Review Article

Cognitive Impairment in Studies of 5HTTLPR and Psychosis in Alzheimer's Disease: A Systematic Review

Byron Creese · Clive Ballard · Emma Jones

Wolfson Centre for Age-Related Diseases, King's College London, London, UK

Key Words

Cognition · SLC6A4 · Dementia · Psychosis · Delusions · Hallucinations

Abstract

Background/Aims: Cognitive impairment is a well-established correlate of psychotic symptoms in Alzheimer's disease (AD-P). We review whether this relationship has confounded previous genetic association studies of 5HTTLPR and AD-P. **Methods:** We reviewed all studies on 5HTTLPR and conducted a semi-quantitative analysis. **Results:** Three out of 4 studies with low MMSE reported a significant association, while 1 out of 4 with high MMSE reported a significant association. **Conclusions:** Variation in cognitive impairment in past studies has contributed to the inconsistency in findings. The findings presented here bring a greater clarity to our understanding of the role of 5HTTLPR in AD-P.

Copyright © 2013 S. Karger AG, Basel

Background

Worldwide there are an estimated 35 million people living with dementia, the majority of whom have Alzheimer's disease (AD) [1]. Together with progressive cognitive and functional decline which characterise AD clinically, many individuals also experience psychosis (delusions and hallucinations or a psychosis syndrome comprising individuals with either or both of these). Long-term follow-up studies estimate the cumulative prevalence of psychosis in AD (AD-P) to be between 30 and 50% [2, 3]. In addition to being highly prevalent, psychotic symptoms are also distressing to patients and their carers and, moreover, are associated with poorer outcomes, in particular more rapid cognitive decline [4].

Dr. Emma Jones
Wolfson Centre for Age-Related Diseases
King's College London, Guy's Campus
London SE1 1UL (UK)
E-Mail emma.3.jones@kcl.ac.uk

Current evidence indicates that antipsychotics confer modest short-term benefits in the treatment of aggression and psychosis in people with AD, with the best evidence base for risperidone [5]. However, there are increasing safety concerns surrounding the use of antipsychotics in people with AD, including increased mortality and risk of cerebrovascular events [6]. When the above factors are balanced it is clear that the treatment options for AD-P are extremely limited, creating an urgent clinical need to identify more effective and safer treatment strategies. The first step in addressing this need has to be a greater understanding of the mechanisms underlying AD-P and, in the absence of animal models, genetic studies have a pivotal role to play in elucidating these.

Psychotic symptoms in AD are highly heritable [7] and linkage has been demonstrated previously [8], providing evidence that genetic variation does contribute to risk. Investigations of loci in serotonergic and dopaminergic gene pathways are among the most well studied in association studies of AD-P. 5HTTLPR is a 44-bp deletion polymorphism in the promoter region of the serotonin transporter gene *SLC6A4*, with 2 alleles; 1 termed long (L) and 1 short (S). The S allele is associated with a lower rate of 5HTT transcription than the L allele [9–11] and therefore may reduce 5HT reuptake capacity, leading to alterations in serotonergic neurotransmission. PET imaging has demonstrated the SS genotype to be associated with lower 5HT_{1A} binding potential than the LL genotype [12], a finding supported by work in 5HTT knockout mice. It is therefore also possible that any effect of the 5HTTLPR polymorphism is mediated via resultant changes in 5HT_{1A} density. Moreover, the therapeutic mechanisms of the most commonly used drugs to treat AD-P, atypical antipsychotics and SSRIs, are blockade of 5HT_{2A} and inhibition of the serotonin transporter, respectively, highlighting the potential importance of serotonergic neurotransmission in AD-P. It is therefore not surprising that serotonergic system genes have been the subject of a good deal of research, with 5HTTLPR being among the most studied and indeed the most biologically plausible candidates. Despite this, the findings here are inconsistent and at best only provide an indication that this polymorphism is associated with AD-P. To interpret these studies correctly and enable them to inform us about treatment development, it is vital to understand the differences in the methodology and cohort characteristics that might explain the discrepancies.

