Are you right-handed, left-handed or are you equally good at using both hands?”. Additional information regarding the genotyping of plasma samples is contained in Nilsson et al., 2006.
5. Alzheimer's Disease and Memory Disorders Center, Baylor College of Medicine (ADMDC-BCM): This diverse sample of Alzheimer's Disease Patients included Caucasians (N = 958), Hispanics (N= 52), African Americans (N=73), and Koreans (N=77). Handedness was determined based on the Oldfield (1971) instrument with right-handedness defined as a LI > 0.48. Further details about this sample are available elsewhere (Kwon et al. 2010). Genotype was determined from peripheral leucocytes according to Hixson and Vernier (1991).
6. The University of California at Davis Alzheimer's Disease Center (UCD-ADC): This organization provides comprehensive assessments of individuals that have memory problems. This dataset is from all individuals seen at the center that

provided both handedness and samples that were genotyped for *APOE* (Average age = 74.4). Genotyping was carried out using the LightCycler ApoE mutation detection kit (Roche Diagnostics, Indianapolis, IN). Briefly, genomic DNA extracted from EDTA blood was amplified by PCR. The 265 bp product was hybridized with dual color probes specific for the detection of the mutations at codons 112 and 158 of the human ApoE gene. Melt curve analysis allows unambiguous genotyping of the six ApoE alleles.

7. National Alzheimer's Coordinating Center (NACC): The NACC Uniform Data Set (UDC) is collected from 29 institutions (Beekly et al. 2007). Each Alzheimer's Disease Center submits data online, longitudinally, with the goal of better understanding participants with mild Alzheimer's disease and mild cognitive impairment and how this contrasts with non-demented controls. PCR procedures are completed according to the best practice method of each contributing institution. Handedness is categorized as right-hand/ambidextrous/left-handed or unknown in response to the intake interview question "Is the subject left- or right-handed (for example, which hand would s/he normally use to write or throw a ball?)". As the UCDADC contributes to the NACC, the findings presented are for all centers except the UCDADC. The average age of African Americans in the UDC is 75 and Caucasians is 74.
8. Avon Longitudinal Study of Parents and Aging (ALSPAC): The ALSPAC study is a prospective investigation whose objective is to explore child health and development. The sample consists of offspring of women from Bristol, United Kingdom (Taylor et al. 2011). Handedness was recorded by a psychologist during neurobehavioral testing. Additional information is available elsewhere (<http://www.bristol.ac.uk/alspac>). An integrated single-label liquid phase assay was utilized for genotyping (Abdollahi et al. 2006).

All of the aforementioned data sources were included in a meta-analysis with the exception of #2 which had no left handed individuals who were 2 carriers. For each dataset, an odds ratio and 95% confidence interval was calculated with each point estimate representing the odds of being left handed in 2 carriers compared to non carriers. Analyses were conducted in STATA version 11 (StataCorp LP, College Station, TX). The overall estimate for the datasets was calculated and a forest plot generated using the "metan" command.

Results

The ApoE genotype distribution in the Willamette University sample was as follows: 2 2, N=2; 2 3, N=13; 2 4, N=3; 3 3, N=111; 3 4, N=38; 4 4, N=2, and was not different from Hardy-Weinberg proportions ($p > .10$). Left-handedness, defined based on writing hand, was not appreciably increased by the presence of 2 (Table 1). The Laterality Index from the Edinburgh Inventory (higher scores = more consistently right-handed) was +69.9 (± 9.5) in 2+ and 63.5 (± 3.4) in 2- ($t(162) = 0.58$, $p = .56$). The results were unchanged with right-handedness defined as Laterality Index > 40 and non-right-handedness as a Laterality Index ≤ 40 .

