The association of the dopamine transporter gene and the dopamine receptor 2 gene with delirium, a meta-analysis

BARBARA C. VAN MUNSTER[1,2,*], SOPHIA E.J.A. DE ROOIJ[2], MOJGAN YAZDANPANAH[3], PENTTI J. TIENARI[4], KAISU H. PITKÄLÄ[5], ROBERT J. OSSE[6], DIMITRIOS ADAMIS[7], ORLA SMIT[8], MARIJKE S. VAN DER STEEN[9], MIRIAM VAN HOUTEN[10], TERHI RAHKONEN[11], RAIMO SULKAVA[11], JOUKO V. LAURILA[12], TIMO E. STRANDBERG[13], JOKE H.M. TULEN[6], LOUWERENS ZWANG[14], ALASTAIR J.D. MACDONALD[15], ADRIAN TRELOAR[16], ERIC J.G. SIJBRANDS[3], AEILKO H. ZWINDERMAN[1], JOHANNA C. KOREVAAR[1]

[1] Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands
[2] Department of Internal Medicine, Academic Medical Center, Amsterdam, the Netherlands
[3] Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands
[4] Department of Neurology, Helsinki University Central Hospital and Molecular Neurology Programme, Biomedicum, University of Helsinki, Helsinki, Finland
[5] Helsinki University Central Hospital, Unit of General Practice, Helsinki, Finland
[6] Department of Psychiatry, Erasmus MC, Rotterdam, the Netherlands
[7] Psychiatry, Research and Academic Institute of Athens, Athens, Greece
[8] Department of Internal Medicine, VU Medical Center, Amsterdam, the Netherlands
[9] Intensive Care, Gelderse Vallei Hospital, Ede, the Netherlands
[10] Department of Geriatrics, Parnassia, Den Haag, the Netherlands
[11] Department of Geriatrics, School of Public Health and Clinical Nutrition, University of Kuopio, Kuopio, Finland
[12] Helsinki University Central Hospital, Clinics of General Internal Medicine and Geriatrics, Helsinki, Finland
[13] Oulu University Hospital, Unit of General Practice, Oulu, Finland
[14] Department of Clinical Chemistry, Erasmus MC, Rotterdam, the Netherlands
[15] Elderly Care Unit, St Thomas' Hospital, Westminster, London, UK
[16] Memorial Hospital, Shooters Hill, London, UK

ABSTRACT

Delirium is the most common neuropsychiatric syndrome in elderly ill patients. Previously, associations between delirium and the dopamine transporter gene (solute carrier family 6, member 3 (SLC6A3)) and dopamine receptor 2 gene (DRD2) were found. The aim of this study was to validate whether markers of the SLC6A3 and DRD2 genes are were associated with delirium in independent populations. Six European populations collected DNA of older delirious patients. Associations were determined per population and results were combined in a meta-analysis. In total 820 medical inpatients, 185 cardiac

surgery patients, 134 non-cardiac surgery patients and 502 population-based elderly subjects were included. Mean age was 82 years (SD 7.5 years), 598 (36%) were male, 665 (41%) had pre-existing cognitive impairment, and 558 (34%) experienced delirium. The SLC6A3 rs393795 homozygous AA genotype was more frequent in patients without delirium in all populations. The meta-analysis showed an Odds Ratio (OR) for delirium of 0.4 (95% confidence interval (C.I.) 0.2–0.6, P=0.0003) for subjects with AA genotype compared to the AG and GG genotypes. SLC6A3 marker rs1042098 showed no association with delirium. In meta-analysis the DRD2 rs6276 homozygous GG genotype showed an OR of 0.8 for delirium (95% C.I. 0.6–1.1, P=0.24). When subjects were stratified for cognitive status the rs6276 GG genotype showed ORs of 0.6 (95% C.I. 0.4–1.0, P=0.06) and 0.8 (95% C.I. 0.5–1.5, P=0.51) for delirium in patients with and without cognitive impairment, respectively. In independent cohorts, a variation in the SLC6A3 gene and possibly the DRD2 gene were found to protect for delirium. © 2009 Wiley-Liss, Inc.

INTRODUCTION

Delirium is an acute neuropsychiatric syndrome precipitated by a somatic factor, like any medical disease, surgery, substance intoxication or substance withdrawal [American Psychiatric Association, 1990]. It is characterized by fluctuating changes in consciousness and reduced attention and manifests itself in up to 50% of elderly hospital inpatients, many with pre-existing dementia [Cole, 2004]. Though patients usually recover after treating the precipitating factor, having delirium is independently associated with increased mortality, impaired physical and cognitive recovery and increased healthcare costs [Inouye, 2006]. In spite of the fact that delirium is the most frequently encountered neuropsychiatric syndrome among elderly patients, the pathophysiological process is still largely hypothetical. Although genetics offers the possibility to contribute knowledge, studies on genetics in delirium in elderly patients have been scarce until now [Adamis et al., 2009; van Munster et al., 2009].