In addition to looking at the sample groups themselves for reasons why studies may fail to replicate (ethnicity, sample size, phenotype definition), it is also important to look at the clinical features of each sample. A key clinical feature associated with AD-P is disease severity; this is a particularly important consideration given the substantial variation both within and between some prior genetic association studies. There is a wide body of evidence supporting an association between AD-P and disease severity measured antemortem, and it is further strengthened by postmortem studies showing a correlation between severity of tau pathology and AD-P [13]. Estimates of frequencies of hallucinations in mild, moderate and severe AD range from 0 to 21, 10 to 23 and 22 to 56%, respectively, and for delusions there is a similar trend: from 7 to 25, 25 to 45 and 28 to 54%, respectively [14–17]. A 5-year follow-up study plotting cognitive impairment quantitatively against symptom frequency found that by year 1, hallucinations and delusions increased from 8 to 16% and from 40 to 48%, respectively (when MMSE was approximately 16) [18]. By year 5 (when MMSE was approximately 10), hallucination frequencies declined to 13% while delusions declined to 34%, suggesting a non-linear relationship. Measures of quantitative symptom scores rather than frequencies yield similar results, that is hallucinations and delusions peaking in the moderate/moderate-severe stages, suggesting cognitive impairment is an important variable for those genetic studies treating psychosis as a quantitative variable [19, 20].

It follows that focussing on patients with mild AD who have not yet gone through the main risk period may be an important bias. While this has been noted as important going

Fig. 1. Flow diagram illustrating results of electronic and manual searches and study identification process.

forward in previous reports [21, 22], its impact on past research has yet to be quantified but is essential to form a correct interpretation.

Our aim was therefore to complete a systematic review of studies examining the relationship between AD-P and the 5HTTLPR polymorphism to quantify the impact of disease severity on whether a significant association was identified.

Methods

Where relevant to the present review, the criteria set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist were followed [23].

Study Identification and Selection

The results of the following identification process and study selection are illustrated in figure 1. A search of PubMed/MEDLINE and Scopus was conducted using the search term '(dementia or Alzheimer*) AND (serotonin or 5ht*) AND (polymorphism or gene*)'. The only limit on the search was that articles had to be written in English. The resulting 649 records over the 2 lists were screened for candidate gene association studies of the 5HTTLPR polymorphism in relation to psychotic, delusional or hallucination symptoms in AD. References contained in review articles and meta-analyses [21, 24–26] were also manually searched for any additional studies not picked up by the above search. Any duplicate articles were excluded.

Ten articles were found using the aforementioned method, and these were screened in detail to meet the following inclusion criteria: (1) standardised diagnosis of AD; (2) psychotic symptoms (delusions, hallucinations or psychosis) assessed using standardised assessment tool, and (3) cognitive impairment measured using MMSE and reported.

One study did not report MMSE, leaving 9 in total. However, 2 studies were carried out by Borroni et al. [27, 28] in 2006, using very similar cohorts, both reporting significant findings. In order to exclude any bias resulting from including non-independent cohorts, we used the Borroni et al. [27] study with the analysis most similar to the other studies included, leaving 8 studies included in the final review (table 1).

Table 1. 5HTTLPR genetic association studies of psychosis

Study	n	Clinical setting	Fe- males %	S allele frequen- cy, %	Symp- tom	Symptom definition	Symptom frequency %	Design	MMSE ¹ Score ± SD	Assessment tool	Findings
Albani [35]	235	hospital outpatients	69	48	P, D, H	P: D and H; others: score ≥1	P: NR; D: 17; H: 11	cross- sectional	18.7 ± 5.8	SBI-BP	NS
Borroni [27]	234	university centre for AD	72	53	P	D, H or mis- identification present for ≥1 month	35	cross- sectional	17.6 ¹ (16.4 ± 6.5; 18.8 ± 6.5)	DSM-IV	SS genotype/ S allele
Ha [36]	65	hospital clinic	59	75	D	present/ absent	66	cross- sectional	15.2 ± 5.6	BEHAVE-AD	NS
Pritchard [34]	367	memory clinic	56	57	P, D, H	P: D and H at any stage; others: present at any stage	P: 39; D: 62; H: 44	pro- spective	18.6 ± 4.2	NPI	NS
Proitsi [29]	1,008	secondary care services	72	42	P	P: CFA ⁴ model, D and/or H	N/A: quantitative NPI score	cross- sectional	12.8 ± 8.8	NPI	SS genotype *COMT G interaction
Quaranta [30]	148	university neuropsy- chology unit	68	47	P	D or H present for ≥1 month and NPI ≥2	35	cross - sectional	15.9 ¹ (13.8 ± 4.6; 18 ± 5.7)	NPI + clinician	LL genotype/ L allele
Sweet [31]	332	outpatients and community	64	52	P	D or H	43	pro- spective	13.8 ± 7.2	E-BEHAVE-AD + CBRS	LL genotype/ L allele
Ueki [37]	200	NR	67	89	D, H	present at any stage	D: 22; H: 12	pro- spective	19.2 ¹ (19 ± 3.5; 19.4 ± 3.3)	BEHAVE-AD	NS