In several additional datasets, non-right handed participants never had an excess of 2+. This includes the NACC which had an adequate N to examine self-identified Caucasians and African-Americans separately. Within Caucasians, no effect of 2 was observed when males ($\chi^2(1) = 0.50$, $p = .48$) or females ($\chi^2(1) = 0.30$, $p = .58$) were analyzed separately. Curiously, in the UCDADC sample, 2+ was more common in right-handers although this barely met the statistical criteria ($p = .0485$). Similarly, further analysis revealed that the only investigation to report an odds ratio greater than 1.15 was the original report by Bloss

et al., 2010). A meta-analysis of all ten datasets revealed a pooled odds ratio of 0.92 (Figure 1).

Discussion

There are many explanations that could be offered for the failure to replicate the excess of 2 carriers among left-handers identified previously (Bloss et al., 2010). A lack of power is an obvious reason for discrepancies in these types of behavioral genetic investigations especially as both sinistrality and 2 occurred relatively infrequently. However, as the seven additional datasets that were unable to detect group differences each had power 0.99, this explanation is exceedingly unlikely. Differences in the sample characteristics (e.g. the mixed ancestry in Bloss et al. 2010) may also be essential or the earlier findings may be a Type I error. The additional analyses that were completed on several datasets collected by other laboratories (Table 1) included participants that were younger (Gaynor et al., 2009; Ruiz et al. 2010; Taylor et al. 2011) and older (Beekley et al., 2007; Nilsson et al., 1997; UCDADC). A benefit of examining multiple datasets is there may be less social pressure to modify hand usage among younger cohorts. Some of the datasets were obtained with the objective of learning about a particular disease (Beekley et al. 2007; Gaynor et al. 2009) and others were collected from very broadly defined populations (Deery et al., 2007; Nilsson et al., 1997; Ruiz et al., 2010). As the only other statistical difference was in the opposite of the anticipated direction (UCDADC), it may be safely concluded that ApoE, acting alone, does not determine sinistrality.

The quest to identify the biological basis of handedness has an extensive history (Llaurens et al., 2009). One very interesting finding is that both monozygotic and dizygotic twins were more likely to be discordant (i.e. one right-handed and one left-handed) than siblings (Rife et al., 1940, although see Medland et al. 2005). Medland and colleagues also noted that, after correcting for the potentially confounding effects of birthweight, only one-quarter of the variance in handedness was attributable to additive genetic factors with the remainder accounted for by non-shared environmental determinants (Medland et al. 2009). Others believe that the genetic contribution may even be more modest (Vuoksima et al. 2009). Overall, these findings do not easily fit a simplistic genetic model for handedness. Possibly, either other (non-ApoE) genes are involved (Medland et al. 2005; Francks et al. 2007; Crow et al. 2009) or, possibly, this trait is influenced by multiple genes which each account for a relatively modest proportion of the variance attributable to genetic factors. While the tenet of Occam's razor favors parsimony, the model of one gene being solely responsible for all cases of complex phenotypes is no longer accepted for autism or schizophrenia (Betancur, 2011; Gejman et al. 2011).

In closing, we speculate that further progress into the origins of individual differences in handedness may come from researchers equipped with a deep appreciation for the poly-deterministic character of complex behaviors who are also conversant with the tools of molecular biology and epigenetics.