A recently performed candidate gene association study on delirium in the elderly showed that the AA genotype of the dopamine transporter gene (solute carrier family 6, member 3 (SLC6A3)) (rs393795) protected for the development of delirium [van Munster et al., 2009]. Furthermore, after adjustment for age, cognitive impairment and functional impairment, two single nucleotide polymorphisms (SNPs) in the SLC6A3 gene (rs393795 and rs1042098) and one SNP in the dopamine receptor 2 (DRD2) gene (rs6276) were independently associated with delirium. The SLC6A3 gene on the 5p15.3 chromosome is coding for the dopamine transporter which regulates extracellular dopamine concentrations [van Dyck et al., 2005]. Up to now, these polymorphisms have never been described in relation to another disease than delirium. The DRD2 gene on the 11q22-q24 chromosome is one of the most frequently studied genes in complex behavioral disorders and is associated with diverse delirium-overlapping phenotypes, like Attention Deficit Hyperactivity Disorder, schizophrenia and movement disorders [Noble, 2003]. The rs6276 SNP in the 3′ untranslated region has been described in association with various alcohol related phenotypes which might be due to a lower transcription/translation rate resulting in decreased D2 receptor availability [Lucht et al., 2007].

The most widely propagated pathophysiological theory states that (relative) dopamine excess compared to acetylcholine could mediate the characteristic symptoms of delirium [Trzepacz, 2000]. It is possible that the mutant genotype of the SLC6A3 gene or the DRD2 gene leads to a lower cerebral basal dopamine activity in patients and therefore reduces the

risk for delirium. The previous results suggest a role for dopamine via the dopamine transporter and DRD2 in the pathogenesis of delirium; nonetheless validation in independent study cohorts is needed to rule out spurious associations. The aim of this study was to investigate whether rs393795 and rs1042098 in the SLC6A3 gene and rs6276 in the DRD2 were associated with delirium in various European populations of older patients.

MATERIALS AND METHODS

An extensive search was done to find validation cohorts. Inclusion criteria were studies that included patients of 65 years and older with information on delirium and were able to provide DNA and that were approved by the institutional Medical Ethics Committee. An appeal was done for cohorts to cooperate at the European Delirium Association Meeting 2008 [Maclullich et al., 2007]. Additionally, authors who published genetic results of delirium in elderly population were invited to participate [Adamis et al., 2007; Ely et al., 2007; Leung et al., 2007; Tagarakis et al., 2007]. Five new cohorts fulfilled the inclusion criteria and were able to participate. An overview of all cohorts will be presented below and in Table I; detailed information of all cohorts can be found in the corresponding original publications.

(1) The Amsterdam cohort is an ongoing study in the Academic Medical Centre in Amsterdam aimed at elucidating pathophysiological and risk factors for delirium [van Munster et al., 2009]. The included cohort consisted of 720 patients aged 65 years and older, acutely admitted to the medical department or to the surgical department following hip fracture. No results were obtained for the 3 SNPs in 18 patients. Delirium was diagnosed by the Confusion Assessment Method [Inouye et al., 1990]. The "Informant Questionnaire on Cognitive Decline-short form" was used to score predelirium global cognitive impairment with a cut-off of 62.4 [Jorm, 1994; de Jonghe et al., 1997]. Functional impairment was scored by the Katz Index of Activities of Daily Living (ADL) for functionality; patients with a score of 7 or more were considered as functionally impaired [Weinberger et al., 1992].

(2) The study cohort of Haarlem (unpublished) was performed by the same methods of the Amsterdam cohort on the high care department of medicine in the Kennemer Gasthuis in Haarlem. Eighty-nine patients were included, but DNA of 26 patients was unsuccessfully genotyped and of 8 patients the CAM score was missing.

(3) The Finland cohort is composed of two studies. We combined results of the population-based Vantaa 85+ study cohort with the hospital-based Helsinki cohort because this large Finnish study only included patients with delirium (cases) without controls.The Vantaa 85+ study [Rahkonen et al., 2001; Peuralinna et al., 2008] is a population based health survey focused on the clinical epidemiology and pathology of dementia and related cognitive disorders. The basic population consisted of all people (n=601) born before April 1906 living in the city of Vantaa, Southern Finland on April 1991. Delirium (based on DSM-III-R) was scored using data from a follow-up period of 3 years with all medical records from hospitals and municipal health centers in the region as well as retrospectively from the patients' medical history [American Psychiatric Association, 1990]. Cognitive and functional impairment using information from proxies, neurologist's clinical examination, the Mini-Mental State examination [Folstein et al., 1975], Activities of Daily Living (ADL) [Katz et al., 1963] and Instrumental Activities of Daily Living (IADL) [Lawton and Brody, 1969]. The consensus of two neurologists was needed before the diagnosis of dementia was made (using the DSM-III-R criteria). Of 518 people DNA was available, of 15 patients the 3 SNPs could not be determined and of 1 patient the DSM III-R was missing.

