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The functional minisatellite at the 3'-UTR of *SLC6A3/DAT1* and dementia spectrum disorders: an association study in a population of Central Italy

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Abstract

Background Dementia comprises a spectrum of neurodegenerative disorders marked by progressive cognitive and behavioural decline, with Alzheimer's disease (AD) being the most prevalent form. While several genetic factors have been implicated in AD pathogenesis, a significant portion of heritability remains unexplained. One potential contributor to this "missing heritability" is structural variation within non-coding regions, such as variable-number tandem repeats (VNTRs). This study investigated the 40-bp VNTR located in the 3' untranslated region of the *SLC6A3/DAT1* (henceforth referred to as *DAT1*) gene, a polymorphism previously associated with dopamine regulation and psychiatric conditions, for potential associations with dementia spectrum disorders and related neuropsychiatric phenotypes.

Methods A cohort of 799 elderly individuals from Central Italy, including AD, mild cognitive impairment (MCI), mixed dementia, and control subjects, was genotyped for the *DAT1* VNTR and the *APOE* alleles. Neuropsychiatric evaluation was performed using the Neuropsychiatric Inventory (NPI).

Results No significant association was observed between *DAT1*-VNTR genotypes and any dementia diagnosis. However, neuropsychiatric analysis revealed significant associations between *DAT1*-VNTR genotypes and behavioural symptoms. Carriers of the short (*S) allele showed association with apathy (especially in the presence of *APOE**4), irritability, and disinhibition. The *S/*S genotype was notably linked to elevated NPI scores for irritability and disinhibition.

Conclusions These findings suggest that while the *DAT1* VNTR is not directly associated with dementia diagnoses, it may contribute to modulating neuropsychiatric symptoms across dementia types. The results emphasize the importance of investigating non-coding genetic variants and their interactions with established risk alleles, such as *APOE**4. Larger studies are needed to validate these findings and explore the functional consequences of *DAT1* variation in neurodegeneration. This work contributes to our understanding of the dopaminergic system's influence

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on behavioural phenotypes in dementia. It warrants the VNTR as a candidate contributing to neuropsychiatric symptom variability in aging populations.

Keywords Alzheimer's disease, Association Study, Dementia, Dopamine, Polymorphism, VNTR

Background

Dementia is a clinical syndrome characterised by a progressive decline in cognitive function that interferes with daily life and independence. The term encompasses a spectrum of neurodegenerative conditions [1, 2] that share similar symptomatology, such as memory loss, language impairment, behavioural changes, and executive dysfunction. The most prevalent of these disorders is the well-characterized Alzheimer's disease (AD), followed by other common types, such as vascular dementia (VaD), frontotemporal dementia (FTD), and Lewy body dementia (LBD). Other, less widespread, disorders are Parkinson's disease dementia (PDD) and mixed dementia (the co-occurrence of clinical features of both AD and VaD).

While several genetic factors for AD development and progression have been identified and elucidated [3], the underlying cause of the so-called 'missing heritability' in AD remains unclear. Indeed, the estimated heritability of late-onset AD (LOAD) – the most common form of the disease – ranges from 58% to 79% in twin studies [4]. However, the outcome of Genome-wide Complex Trait Analysis (GCTA) could only confirm 33% of this heritability [5], leaving nearly half of the expected heritability unaccounted for.

One prevailing hypothesis is that the missing heritability problem stems from how genetic association studies have traditionally been conducted: most studies have focused on single-nucleotide polymorphisms (SNPs), particularly in coding regions. The analysis of this variant type in Genome-Wide Association Studies (GWAS) is more straightforward and cost-effective. Furthermore, short-read (75–150 bp) next-generation sequencing (NGS) fails to capture structural variants, as their size often exceeds the length of the sequencing reads. Therefore, what has largely been overlooked is the so-called dark genome, which comprises the non-coding regions of the human genome and accounts for roughly 98% of our DNA. These regions can influence gene expression regulation and contribute significantly to genome variability, as seen with variable-number tandem repeats (VNTRs). Still, they usually cannot be properly aligned or mapped [6, 7].