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References

- Abdoahi MR, Guthrie PA, Smith GD, Lawlor DA, Ebrahim S, Day IN. Integrated single-label liquid-phase assay of APOE codons 112 and 158 and a lipoprotein study in British women. *Clin Chem*. 2006; 52:1420–1423. [PubMed: 16644874]
- Acevedo SF, Piper BJ, Craytor MJ, Benice TS, Raber J. Apolipoprotein E4 and sex affect neurobehavioral performance in primary school children. *Pediatr Res*. 2010; 67:293–299. [PubMed: 19952867]
- Annett M. A model of the inheritance of handedness and cerebral dominance. *Nature*. 1964; 204:59–60. [PubMed: 14240116]
- Beekly DL, Ramos EM, Lee WW, Deitrich WD, Jacka ME, Wu J, Hubbard JL, Koepsell TD, Morris JC, Kukull WA. The National Alzheimer's Coordinating Center (NACC) database: The Uniform Data Set. *Alz Dis Assoc Dis*. 2007; 21:249–258.
- Bekris LM, Yu CE, Bird TD, Tsuang DW. Genetics of Alzheimer disease. *J Geriatr Psychiatry Neurol*. 2010; 23:213–227. [PubMed: 21045163]
- Berteau-Pavy F, Park B, Raber J. Effects of sex and APOE 4 on object recognition and spatial navigation in the elderly. *Neuroscience*. 2007; 147:6–17. [PubMed: 17509769]
- Betancur C. Etiological heterogeneity in autism spectrum disorders: More than 100 genetic and genomic disorders and still counting. *Brain Res*. 2011; 1380:42–77. [PubMed: 21129364]
- Bloss CS, Delis DC, Salmon DP, Bondi MW. APOE genotype is associated with left-handedness and visuospatial skills in children. *Neurobiol Aging*. 2010; 31:787–795. [PubMed: 18606479]
- Carter-Saltzman L. Biological and sociocultural effects on handedness: Comparison between biological and adoptive families. *Science*. 1980; 209:1263–1265. [PubMed: 7403887]
- Cheung KH, Miller PL, Kidd JR, Kidd KK, Osier MV, Pakstis AJ. ALFRED: a Web-accessible allele frequency database. *Pac Symp Biocomput*. 2000; 2000:639–50. [PubMed: 10902212]
- Christensen K, Johnson TE, Vaupel JW. The quest for genetic determinants of human longevity: Challenges and insights. *Nat Rev Genet*. 2006; 7:436–448. [PubMed: 16708071]
- Corbo RM, Schacchi R. Apolipoprotein E (APOE) allele distribution in the world. Is APOE*4 a 'thrifty' allele? *Ann Hum Genet*. 1999; 63:301–310. [PubMed: 10738542]
- Crow TJ, Close JP, Dagnalla AM, Priddlea TH. Where and what is the right shift factor or cerebral dominance gene? A critique of Francks et al (2007). *Laterality*. 2009; 14:3–10. [PubMed: 19125366]
- Deary IJ, Whiteman MC, Pattie A, Starr JM, Hayward C, Wright AF, Carothers A, Whalley LJ. Cognitive change and the APOE epsilon 4 allele. *Nature*. 2002; 418:932. [PubMed: 12198535]
- Deary IJ, Gow AJ, Taylor MD, Corley J, Brett C, Wilson V, Campbell H, Whalley LJ, Visscher PM, Porteous DJ, Starr JM. The Lothian Birth Cohort 1936: A study to examine influences on cognitive ageing from age 11 to age 70 and beyond. *BMC Geriatr*. 2007; 7:28–40. [PubMed: 18053258]
- Eisenberg DT, Kuzawa CW, Hayes MG. Worldwide allele frequencies of the human apolipoprotein E gene: climate, local adaptations, and evolutionary history. *Am J Phys Anthropol*. 2010; 143:100–111. [PubMed: 20734437]
- Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis for the social, behavioral, and biomedical sciences. *Behav Res Meth*. 2007; 39:175–191.
- Francks C, Maegawa S, Laurén J, Abrahams BS, Velayos-Baeza A, Medland SE, Colella S, Groszer M, McAuley EZ, Caffrey TM, Timmusk T, Pruunsild P, Koppel I, Lind PA, Matsumoto-Itaba N, Nicod J, Xiong L, Joob R, Enard W, Krinsky B, Nanba E, Richardson AJ, Riley BP, Martin NG, Strittmatter SM, Möller HJ, Rujescu D, St Clair D, Muglia P, Roos JL, Fisher SE, Wade-Martins R, Rouleau GA, Stein JF, Karayiorgou M, Geschwind DH, Ragoussis J, Kendler KS, Airaksinen MS, Oshimura M, DeLisi LE, Monaco AP. LRRTM1 on chromosome 2p12 is a maternally