(4) The Helsinki cohort was retrieved from a randomized controlled trial with multicomponent geriatric intervention in patients with delirium admitted to an acute geriatric hospital in Helsinki [Pitkala et al., 2008]. Delirium was screened with CAM and confirmed with DSM-IV criteria. Each patient's premorbid dementia status was based on information

from interviews of proxies, the Clinical Dementia Rating scale, DSM-IV criteria of dementia, and reviews of medical records confirming whether these patients had undergone full assessment for diagnosis of dementia [Hughes et al., 1982]. Functional impairment was based on a Barthel score below 90 [Mahoney and Barthel, 1965]. Of the 174 included patients, DNA was available of 107 and DNA results for 106 patients.

(5) The London cohort was used for genetic analysis before [Adamis et al., 2007]. A cohort of 164 acutely ill patients, 70 years or older, admitted to an elderly medical unit were studied to identify and follow the clinical course of delirium. Delirium was scored by the CAM. Cognitive impairment was based on the medical history and functional impairment on the 10-item Barthel questionnaire below 13 points [Granger et al., 1979]. DNA was available for 100 patients, but genotyping of 5 patients was unsuccessful for all SNPs. Unfortunately rs393795 could not be determined for any patient, even not in duplo.

(6) The Rotterdam cohort is an ongoing study in patients over 65 years of age admitted for elective cardiothoracic surgery at the Erasmus Medical Center in Rotterdam [Osse et al., 2009]. The included cohort consisted of 211 patients whereof DNA was unavailable or insufficient of quality for 18 patients. Delirium was scored by the CAM-ICU, but for 9 patients it was impossible to apply the scale [Ely et al., 2001]. Pre-existent cognitive impairment was measured by the MMSE pre-operatively, with a cutoff below 24 indicating impairment [Folstein et al., 1975; Heeren et al., 1990]. Patients were considered functionally impaired when they received any help in ADL.

[TABLE 1]

GENOTYPING

Genotyping was performed blinded for delirium status. SNPs were determined using Taqman allelic discrimination Assay-By-Design (Applied Biosystems, Foster City, CA). Primer and probe sequences are presented in the Supplement Table I. We used the reverse strand design for rs1042098 and rs393795 polymorphisms of the SLC6A3 gene. The assays utilized 2ng of genomic DNA and 2µl reaction volumes. The amplification and extension protocol was as follows: an initial activation step of 10min at 95° proceeded 40 cycles of denaturation at 95° for 15sec and annealing and extension at 50° for 60sec. Allele-specific fluorescence was then analyzed on an ABI prism 7900HT sequence detection system version 2.2 (Applied Biosystems).

STATISTICS

Statistical Package for the Social Sciences (SPSS) version 15.0 was used for data analysis. Chi-square tests were used for association analysis between delirium and genotypes. A two-tailed P-value of below 0.05 was considered statistically significant. An univariable and a multivariable logistic regression analysis with backward selection procedure was performed with delirium as dependent variable and age (years), rs393795, rs1042098, rs6276 pre-existent cognitive, and functional impairment as independent variables.

The meta-analysis was performed with Review Manager 5 software of The Cochrane Collaboration. The odds ratio (OR) and 95% confidence interval (CI) for delirium in homozygotic carriers of the mutation with reference to the heterozygotic and homozygotic wild-type were calculated for each study and the average OR over all the studies was calculated by Mantel–Haenszel method for fixed effects. The weight for each study determining how much each individual study contributed to the pooled estimate was calculated on the basis of the variance in OR in each study. Heterogeneity in OR between studies was tested with the Chi-square test and I-square statistics.

RESULTS

In total 1,641 patients were included: 820 medical inpatients, 185 cardiac surgery patients, 134 non-cardiac surgery patients, and 502 population-based elderly subjects (Table I). Of the total population 598 (36%) were male, 558 (34%) experienced delirium, and the mean age was 82 years (SD: 7.5). Six hundred sixty-five (41%) had pre-existing cognitive impairment and in all cohorts pre-existing cognitive impairment was significantly associated with delirium except for the cohort of Haarlem.