¹ Overall mean MMSE not reported; figure derived from MMSE of psychotic and non-psychotic participants, respectively (in parentheses). P = Psychosis; D = delusions; H = hallucinations; CFA = confirmatory factor analysis; NS = not significant; NR = not reported.

Results

In total, there have been 8 published 5HTTLPR studies meeting the stipulated inclusion criteria (table 1). Gender proportion was similar across the 8 studies. Similarly, participants in all studies came from similar sources, that is hospital outpatient clinics. Five studies employed a cross-sectional design, while 3 were carried out in prospectively studied cohorts. Other potential confounds such as age of onset and disease duration were not consistently reported across the studies so it is not possible to discuss these factors in the present review.

As shown in figure 2, 4 out of 8 studies reported a significant association between the 5HTTLPR polymorphism and psychotic symptoms in dementia [27, 29–31]; 2 found the LL genotype/L allele to be associated, while 1 found the SS genotype/S allele associated and the last reported only an interaction between SS and COMT to be associated.

Six of the 8 studies investigated a psychotic phenotype of some kind; definitions are listed by study in table 1. Of the remaining 2 studies not using a psychosis phenotype, 1 investigated delusions only while another investigated delusions and hallucinations separately; in each case no significant association was found.

Fig. 2. Individual studies plotted by MMSE and whether or not a significant finding was reported. The dotted line represents the median MMSE (16.75) of the 8 studies included.

Allele frequencies were distributed as expected according to ethnicity [32, 33]. Among the 6 European ancestry cohorts [27, 29–31, 34, 35] the S allele was carried by 42–57% of individuals, while this figure was much higher at 75 and 89% in the 2 Asian cohorts, respectively [36, 37]. Neither of the Asian studies reported a significant association, leaving the 4 previously mentioned significant studies among the 6 European cohorts.

The median MMSE score of the 8 studies included was 16.75. On examination of mean sample MMSE scores plotted according to whether or not the result was significant (fig. 2), it can be seen that those studies reporting a significant finding have, on the whole, lower MMSE scores than those which report no association. Specifically, 3 out of 4 studies with a mean MMSE of 16.75 or below reported a significant finding, while 1 out of 4 with a mean MMSE above 16.75 reported a significant association.

Four of the 8 studies incorporated disease severity into their statistical analyses [27, 29, 30, 34], and 3 of these reported a significant finding, 2 for the SS genotype [27, 29, 30] and 1 for the LL genotype [30]. The one study not reporting an association [34] had a sample with a relatively high MMSE (18.6 ± 4.2). Of the remaining 4 which did not incorporate MMSE into their analysis [31, 35–37], 1 reported a significant finding [31] and this study was 1 of 2 which had a sample MMSE of lower than 16.75 (the other being the study by Ha et al. [36]).

If the 2 Asian studies are excluded, all 3 of the remaining lower MMSE studies and 1 of the 3 remaining higher MMSE studies report significant associations (the median remains the same at 16.75).

Discussion

We present a review that quantifies the extent to which cognitive impairment (measured by MMSE) may have acted as a confounding variable in the literature on association studies of the 5HTTLPR polymorphism in AD-P. Three out of 4 studies with a sample MMSE below

the median reported a significant finding compared with 1 out of 4 among those above 16.75. This brings greater clarity to our understanding of the role of the 5HTTLPR polymorphism and suggests that it is a clear risk factor for psychosis in people with AD. This conclusion is strengthened by the fact that 3 of the 4 studies which factored MMSE into their analyses reported a significant association.