One of the most studied VNTRs is the one located at the 3'-untranslated region (3'-UTR) of the *DAT1* gene. This gene encodes a dopamine transporter, which regulates dopamine levels in brain cells by facilitating the reuptake of the molecule from the synaptic cleft back into the cytosol of presynaptic neurons. The 40 bp VNTR at the 3'-UTR of the *DAT1* gene (rs28363170) presents multiple alleles, with copy numbers ranging from 3 to 11; however, the 9-repeat and 10-repeat alleles are the most prevalent [8]. The VNTR has been extensively investigated for its possible association with several neuropsychiatric conditions, such as attention-deficit/hyperactivity disorder (ADHD) and schizophrenia [9–13]. Moreover, although located in the 3'-UTR, the VNTR influences *DAT1* gene expression: higher repeat numbers are associated with increased gene expression [14].

While being traditionally linked to Parkinson's disease (PD), dopamine also seems to have a role in various aspects of AD pathology. For instance, dopaminergic system alterations and subsequent disruption can occur early in AD development and continue to worsen as the disease advances [15]. Additionally, dopaminergic neuronal loss impairs memory and reward in AD models [16], potentially reducing dopamine levels in areas such as the hippocampus [17]. Moreover, dopamine system dysregulation is also linked to a plethora of non-cognitive symptoms frequently observed in subjects with AD, including apathy, agitation, and mood disorders [18].

To date, many *DAT1* variants have gathered significant attention as potential contributors to AD development and progression, and cognitive impairment. Notably, rs6347 has been associated with various phenotypes in AD. For instance, a *DAT1*(rs6347)**BDNF*(rs6265) interaction was seen to predict Aβ-PET, tau-PET, and hippocampal atrophy, with carriers of both minor alleles (*DAT1* C/C and *BDNF* Met carriers) showing greater pathology and atrophy [19]. Additionally, individuals homozygous for the C allele at rs6347 performed worse on the Mini-Mental State Examination (MMSE). At the same time, no differences were observed in those carrying either 0 or 1 copy of the allele, suggesting a recessive model of effect of the minor allele on cognitive decline; moreover, carrying the C allele was associated with greater overall ventricular expansion – an established marker of AD progression [20] – over 2 years [21]. Another variant, rs464049, was found to interact with the *APOE**4 allele – a well-known genetic risk factor for AD [3] – and apathy in mild cognitive impairment (MCI) and subjects with AD, pointing to a potential dopaminergic contribution to neuropsychiatric symptoms in AD [22]. Finally, rs28363170, which defines the indel distinguishing 9- and 10-repeat *DAT1* VNTR alleles, has been linked to age-related decline in working memory. Although both alleles show a similar rate of age-related decline in striatal function during working memory updating, 10-repeat homozygotes, who have lower baseline levels of striatal function, may reach

a critical threshold of decreased function and exhibit impaired cognitive processes earlier in life than 9-repeat carriers [23]. Furthermore, while one study found an association between the 9-repeat allele and irritability in AD, and between the 10-repeat allele and aberrant motor behaviour (AMB), these associations failed to remain significant after correction for multiple testing [24].

Although population-specific, two findings are worth mentioning: the rs6347-A allele was linked to a moderate stage of dementia in the Taiwanese population [25], while the dose-dependent genetic susceptibility to AD was correlated with the inheritance of the *DAT1* VNTR 9-repeat allele [26] in the Hungarian population.

Thus, despite several lines of evidence pointing to a direct involvement of *DAT1* gene variants in AD physiopathology and related neuropsychiatric features, the role of its 3'-UTR functional minisatellite remains unclear. The present work aims to investigate the association between the *DAT1*-VNTR genotype and related neuropsychiatric scores and dementia spectrum pathologies in a large, clinically well-characterized sample derived from memory clinics, with detailed diagnoses of cognitive disorders and dementia.