Tables IIa–IIc show the association between the three different SNPs and delirium separately for every population. The genotype distribution of rs393795 in the SLC6A3 gene was significantly different between patients with delirium and patients without delirium, with the homozygous AA genotype being more frequent in patients without delirium in all populations separately except for the population of Haarlem (P=0.001–0.67). For the rs1042098 in the SLC6A3 gene, the trend for association with delirium was different for all populations. The homozygous TT genotype was significantly more frequent than the CT and CC genotype together in the post hoc test in patients without delirium in the London population (P=0.04), but less frequent in patients without delirium in the Amsterdam population (P=0.03) (Table IIb). Finally, for the rs6276 in the DRD2 gene a trend was found in the two Dutch cohorts and the two Finnish cohorts, with the homozygous mutant being more frequent in patients without delirium (P=0.06–0.41).

[TABLE 2A]

[TABLE 2B]

[TABLE 2C]

In the populations combined, delirium was associated with older age (OR=1.03, 95% CI: 1.01–1.04, P=0.002), cognitive impairment (OR=5.4, 95% CI: 4.2–6.9, P<0.001) and functional impairment (OR=1.8 CI: 1.4–2.2, P<0.001) in univariate logistic regression analyses. In a multivariable logistic regression analysis cognitive impairment, rs393795 (SLC6A3) and rs6276 (DRD2) were significantly associated with delirium (Table III). Homozygous AA genotype of the SLC6A3 gene showed a 70% decrease for the risk of delirium and the homozygous GG genotype of the DRD2 gene a 50% decrease. Pre-existing cognitive impairment was significantly associated with rs6276, with an OR of 1.54 (95% CI: 1.11–2.13, P=0.02) for the homozygous GG genotype compared to AA and AG genotypes.

[TABLE 3]

In the meta-analysis, no heterogeneity was detected in the different OR's between studies. Figure 1a,b shows the unadjusted ORs of the two SNPs in the SLC6A3 gene for the different populations separately and combined. The model of rs393795 shows a reduced risk for delirium in homozygous AA genotype (OR=0.37, 95% CI 0.21–0.63, P=0.0003) (Fig. 1a). The association was also significant without the data of the original Amsterdam cohort (OR=0.5, 95% CI 0.2–1.0, P=0.04). The rs6276 SNP shows no significant association with delirium in the meta-analysis of the total populations (OR=0.8, 95% CI 0.6–1.1, P=0.24) (Fig. 1c). If this SNP is analyzed in the populations stratified for pre-existing cognitive impairment, the OR is 0.6 (95% CI 0.4–1.0, P=0.06) in patients with cognitive impairment and 0.8 (95% CI 0.5–1.5, P=0.51) in patients without cognitive impairment.

[FIGURE 1]

DISCUSSION

In this international validation study among elderly hospital patients the homozygous AA genotype of rs393795 in the SLC6A3 gene was more frequent in patients without delirium in all available populations as well as in the meta-analysis Furthermore, the homozygous GG genotype of rs6276 in the DRD2 gene was more frequent in patients without delirium after adjustment for cognitive impairment. The rs1042098 in the SLC6A3 gene showed no association with delirium in all analyses.

Given the fact that in all cohorts separately, and in the total cohort without the original cohort, the rs393795 in the SLC6A3 gene was associated with delirium, this variation seems truly associated with delirium. The genetic constitution of the SLC6A3 gene can affect the availability or function of dopamine transporters in the striatum and modulate cerebral dopamine concentration [van Dyck et al., 2005; Nikolaus et al., 2007]. A lower cerebral basal dopamine concentration in patients with the mutant genotype of the SLC6A3 gene could diminish the risk for delirium. The rs393795 SNP is intronic, but shows linkage disequilibrium with three exons nearby. As far as we know, there is no functional SNP known that is highly correlated with rs393795. On the other hand numerous intronic sequences have recently been found to encode microRNAs, small single-stranded regulatory RNAs which are responsible for RNA-mediated gene silencing [Ying and Lin, 2009]. A future step could involve sequencing this region in search for functional variants.

After stratification for pre-existing cognitive impairment the rs6276 SNP in the DRD2 gene diminishes the risk for delirium, which is borderline significant only in patients with cognitive impairment. This statistical significance is possibly based on the higher power of the group of patients with cognitive impairment in comparison to the group of patients without cognitive impairment due to the higher frequency of delirium (55% vs. 19%) and the G-allele (16% vs. 11%) in the cognitively impaired population. These higher frequencies are related to the fact that rs6276 increases the risk for cognitive impairment and cognitive impairment increases the risk for delirium. Remarkably, as far as we know, no associations between dementia or cognitive impairment and the DRD2 have been found before, despite GWA studies on this subject. A reliable diagnosis of cognitive impairment during or after delirium is complicated, since cognitive impairment can be a feature as well as a consequence of delirium itself. It could be that the pre-existing cognitive impairment is partly caused by depression which is frequently present in the elderly and associated with the DRD2 [Noble, 2003]. Still, limited to the results of the DRD2 gene in the meta-analysis without stratification, a protective effect of rs6276 can be suspected. Verification in larger cohorts in the future would be interesting since a causal relation could be suspected based on the fact that DRD2 antagonists are helpful in providing symptomatic relief of delirium [Alagiakrishnan and Wiens, 2004]. Interestingly, interaction between the dopamine transporter and the DRD2 gene could also play a role since a different polymorphism in the DRD2 gene (rs1800497) is associated with higher density of the dopamine transporter [Laine et al., 2001].