We have presented evidence indicating that cognitive impairment may have confounded previous 5HTTLPR/AD-P studies. However, what cannot be deciphered is whether 5HTTLPR is associated with psychosis directly, indirectly through cognitive impairment or independently with both. A possible mechanism by which 5HTTLPR may influence cognition is via 5HT_{1A} receptors. There is evidence from 5HTT knockout mice and in vivo PET imaging in man that the density of 5HT_{1A} receptors is linked to the presence of 5HTT reuptake sites [12, 38]. 5HT levels in AD have been found to negatively correlate with more rapid cognitive decline, while 5HT_{1A} density is positively correlated [39].

Moreover, tryptophan depletion has been shown to induce cognitive deficits [40], although the downstream mechanism underlying this is not known. Yuen et al. [41] have proposed that reduced NMDA receptor signalling resulting from 5HT_{1A} activation in the prefrontal cortex is a key regulator of cognition. Moreover, 5HT_{1A}-mediated dopamine release in the medial prefrontal cortex is thought to be a key property of atypical antipsychotics [42]. Accordingly, the 5HTTLPR L allele may fit into this mechanism by compounding the already reduced levels of 5HT receptors associated with dementia leading to less activation of 5HT_{1A} receptors relative to the S allele, impacting cognition and psychosis as described above.

The above is based on possible mechanisms of cognitive decline and psychosis and a putative role for 5HTTLPR in each. Before it can be accepted, much more research needs to be carried out to clarify the direction of the relationship between AD-P and 5HTTLPR. Furthermore, much more work needs to be done in order to elucidate fully the relationships with 5HTTLPR described. What is more intractable still is how psychosis may link to cognitive impairment. More rapid cognitive decline is an established correlate of psychosis in AD [43]; there is also evidence that preceding cognitive decline is also associated [44]. It will therefore be important for subsequent research to examine the possible role of 5HTTLPR in cognitive decline independent of psychosis.

The exploration of other potential clinical and demographic confounding variables was limited by the inconsistent reporting among previous studies. However, those that we were able to review were gender, the source of participants and ethnicity. The former 2 variables appeared to be broadly similar among all the studies. Conversely, both of the Asian studies failed to report a significant association and this may have been driven by the substantially higher frequency of the S allele among these populations. When excluded from the review, although 2 studies were lost in doing so, the relationship between cognitive impairment and significant association did strengthen: all 3 lower MMSE studies were positive, while only 1 out of 3 higher MMSE studies was positive. Ethnicity has been highlighted as important in previous, more general reviews, but as the first review specifically of this polymorphism, we are able to refine our initial conclusion and propose that a relationship between 5HTTLPR and psychosis may not exist in the Asian population, and that among Europeans the relationship may only be present among those with greater cognitive impairment.

What has been highlighted here is the importance of consistency in phenotypic definition and perhaps that psychotic symptom phenotypes in AD should be described with reference to cognitive impairment. With these considerations, more work is needed to fully determine the role of 5HTTLPR in AD-P. Moreover, recent pharmacogenetic research by Dombrowski et al. [45] suggests 5HTTLPR may explain some of the variance in citalopram and risperidone treatment response, adding another dimension to the importance of a definitive understanding of this polymorphism by potentially enabling more individualised treatments based

upon likelihood of treatment response and adverse events surrounding pharmacological treatments targeting the 5HT system and highlighting an important role for pharmacogenetics in future trials examining the treatment of AD-P.

The conclusions presented here are necessarily tempered by the limitations of those studies included in the review. The Clinical Dementia Rating Scale and Functional Assessment Staging Tool were used in addition to the MMSE in 2 studies [27, 37], but the MMSE was the only measure of cognitive impairment common to all 8 studies and as such was the sole measure reviewed here. We acknowledge that a more comprehensive picture of cognitive impairment would be provided by more detailed cognitive assessments such as the Severe Impairment Battery or if the MMSE were accompanied by clinical ratings.