Methods

Study population

This cross-sectional study analysed data from the GERIatric COgnitive evaluation study (GERICO), an ongoing research project on older adults referred to the Memory Clinic at the Geriatric Center for Cognitive Disorders and Dementia (CDCD), within the Gerontology and Geriatrics section of the Department of Medicine and Surgery at the University of Perugia, Italy. More details about the project have been previously published [27].

Of the 1731 individuals recruited from February 2015 to June 2023, we excluded 483 individuals with missing Neuropsychiatric Inventory data and 449 individuals without blood samples stored for research and genetic analysis. The final sample comprises 799 unrelated Caucasian individuals aged 60–97 years, including 503 females and 296 males. Information on sociodemographic and anthropometric factors, functional performance, medical conditions, medication use, and cognitive function was assessed through routine clinical examinations conducted by trained nurses, neuropsychologists, and geriatricians. Blood samples were collected after fasting and analyzed at the University of Perugia's laboratory. DNA was extracted by the salting-out method [28] and stored at -20° C until genetic analyses were performed at the Laboratory of Genomic and Molecular Epidemiology (GAME) at the School of Biosciences and Veterinary Medicine, University of Camerino, Italy.

The Central Italian elderly cohort analysed in this study is particularly suitable for investigating the contribution of non-coding dopaminergic variants to dementia-related phenotypes. Central Italy is characterised by a relatively homogeneous genetic structure, with limited recent migration and well-documented population continuity [29–31], reducing the risk of population stratification bias in genotype–phenotype analyses. Moreover, this cohort derives from a single, regionally organised memory clinic network with harmonised diagnostic procedures, ensuring high clinical consistency across dementia subtypes. These features make this population an appropriate and well-controlled context in which to evaluate the behavioural impact of *DAT1* variation.

Ethical approval for the GERICO study was granted by Umbria CER (Comitato Etico Regionale), Umbria Regional Ethics Committee Prot. N. CE-2078/25 del 16/04/2025.

Clinical assessment of cognitive disorders and neuropsychiatric symptoms

As part of the standard Multidimensional Geriatric Evaluation conducted at the CDCD Memory Clinic, a comprehensive neuropsychological assessment was carried out. The evaluation integrates physical, cognitive, and mental health domains, along with functional, social, and environmental factors, to support the clinical diagnosis of cognitive impairment and related disorders. The diagnosis of Subjective Cognitive Decline (SDC) was based on the definition of perceived decline in memory and/or other cognitive abilities relative to previous levels of performance, in the absence of objective neuropsychological deficits [32]. Mild cognitive impairment (MCI) was diagnosed when objective neuropsychological deficits were present without dementia and daily functioning was preserved, according to the criteria [33], distinguishing between amnestic (aMCI) and non-amnestic (naMCI) subtypes [34, 35]. The diagnostic procedure was also consistent with the Italian clinical guidelines for the assessment and classification of MCI [36]. The diagnosis of Major Neurocognitive Disorder, commonly defined as dementia, was based on DSM-5 [37]. Subtypes included AD, diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [38], VaD on the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria [39], FTD on the criteria described by Neary et al. [40], LBD on the criteria by McKeith et al. [41], and PDD according to Emre et al. [42] and mixed dementia (co-occurring clinical features of both AD and VaD), based on standard criteria. Cognitive severity was rated using the Clinical Dementia Rating Scale (CDR), ranging from

0 (cognitively unimpaired/SCD), 0.5 (MCI), 1–4 (mild to severe dementia) [43].

For the current study, participants were grouped into 143 controls (CTRL), consisting of cognitively unimpaired subjects or with Subjective Cognitive Decline (SCD), with a CDR score of 0; 269 participants with MCI and CDR = 0.5; 202 participants with AD, and 145 individuals with mixed dementia (Mix Dem) (CDR range 1–4). Additionally, 40 participants with less common diagnostic categories were included: vascular dementia (VaD, $n = 18$), frontotemporal dementia (FTD, $n = 10$), dementia with Lewy bodies (DLB, $n = 6$), progressive supranuclear palsy (PSP, $n = 2$), corticobasal degeneration (CBD, $n = 1$), Creutzfeldt–Jakob disease (CJD, $n = 1$), normal pressure hydrocephalus (NPH, $n = 1$), and Parkinson's disease dementia (PDD, $n = 1$). Due to the small sample size of each group, these cases were combined into a single category labelled "Other" (CDR range 1–4).