An important limitation for the meta-analysis is the sample size of the majority of the populations. However, genetic research in delirium is only starting and large cohorts for reliable validation are not yet available [Adamis et al., 2009]. The two largest populations, Amsterdam and the combined Finnish cohort, showed the same trend for the two SNPs of interest. The sample size of the combined cohort is large enough for genetic association studies [Edwards et al., 2005]. Although, the results in all cohorts showed no important statistical heterogeneity in the various meta-analyses, clinical and methodological diversity cannot be ruled out. The difference in assessment of delirium might could have led to misclassification of cases in the Vantaa cohort in which delirium was diagnosed

retrospectively by medical records. Moreover, the reliability of the diagnosis of pre-existing cognitive impairment by IQCODE, MMSE, CDR or medical history, varied among cohorts. However by all different methods, pre-existing cognitive impairment was correctly identified as risk factor for delirium in four of the five cohorts [Elie et al., 1998]. The two largest cohorts did measure the highest frequency of cognitive impairment, next to the London cohort, which could be related to the difference in assessment or to the true difference in frequency of pre-existing cognitive impairment. Different predisposing and precipitating factors could theoretically lead to a variation in the contribution of genetics to the risk for delirium. The protective effect of genetic factors will be largest in patients without delirium despite the presence of major predisposing and precipitating factors.

In conclusion, this study showed that the SLC6A3 gene (rs393795) and possibly the DRD2 gene (rs6276) were associated with delirium. Future utilization of large-scale association studies followed by multivariable analyses, which include risk factors as well as genetic data, will hopefully further disentangle the complex genetics of delirium.

ACKNOWLEDGEMENTS

The authors wish to thank the research nurses, AWJ Giesbers, JL Popma, CMM van Rijn, ACL Scheffer and MJA van der Zwaan. der Zwaan and Intensive Care physician Marijke Steen. Terhi Peuralinna and Lilja Jansson are thanked for technical assistance in handling the Finnish samples.

REFERENCES

Adamis D, Treloar A, Martin FC, Gregson N, Hamilton G, Macdonald AJ. 2007. APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients. Int J Geriatr Psychiatry 22: 688–694.

Adamis D, van Munster BC, Macdonald AJ. 2009. The genetics of deliria. Int Rev Psychiatry 21: 20–29.

Alagiakrishnan K, Wiens CA. 2004. An approach to drug induced delirium in the elderly. Postgrad Med J 80: 388–393.

American Psychiatric Association. 1990. Diagnostic and Statistical Manual of Mental Disorders: DSM IIIR. Washington, DC: American Psychiatric Association.

Cole MG. 2004. Delirium in elderly patients. Am J Geriatr Psychiatry 12: 7–21.

de Jonghe JF, Schmand B, Ooms ME, Ribbe MW. 1997. Abbreviated form of the Informant Questionnaire on cognitive decline in the elderly. Tijdschr Gerontol Geriatr 28: 224–229.

Edwards BJ, Haynes C, Levenstien MA, Finch SJ, Gordon D. 2005. Power and sample size calculations in the presence of phenotype errors for case/control genetic association studies. BMC Genet 6: 18.

Elie M, Cole MG, Primeau FJ, Bellavance F. 1998. Delirium risk factors in elderly hospitalized patients. J Gen Intern Med 13: 204–212.

Ely EW, Girard TD, Shintani AK, Jackson JC, Gordon SM, Thomason JW, et al. 2007. Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients. Crit Care Med 35: 112–117.

Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. 2001. Evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 29: 1370–1379.

Folstein MF, Folstein SE, McHugh PR. 1975. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12: 189–198.

Granger CV, Albrecht GL, Hamilton BB. 1979. Outcome of comprehensive medical rehabilitation: Measurement by PULSES profile and the Barthel Index. Arch Phys Med Rehabil 60: 145–154.

Heeren TJ, Lagaay AM, von Beek WC, Rooymans HG, Hijmans W. 1990. Reference values for the Mini-Mental State Examination (MMSE) in octo- and nonagenarians. J Am Geriatr Soc 38: 1093–1096.

Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. 1982. A new clinical scale for the staging of dementia. Br J Psychiatry 140: 566–572.