- suppressed gene that is associated paternally with handedness and schizophrenia. *Mol Psychiatry*. 2007; 12:1129–39. [PubMed: 17667961]
- Gaynor JW, Nord AS, Wernovsky G, Bernbaum J, Solot CB, Burnham N, Zackai E, Heagerty PJ, Clancy RR, Nicolson SC, Jarvik GP, Gerdes M. Apolipoprotein E genotype modifies the risk of behavior problems after infant cardiac surgery. *Pediatrics*. 2009; 124:241–250. [PubMed: 19564306]
- Gejman PV, Sanders AR, Kendler KS. Genetics of Schizophrenia: New findings and challenges. *Annu Rev Genomics Hum Genet*. 2011 in press.
- Genin E, Hannequin D, Wallon D, Sleegers K, Hiltunen M, Combarros O, Bullido MJ, Engelborghs S, De Deyn P, Berr C, Pasquier F, Dubois B, Tognoni G, Fiévet N, Brouwers N, Bettens K, Arosio B, Coto E, Del Zompo M, Mateo I, Epelbaum J, Frank-Garcia A, Helisalmi S, Porcellini E, Pilotto A, Forti P, Ferri R, Scarpini E, Siciliano G, Solfrizzi V, Sorbi S, Spalletta G, Valdivieso F, Vepsäläinen S, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossù P, Hanon O, Piccardi P, Annoni G, Seripa D, Galimberti D, Licastrò F, Soininen H, Dartigues JF, Kamboh MI, Van Broeckhoven C, Lambert JC, Amouyel P, Campion D. APOE and Alzheimer disease: a major gene with semi-dominant inheritance. *Mol Psychiatry*. 2011; 16:903–907. [PubMed: 21556001]
- Hixson JE, Vermier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Research*. 1990; 31:545–548. [PubMed: 2341813]
- Kwon OD, Khaleeq A, Chan W, Pavlik VN, Doody RS. Apolipoprotein E polymorphism and age at onset of Alzheimer's disease in a quadriethnic sample. *Dement Geriatr Cogn Disord*. 2010; 30:486–491. [PubMed: 21252542]
- Llaurens V, Raymond M, Faurie C. Why are some people left-handed? An evolutionary perspective. *Phil Trans R Soc B*. 2009; 364:881–894. [PubMed: 19064347]
- Medland SE, Duffy DL, Spurdle AB, Wright MJ, Geffen GM, Montgomery GM, Martin NG. Opposite effects of Androgen Receptor CAG repeat length on increased risk of left-handedness in males and females. *Behav Genet*. 2005; 35:735–744. [PubMed: 16273319]
- Medland SE, Duffy DL, Wright MJ, Geffen GM, Martin NG. Handedness in twins: Joint analysis of data from 35 samples. *Twin Res Hum Genet*. 2006; 9:46–53. [PubMed: 16611467]
- Medland SE, Duffy DL, Wright MJ, Geffen GM, Hay DA, Levy F, van-Beijsterveldt CE, Willemsen G, Townsend GC, White V, Hewitt AW, Mackey DA, Bailey JM, Slutske WS, Nyholt DR, Treloar SA, Martin NG, Boomsma DI. Genetic influences on handedness: Data from 25,732 Australian and Dutch twin families. *Neuropsychologia*. 2009; 47:330–337. [PubMed: 18824185]
- Nilsson LG, Backman L, Erngrund K, Nyberg L, Adolfsson R, Bucht G, Karlsson S, Widing M, Winblad B. The Betula Prospective Cohort Study: Memory, health, and aging. *Aging Neuropsychol Cogn*. 1997; 4:1–32.
- Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 1971; 9:97–113. [PubMed: 5146491]
- Ordovas JM, Litwack-Klein L, Wilson PW, Schaefer MM, Schaefer EJ. Apolipoprotein E isoform phenotyping methodology and population frequency with identification of apoE1 and apoE5 isoforms. *J Lipid Res*. 1987; 28:371–380. [PubMed: 3585172]
- Raber J, Huang Y, Ashford JW. ApoE genotype accounts for the vast majority of AD risk and AD pathology. *Neurobiol Aging*. 2004; 25:641–650. [PubMed: 15172743]
- Rife DC. Handedness, with special reference to twins. *Genetics*. 1940; 25:178–186. [PubMed: 17246963]
- Rodriguez S, Gaunt TR, Day INM. Hardy-Weinberg equilibrium testing of biological ascertainment for Mendelian randomization studies. *Am J Epidemiol*. 2009; 169:505–514. [PubMed: 19126586]
- Ruiz JR, Castillo R, Labayen I, Moreno LA, Fuentes MG, Lamuño DG, Alvarez Granda JL, Lucia A, Ortega FB. Individual and combined effects of ApoE and MTHFR 677C/T polymorphisms on cognitive performance in Spanish adolescents: the AVENA study. *J Pediatr*. 2010; 156:978–984. [PubMed: 20223480]
- Small BJ, Rosnick CB, Fratiglioni L, Bäckman L. Apolipoprotein E and cognitive performance: A meta-analysis. *Psychol Aging*. 2004; 19:592–600. [PubMed: 15584785]