There is evidence that individual psychotic symptoms differ in their underlying neurobiological associations [46] as well as their clinical presentation [47], and it is therefore vital that suitable phenotypes are identified and used consistently in the future. We present evidence to suggest cognitive impairment should be considered as part of this phenotype, but there is less scope to draw firm conclusions about the definitions of the psychotic symptoms themselves. Although all studies were selected on the basis of their investigation of delusions, hallucinations or psychosis, the phenotype definitions did vary somewhat. The 2 Asian cohorts were the only ones that did not investigate a psychosis phenotype; it is therefore not possible to say whether it is specifically a combined phenotype that is related to 5HTTLPR, and if so susceptible to moderation by cognitive impairment, rather than individual symptoms, as ethnicity may have been driving the results here. A further constraint to this interpretation is that only 2 of the 6 European studies reporting on a psychosis phenotype also reported on delusions and hallucinations separately. Although in each case this did not change the results (they both remained negative), the fact that these are just 2 studies makes it impossible to draw conclusions about the relationship between 5HTTLPR, individual psychotic symptoms and cognitive impairment.

Prospectively assessed cohorts offer the best opportunities for accurate symptom classification. They offer far more accurate differentiation between transient psychotic-like phenomena such as delirium and persistent psychosis; however, their use in AD-P genetic research, presumably largely due to practical constraints, is limited. There is evidence that multiple or recurrent psychotic symptoms are more highly heritable than single symptoms occurring at any assessment (61 and 30%, respectively) [7]. However, even among those studies reviewed here that employed prospective designs, the multiple and/or recurrent definition was not adopted, leaving non-genetic factors to play a much greater role in the phenotype, a clear issue when aiming to establish the role of genetic variability in a symptom.

What we cannot disentangle based on this review is why half of the significant studies reported the L allele as associated with psychosis, 1 reported the association to be with the S allele and 1 reported a significant effect in the presence of the COMT val158met polymorphism. There are 2 possible sources of this variation. The first is differences in the sample characteristics, with the most obvious source being phenotype definition. Unlike Sweet et al. [31] and Quaranta et al. [30] (who both report the LL genotype as the risk), Proitsi et al. [29] do not stipulate any exclusion criteria which would mitigate the impact of transient episodes of delirium on NPI symptom score in their study. Delirium is common in dementia and unless participants are assessed serially or measures are taken to account for delirium, there is a risk that participants could wrongly score highly on ratings of psychotic symptoms, particularly hallucinations. This is further complicated by research showing that delirium accelerates cognitive decline in dementia [48]. Therefore, there may be different biological mechanisms underlying delirium and psychosis which may give rise to the different results here.

The second source of variation is at the genetic level. rs25531 is an SNP in *SLC6A4*, and its G allele, which occurs in carriers of the 5HTTLPR L allele, reduces the transcription rate to

similar levels as the S allele [49]. However, it was not genotyped in any of the significant studies reviewed here. The presence of this SNP in the Sweet et al. [31] and Quaranta et al. [30] cohorts could conceivably remove the L allele association, or in the case of Proitsi et al. [29] strengthen the S allele association so that a main effect is observed. In people with depression, analysis of haplotypes containing 5HTTLPR and 4 other SNPs located throughout *SLC6A4* has demonstrated differential effects of haplotypes containing the S allele and L allele. Specifically, a positive association was found with the most common haplotype, which contained the S allele, while 2 other haplotypes, 1 containing the L allele and 1 the S allele, were both found to be protective [50]. This was a study in a non-demented population investigating a different phenotype; however, it does effectively illustrate that modification of the 5HTTLPR effect may occur through the presence of SNPs elsewhere in the gene. Future analysis of this kind will greatly help in advancing current understanding of 5HTTLPR, cognitive impairment and psychosis in AD.

It should be acknowledged that this review has only been conducted on 8 studies, and due to the substantial differences between them with regard to methodology and analysis it was not possible to conduct a meta-analysis; therefore, our conclusions should be tempered by this. Although we are unable to statistically test this relationship, what we have described extends the findings from a substantial number of studies highlighting more severe cognitive impairment as a risk for psychosis and demonstrates that this is likely to have influenced the results of previous genetic association studies of 5HTTLPR.

Our aim was to quantify the issue of cognitive impairment in genetic studies of the 5HTTLPR polymorphism and AD-P, which has been the subject of much discussion previously. In summary, we have presented a review showing most of the significant findings of studies of 5HTTLPR and psychosis in AD have been carried out in cohorts with more severe cognitive impairment. In order to accurately describe the relationship between 5HTTLPR and psychosis, future studies should consider the cognitive impairment of their sample, select non-psychotic controls accordingly and interpret their findings with reference to the level of cognitive impairment of the sample.