Inouye SK. 2006. Delirium in older persons. N Engl J Med 354: 1157–1165.

Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. 1990. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. Ann Intern Med 113: 941–948.

Jorm AF. 1994. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): Development and cross-validation. Psychol Med 24: 145–153.

Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. 1963. Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychosocial function. JAMA 185: 914–919.

Laine TP, Ahonen A, Rasanen P, Pohjalainen T, Tiihonen J, Hietala J. 2001. The A1 allele of the D2 dopamine receptor gene is associated with high dopamine transporter density in detoxified alcoholics. Alcohol Alcohol 36: 262–265.

Lawton MP, Brody EM. 1969. Assessment of older people: Self-maintaining and instrumental activities of daily living. Gerontologist 9: 179–186.

Leung JM, Sands LP, Wang Y, Poon A, Kwok PY, Kane JP, et al. 2007. Apolipoprotein E e4 allele increases the risk of early postoperative delirium in older patients undergoing noncardiac surgery. Anesthesiology 107: 406–411.

Lucht M, Barnow S, Schroeder W, Grabe HJ, Rosskopf D, Brummer C, et al. 2007. Alcohol consumption is associated with an interaction between DRD2 exon 8 A/A genotype and self-directedness in males. Neuropsychobiology 56: 24–31.

Maclullich AM, Meagher DJ, Laurila JV, Kalisvaart KJ. 2007. The European delirium association. J Psychosom Res 62: 397–398.

Mahoney FI, Barthel DW. 1965. Functional evaluation: The Barthel index. Md State Med J 14: 61–65.

Nikolaus S, Antke C, Kley K, Poeppel TD, Hautzel H, Schmidt D, et al. 2007. Investigating the dopaminergic synapse in vivo. I. Molecular imaging studies in humans. Rev Neurosci 18: 439–472.

Noble EP. 2003. D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes. Am J Med Genet Part B 116B: 103–125.

Osse RJ, Tulen JH, Hengeveld MW, Bogers AJ. 2009. Screening methods for delirium: Early diagnosis by means of objective quantification of motor activity patterns using wrist-actigraphy. Interact Cardiovasc Thorac Surg 8: 344–348.

Peuralinna T, Oinas M, Polvikoski T, Paetau A, Sulkava R, Niinisto L, et al. 2008. Neurofibrillary tau pathology modulated by genetic variation of alpha-synuclein. Ann Neurol 64: 348–352.

Pitkala KH, Laurila JV, Strandberg TE, Kautiainen H, Sintonen H, Tilvis RS. 2008. Multicomponent geriatric intervention for elderly inpatients with delirium: Effects on costs and health-related quality of life. J Gerontol A Biol Sci Med Sci 63: 56–61.

Rahkonen T, Eloniemi-Sulkava U, Halonen P, Verkkoniemi A, Niinisto L, Notkola IL, et al. 2001. Delirium in the non-demented oldest old in the general population: Risk factors and prognosis. Int J Geriatr Psychiatry 16: 415–421.

Tagarakis GI, Tsolaki-Tagaraki F, Tsolaki M, Diegeler A, Tsilimingas NB, Papassotiropoulos A. 2007. The role of apolipoprotein E in cognitive decline and delirium after bypass heart operations. Am J Alzheimers Dis Other Demen 22: 223–228.

Trzepacz PT. 2000. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. Semin Clin Neuropsychiatry 5: 132–148.

van Dyck CH, Malison RT, Jacobsen LK, Seibyl JP, Staley JK, Laruelle M, et al. 2005. Increased dopamine transporter availability associated with the 9-repeat allele of the SLC6A3 gene. J Nucl Med 46: 745–751.

van Munster BC, Yazdanpanah M, Tanck MW, de Rooij SE, van de GE, Sijbrands EJ, et al. 2009. Genetic polymorphisms in the DRD2, DRD3, and SLC6A3 gene in elderly patients with delirium. Am J Med Genet B Neuropsychiatr Genet [Epub ahead of print].

Weinberger M, Samsa GP, Schmader K, Greenberg SM, Carr DB, Wildman DS. 1992. Comparing proxy and patients' perceptions of patients' functional status: Results from an outpatient geriatric clinic. J Am Geriatr Soc 40: 585–588.

Ying SY, Lin SL. 2009. Intron-mediated RNA interference and microRNA biogenesis. Methods Mol Biol 487: 387–413.