- Taylor AE, Guthrie PAI, Smith GD, Golding J, Sattar N, Hingorania AD, Deanfield JE, Day INM. IQ, Educational attainment, memory, and plasma lipids: Associations with Apolipoprotein E genotype in children. *Biol Psychiatry*. 2011 in press.
- Vuoksima E, Koskenvuo M, Rose RJ, Kaprio J. Origins of handedness: A nationwide study of 30,161 adults. *Neuropsychologia*. 2009; 47:1294–1301. [PubMed: 19428393]

Figure 1.

Forest plot of left handedness in relation to Apolipoprotein E2 allele carriage. Odds ratios (OR) represent odds of being left handed in E2 carriers compared to non carriers. Point estimates and 95% confidence intervals (CI) are represented by circles and horizontal lines respectively. The sizes of the boxes around the point estimate are in proportion to the weight given to each study in the combined studies OR. UCDADC: University of California, Davis, Alzheimer's Disease Center; NACC: National Alzheimer's Coordinating Center.

Table 1

Comparison of samples that were tested for an association between apolipoprotein E2 and handedness. E2+ = 2 or 2 3, AVENA = Alimentación y Valoración del Estado Nutricional en Adolescentes (Food and Assessment of the Nutritional Status of Adolescents, Ruiz et al. 2010); UCDAADC = University of California Davis Alzheimer's Disease Center, NACC = National Alzheimer's Coordinating Center, AA = African Americans, na = not applicable.

Source	N	E2+	Ratio		
			Total (Non-right/E2+)	Age	Non-right/Right
Bloss et al., 2008	147 (17/24)	11-16	41.2% / 13.1%	8.69 / .003	3.15
Present findings	166 (15/15)	17-22	6.7% / 9.3%	0.11 / .737	0.72
Gaynor et al., 2009	361 (71/42)	4-5	12.7% / 11.4%	0.09 / .760	1.11
Taylor et al., 2011	3,787 (447/559)	7-9	12.8% / 15.0%	1.63, .202	0.85
AVENA	360 (22/29)	13-18.5	0.0% / 8.6%	2.05, .152	na
Deary et al., 2007	990 (58/124)	11	13.8% / 12.4%	0.09 / .764	1.11
Nilsson et al., 1997	2,641 (199/336)	35-80	12.1% / 12.8%	0.09 / .771	0.94
Kwon et al., 2010	1,229 (69/56)	70s	4.3% / 4.6%	.001 / .930	0.95
UCDAADC	1,397 (104/129)	39-95	3.8% / 9.7%	3.89 / .049	0.40
NACC: AA	903 (58/114)	41-100	12.1% / 12.7%	0.00 / .895	0.95
NACC: Caucasians	7,559 (727/782)	21-112	9.8% / 10.4%	0.29 / .590	0.94
Total	19,540 (1,787/2,210)	4-112	10.7% / 11.4%	0.76 / .383	0.94