References

- 1 WorldAlzheimerReport-ExecutiveSummary.pdf. <http://www.alz.co.uk/research/files/WorldAlzheimerReport-ExecutiveSummary.pdf>.
- 2 Levy ML, Cummings JL, Fairbanks LA, Bravi D, Calvani M, Carta A: Longitudinal assessment of symptoms of depression, agitation, and psychosis in 181 patients with Alzheimer's disease. *Am J Psychiatry* 1996;153:1438–1443.
- 3 Aalten P, de Vugt ME, Jaspers N, Jolles J, Verhey FRJ: The course of neuropsychiatric symptoms in dementia. Part I: findings from the two-year longitudinal Maasbed study. *Int J Geriatr Psychiatry* 2005;20:523–530.
- 4 Drevets WC, Rubin EH: Psychotic symptoms and the longitudinal course of senile dementia of the Alzheimer type. *Biol Psychiatry* 1989;25:39–48.
- 5 Corbett A, Smith J, Creese B, Ballard C: Treatment of behavioral and psychological symptoms of Alzheimer's disease. *Curr Treat Options Neurol* 2012;14:113–125.
- 6 Ballard C, Howard R: Neuroleptic drugs in dementia: benefits and harm. *Nat Rev Neurosci* 2006;7:492–500.
- 7 Bacanu SA, Devlin B, Chowdari KV, DeKosky ST, Nimgaonkar VL, Sweet RA: Heritability of psychosis in Alzheimer disease. *Am J Geriatr Psychiatry* 2005;13:624–627.
- 8 Hollingworth P, Hamshere ML, Holmans PA, O'Donovan MC, Sims R, Powell J, Lovestone S, Myers A, DeVrieze FW, Hardy J, Goate A, Owen M, Williams J: Increased familial risk and genomewide significant linkage for Alzheimer's disease with psychosis. *Am J Med Genet B Neuropsychiatr Genet* 2007;144B:841–848.
- 9 Collier DA, Stober G, Li T, Heils A, Catalano M, Di Bella D, Arranz MJ, Murray RM, Vallada HP, Bengel D, Muller CR, Roberts GW, Smeraldi E, Kirov G, Sham P, Lesch KP: A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. *Mol Psychiatry* 1996;1:453–460.