TABLES AND FIGURE

Table 1

TABLE I. Characteristics of Populations Included in the Meta-Analysis

Study	Amsterdam	Haarlem	Finland (Vantaa)	Finland (Helsinki)	London	Rotterdam
Total number	702	55	502	106	93	183
Population	Medical (n = 588) Non-cardiac surgery (n = 114)	Medical	Elderly community	Medical (n = 84) Non-cardiac surgery (n = 20)	Medical	Cardiac surgery
Male sex (%)	310 (44)	26 (47)	102 (20)	24 (23)	29 (30)	109 (60)
Age-years (SD)	79.3 (8.0)	79.1 (7.5)	87.9 (2.9)	83.2 (5.9)	84.6 (6.2)	76.2 (3.9)
Cognitive impairment	340 (48)	14 (26)	190 (38)	50 (47)	55 (56)	19 (10)
Functional impairment	267 (38)	13 (24)	441 (88)	58 (55)	43 (44)	8 (4)
Alcohol dependence	29 (4)	2 (4)	9 (2)	9 (9)	2 (2)	Unknown
Caucasian ethnicity (%)	617 (88)	53 (96)	502 (100)	106 (100)	92 (94)	179 (98)
Delirium (%)	262 (37)	18 (33)	89 (18)	106 (100)	32 (33)	54 (30)
Delirium scales	CAM	CAM	DSM IIIR	CAM/DSM IV	CAM	CAM

CAM, Confusion Assessment Method; DSM, Diagnostic and Statistical Manual of Mental Disorders.

Table 2a

TABLE IIa. Genotypes of rs393795 in the Dopamine Transporter Gene (Solute Carrier Family 6, Member 3)

Gene	CC	CA	AA	*P*-value
Amsterdam				0.001
Delirium (%)	152 (59)	100 (39)	6 (2)	
No delirium (%)	263 (62)	128 (30)	36 (8)	
Haarlem				0.96
Delirium (%)	11 (65)	6 (35)		
No delirium (%)	19 (66)	10 (34)		
Finland[a]				0.13
Delirium (%)	89 (59)	54 (36)	8 (5)	
No delirium (%)	188 (58)	102 (31)	35 (11)	
Rotterdam				0.67
Delirium (%)	22 (50)	20 (46)	2 (5)	
No delirium (%)	55 (51)	44 (41)	9 (8)	

No results available for the London cohort.
[a]Vantaa and Helsinki analyzed together.

Munster, B.C. van, Rooij, S.E.J.A. de, Yazdanpanah, M., Tienari, P.J., Pitkala, K.H., Osse, R.J., Adamis, D., Smit, O., Steen, M.S. van der, Houten, M. van, Rahkonen, T., Sulkava, R., Laurila, J.V., Strandberg, T.E., Tulen, J.H.M., Zwang, L., Macdonald, A.J.D., Treloar, A., Sijbrands, E.J.G., Zwinderman, A.H., Korevaar, J.C. The association of the dopamine transporter gene and the dopamine receptor 2 gene with delirium: a meta-analysis. American Journal of Medical Genetics: Part B: Neuropsychiatric Genetics: 2010, 153B(2), 648-655

Table 2b

TABLE IIb. Genotypes of rs1042098 in the Dopamine Transporter Gene (Solute Carrier Family 6, Member 3)

Gene	TT	CT	CC	*P*-value
Amsterdam				0.06
Delirium (%)	156 (61)	84 (33)	16 (6)	
No delirium (%)	224 (53)	179 (42)	23 (5)	
Haarlem				0.44
Delirium (%)	12 (67)	6 (33)	0 (0)	
No delirium (%)	24 (65)	10 (27)	3 (8)	
Finland[a]				0.41
Delirium (%)	131 (71)	48 (26)	6 (3)	
No delirium (%)	283 (72)	89 (23)	21 (5)	
London				0.03
Delirium (%)	11 (38)	15 (52)	3 (10)	
No delirium (%)	37 (62)	14 (23)	9 (15)	
Rotterdam				0.55
Delirium (%)	28 (53)	23 (43)	2 (4)	
No delirium (%)	76 (61)	45 (36)	3 (2)	

[a]Vantaa and Helsinki analyzed together.

Table 2c

TABLE IIc. Genotypes of rs6276 in the Dopamine Receptor 2 (DRD2) Gene

Gene	AA	AG	GG	*P*-value
Amsterdam				0.27
Delirium (%)	125 (50)	99 (40)	24 (10)	
No delirium (%)	190 (46)	172 (41)	56 (13)	
Haarlem				0.67
Delirium (%)	10 (56)	7 (39)	1 (6)	
No delirium (%)	16 (44)	16 (44)	4 (11)	
Finland*				0.66
Delirium (%)	100 (53)	71 (38)	18 (10)	
No delirium (%)	204 (51)	146 (37)	48 (12)	
London				0.80
Delirium (%)	12 (50)	8 (33)	4 (17)	
No delirium (%)	29 (49)	23 (39)	7 (12)	
Rotterdam				0.25
Delirium (%)	23 (43)	23 (43)	8 (15)	
No delirium (%)	71 (56)	43 (34)	13 (10)	

*Vantaa and Helsinki analyzed together.

Table 3

TABLE III. Factors Associated With Delirium in an Uni- and Multivariable Logistic Regression Analysis in 1,267 Patients

Identification	OR (95% CI), univariable	*P*-value	OR (95% CI), multivariable	*P*-value
SLC6A3 rs393795	1.0	0.001	1.0	<0.001
AC/CC	1.1 (0.9–1.4)		1.2 (0.9–1.5)	
AA/CC	0.3 (0.2–0.6)		0.3 (0.2–0.6)	
SLC6A3 rs1042098	1.0	0.81		
CT/TT	0.9 (0.7–1.2)			
CC/TT	1.0 (0.6–1.7)			
DRD2 rs6276	1.0	0.24	1.0	0.02
AG/AA	1.0 (0.7–1.2)		0.8 (0.6–1.1)	
GG/AA	0.7 (0.5–1.1)		0.5 (0.4–0.8)	
Age (years)	1.03 (1.01–1.04)	0.002		
Functional impairment (yes/no)	1.8 (1.4–2.2)	<0.001		
Cognitive impairment (yes/no)	5.4 (4.2–6.9)	<0.001	5.7 (4.4–7.3)	<0.001

OR, odds ration; CI, confidence interval; SLC6A3, solute carrier family 6, member 3; DRD2, dopamine receptor 2.
Only significant factors after backward selection of the multivariable analysis are shown.

Munster, B.C. van, Rooij, S.E.J.A. de, Yazdanpanah, M., Tienari, P.J., Pitkala, K.H., Osse, R.J., Adamis, D., Smit, O., Steen, M.S. van der, Houten, M. van, Rahkonen, T., Sulkava, R., Laurila, J.V., Strandberg, T.E., Tulen, J.H.M., Zwang, L., Macdonald, A.J.D., Treloar, A., Sijbrands, E.J.G., Zwinderman, A.H., Korevaar, J.C. The association of the dopamine transporter gene and the dopamine receptor 2 gene with delirium: a meta-analysis. American Journal of Medical Genetics: Part B: Neuropsychiatric Genetics: 2010, 153B(2), 648-655

Figure 1

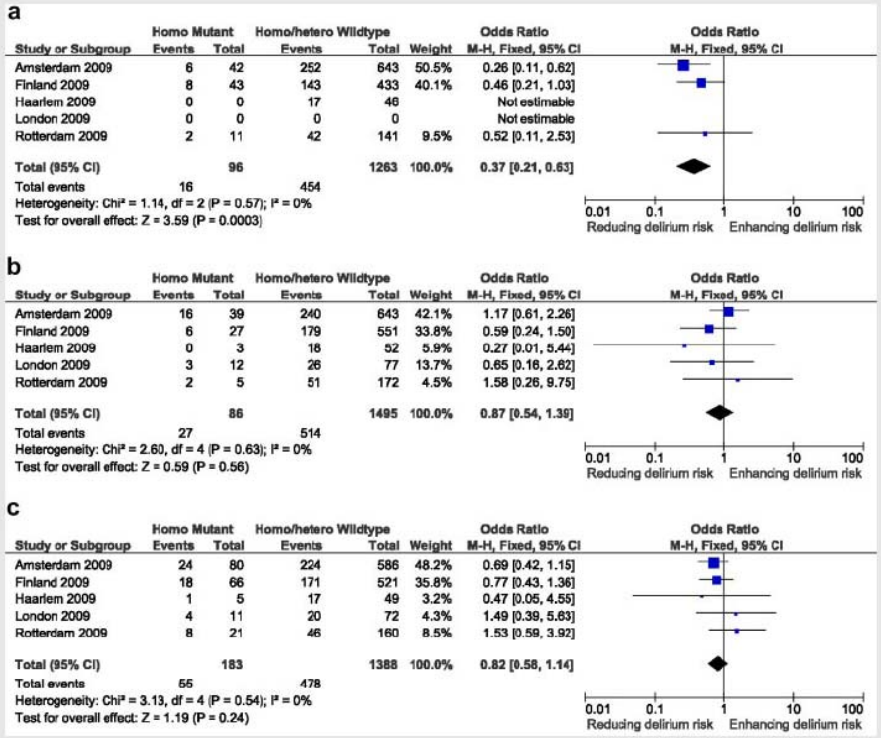

FIG. 1. a: Forest plot of studies of rs393795 in the solute carrier family 6, member 3 (SLC6A3) gene and delirium. b: Forest plot of studies of rs1042098 in the solute carrier family 6, member 3 (SLC6A3) gene and delirium. c: Forest plot of studies of rs6276 in the dopamine receptor 2 (DRD2) gene and delirium. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]