- 10 Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D, Lesch KP: Allelic variation of human serotonin transporter gene expression. *J Neurochem* 1996;66:2621–2624.
- 11 Lesch K, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Muller CR, Hamer DH, Murphy DL: Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 1996;274:1527–1531.
- 12 David SP, Murthy NV, Rabiner EA, Munafo MR, Johnstone EC, Jacob R, Walton RT, Grasby PM: A functional genetic variation of the serotonin (5-HT) transporter affects 5-HT_{1A} receptor binding in humans. *J Neurosci* 2005;25:2586–2590.
- 13 Zubenko GS, Moosy J, Martinez AJ, Rao G, Claassen D, Rosen J, Kopp U: Neuropathologic and neurochemical correlates of psychosis in primary dementia. *Arch Neurol* 1991;48:619–624.
- 14 Lopez OL, Becker JT, Sweet RA, Klunk W, Kaufer DI, Saxton J, Habeych M, DeKosky ST: Psychiatric symptoms vary with the severity of dementia in probable Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* 2003;15:346–353.
- 15 Selbæk G, Kirkevold Ø, Engedal K: The prevalence of psychiatric symptoms and behavioural disturbances and the use of psychotropic drugs in Norwegian nursing homes. *Int J Geriatr Psychiatry* 2007;22:843–849.
- 16 Craig D, Mirakhor A, Hart DJ, McIlroy SP, Passmore AP: A cross-sectional study of neuropsychiatric symptoms in 435 patients with Alzheimer's disease. *Am J Geriatr Psychiatry* 2005;13:460–468.
- 17 Piccininni M, Di Carlo A, Baldereschi M, Zaccara G, Inzitari D: Behavioral and psychological symptoms in Alzheimer's disease: frequency and relationship with duration and severity of the disease. *Dement Geriatr Cogn Disord* 2005;19:276–281.
- 18 Holtzer R, Tang MX, Devanand DP, Albert SM, Wegesin DJ, Marder K, Bell K, Albert M, Brandt J, Stern Y: Psychopathological features in Alzheimer's disease: course and relationship with cognitive status. *J Am Geriatr Soc* 2003;51:953–960.
- 19 Suh G, Kim SK: Behavioral and psychological signs and symptoms of dementia (BPSD) in antipsychotic-naïve Alzheimer's disease patients. *Int Psychogeriatr* 2004;16:337–350.
- 20 Harwood DG, Barker WW, Ownby RL, Duara R: Relationship of behavioral and psychological symptoms to cognitive impairment and functional status in Alzheimer's disease. *Int J Geriatr Psychiatry* 2000;15:393–400.
- 21 DeMichele-Sweet MA, Sweet RA: Genetics of psychosis in Alzheimer's disease: a review. *J Alzheimers Dis* 2010;19:761–780.
- 22 Proitsi P, Powell JF: Missense substitutions associated with behavioural disturbances in Alzheimer's disease (AD). *Brain Res Bull* 2012;88:394–405.
- 23 Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- 24 Borroni B, Costanzi C, Padovani A: Genetic susceptibility to behavioural and psychological symptoms in Alzheimer disease. *Curr Alzheimer Res* 2010;7:158–164.
- 25 Ramanathan S, Glatt SJ: Serotonergic system genes in psychosis of Alzheimer dementia: meta-analysis. *Am J Geriatr Psychiatry* 2009;17:839–846.
- 26 Flirski M, Sobow T, Kloszewska I: Behavioural genetics of Alzheimer's disease: a comprehensive review. *Arch Med Sci* 2011;7:195–210.
- 27 Borroni B, Grassi M, Agosti C, Archetti S, Costanzi C, Cornali C, Caltagirone C, Caimi L, Di Luca M, Padovani A: Cumulative effect of COMT and 5-HTTLPR polymorphisms and their interaction with disease severity and comorbidities on the risk of psychosis in Alzheimer disease. *Am J Geriatr Psychiatry* 2006;14:343–351.
- 28 Borroni B, Grassi M, Agosti C, Costanzi C, Archetti S, Franzoni S, Caltagirone C, Di Luca M, Caimi L, Padovani A: Genetic correlates of behavioral endophenotypes in Alzheimer disease: role of COMT, 5-HTTLPR and APOE polymorphisms. *Neurobiol Aging* 2006;27:1595–1603.
- 29 Proitsi P, Lupton MK, Reeves SJ, Hamilton G, Archer N, Martin BM, Iyegbe C, Hollingworth P, Lawlor B, Gill M, Brayne C, Rubinsztein DC, Owen MJ, Williams J, Lovestone S, Powell JF: Association of serotonin and dopamine gene pathways with behavioral subphenotypes in dementia. *Neurobiol Aging* 2012;33:791–803.
- 30 Quaranta D, Bizzarro A, Marra C, Vita MG, Seripa D, Pilotto A, Sebastiani V, Mecocci P, Masullo C: Psychotic symptoms in Alzheimer's disease and 5-HTTLPR polymorphism of the serotonin transporter gene: evidence for an association. *J Alzheimers Dis* 2009;16:173–180.
- 31 Sweet RA, Pollock BG, Sukonick DL, Mulsant BH, Rosen J, Klunk WE, Kastango KB, DeKosky ST, Ferrell RE: The 5-HTTLPR polymorphism confers liability to a combined phenotype of psychotic and aggressive behavior in Alzheimer disease. *Int Psychogeriatr* 2001;13:401–409.
- 32 Gelernter J, Kranzler H, Cubells JF: Serotonin transporter protein (SLC6A4) allele and haplotype frequencies and linkage disequilibria in African- and European-American and Japanese populations and in alcohol-dependent subjects. *Hum Genet* 1997;101:243–246.
- 33 Kunugi H, Hattori M, Kato T, Tatsumi M, Sakai T, Sasaki T, Hirose T, Nanko S: Serotonin transporter gene polymorphisms: ethnic difference and possible association with bipolar affective disorder. *Mol Psychiatry* 1997;2:457–462.
- 34 Pritchard AL, Pritchard CW, Bentham P, Lendon CL: Role of serotonin transporter polymorphisms in the behavioural and psychological symptoms in probable Alzheimer disease patients. *Dement Geriatr Cogn Disord* 2007;24:201–206.

- 35 Albani D, Prato F, Tettamanti M, Lovati C, Galimberti D, Restelli I, Mariani C, Quadri PL, Scarpini E, Lucca U, Forloni G: The serotonin transporter promoter polymorphic region is not a risk factor for Alzheimer's disease related behavioral disturbances. *J Alzheimers Dis* 2009;18:125–130.
- 36 Ha TM, Cho DM, Park SW, Joo MJ, Lee BJ, Kong BG, Kim JM, Yoon JS, Kim YH: Evaluating associations between 5-HTTLPR polymorphism and Alzheimer's disease for Korean patients. *Dement Geriatr Cogn Disord* 2005;20:31–34.
- 37 Ueki A, Ueno H, Sato N, Shinjo H, Morita Y: Serotonin transporter gene polymorphism and BPSD in mild Alzheimer's disease. *J Alzheimers Dis* 2007;12:245–253.
- 38 Holmes A, Murphy DL, Crawley JN: Abnormal behavioral phenotypes of serotonin transporter knockout mice: parallels with human anxiety and depression. *Biol Psychiatry* 2003;54:953–959.
- 39 Lai MK, Tsang SW, Francis PT, Keene J, Hope T, Esiri MM, Spence I, Chen CP: Postmortem serotonergic correlates of cognitive decline in Alzheimer's disease. *Neuroreport* 2002;13:1175–1178.
- 40 Porter RJ, Lunn BS, Walker LL, Gray JM, Ballard CG, O'Brien JT: Cognitive deficit induced by acute tryptophan depletion in patients with Alzheimer's disease. *Am J Psychiatry* 2000;157:638–640.
- 41 Yuen EY, Jiang Q, Chen P, Gu Z, Feng J, Yan Z: Serotonin 5-HT_{1A} receptors regulate NMDA receptor channels through a microtubule-dependent mechanism. *J Neurosci* 2005;25:5488–5501.
- 42 Ichikawa J, Ishii H, Bonaccorso S, Fowler WL, O'Laughlin IA, Meltzer HY: 5-HT_{2A} and D₂ receptor blockade increases cortical DA release via 5-HT_{1A} receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. *J Neurochem* 2001;76:1521–1531.
- 43 Sweet RA, Nimgaonkar VL, Devlin B, Jeste DV: Psychotic symptoms in Alzheimer disease: evidence for a distinct phenotype. *Mol Psychiatry* 2003;8:383–392.
- 44 Paulsen JS, Salmon DP, Thal LJ, Romero R, Weisstein-Jenkins C, Galasko D, Hofstetter CR, Thomas R, Grant I, Jeste DV: Incidence of and risk factors for hallucinations and delusions in patients with probable AD. *Neurology* 2000;54:1965–1971.
- 45 Dombrowski AY, Mulsant BH, Ferrell RE, Lotrich FE, Rosen JI, Wallace M, Houck PR, Mazumdar S, Pollock BG: Serotonin transporter triallelic genotype and response to citalopram and risperidone in dementia with behavioral symptoms. *Int Clin Psychopharmacol* 2010;25:37–45.
- 46 Forstl H, Burns A, Levy R, Cairns N: Neuropathological correlates of psychotic phenomena in confirmed Alzheimer's disease. *Br J Psychiatry* 1994;165:53–59.
- 47 Ballard C, Bannister C, Graham C, Oyeboode F, Wilcock G: Associations of psychotic symptoms in dementia sufferers. *Br J Psychiatry* 1995;167:537–540.
- 48 Fong TG, Jones RN, Shi P, Marcantonio ER, Yap L, Rudolph JL, Yang FM, Kiely DK, Inouye SK: Delirium accelerates cognitive decline in Alzheimer disease. *Neurology* 2009;72:1570–1575.
- 49 Wendland JR, Martin BJ, Kruse MR, Lesch K, Murphy DL: Simultaneous genotyping of four functional loci of human SLC6A4, with a reappraisal of 5-HTTLPR and rs25531. *Mol Psychiatry* 2006;11:224–226.
- 50 Lazary J, Lazary A, Gonda X, Benko A, Molnar E, Juhasz G, Bagdy G: New evidence for the association of the serotonin transporter gene (*SLC6A4*) haplotypes, threatening life events, and depressive phenotype. *Biol Psychiatry* 2008;64:498–504.