Clinical diagnoses and CDR classifications were fully concordant.

Assessment of NPS

Neuropsychiatric symptoms (NPS) were assessed using the Neuropsychiatric Inventory (NPI) [44, 45], a structured caregiver-based interview designed to assess 12 symptom domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, apathy, euphoria, disinhibition, irritability, aberrant motor activity, night-time behavioural disturbances, and appetite/eating changes.

In accordance with NPI scoring procedures, each domain score was derived by multiplying frequency (0 = "never" to 4 = "very frequently") by severity (1 = "mild" to 3 = "severe"), resulting in a possible range of 0–12. The total NPI score was the sum of the 12 domain scores (range: 0–144).

DAT1-VNTR genotyping

A PCR-based genotyping method targeting the *DAT1* 40-bp VNTR was performed. The reactions were all conducted using 2× Phanta Max Master Mix (Dye Plus) (Vazyme International LLC, Nanjing, PRC), while the primers used for the amplification were those previously described [46]: the forward primer sequence was 5'-TGTGGTGTAGGGAACGGCCTGAG-3', and the reverse primer sequence was 5'-CTTCCTGGAGGTCACGGCTCAAGG-3'. Amplification was performed over 30 cycles, with denaturation at 95° C for 30 s, annealing at 60° C for 15 s, and elongation at 72° C for 45 s. PCR products were separated by 2% agarose gel electrophoresis, and visualization was performed under UV light with Vazyme Ultra GelRed (10,000×) (Vazyme International LLC, Nanjing, PRC).

Blinding of the operator was applied, and samples were genotyped in duplicate. The PCR-based genotyping method was utilised, as it is the standard approach for investigating VNTRs.

APOE genotyping

APOE, as a known risk factor for AD, was also genotyped in the study population. A PCR-based genotyping method was used, employing the same reaction mix as for the *DAT1* 40-bp VNTR. The forward primer sequence 5'-TAAGCTTGGCACGGCTGTCCAAGGA-3' and the reverse one 5'-ACAGAATTCGCCCCGGCCTGGTACAC-3', as previously described [47]. Amplification was performed over 30 cycles, with denaturation at 95° C for 15 s, annealing at 60° C for 15 s, and elongation at 72° C for 45 s. PCR products were then digested with the Restriction Fragment Length Polymorphism (RFLP) method using the Thermo Scientific™ *HhaI* (Thermo Fisher Scientific Inc., Waltham, Massachusetts, USA) enzyme to distinguish the different *APOE* alleles. After restriction, the derived fragments were visualized on a 3.5% agarose gel. In this case, the operator was blinded, and samples were genotyped in duplicate.

Statistical analysis

One-way ANOVA was performed on the entire dataset to compare age and sex means between case groups and controls. For further statistical analyses, the variants were coded in two ways: based on the number of VNTR repeats – where allele *DAT1**9 corresponded to the 9-repeat allele, *DAT1**10 and *DAT1**11 to the 10-repeat and 11-repeat alleles, respectively – and, in a more compact form – where variant *9 was classified as *DAT1**S (for "Short allele") and the variants exceeding 9 repeats as *DAT1**L (for "Long allele") – in line with previously reported functional relevance [14, 48–50].

Allele and genotype frequencies were assessed by direct counting, and the Hardy-Weinberg equilibrium (HWE) was evaluated by comparing the observed and expected frequencies using the contingency table Fisher's Exact test statistics.

Binary logistic regression was performed to investigate the association of the VNTR under study with the development of dementia pathologies, setting "diagnosis" as the dependent variable and "age", "sex", "*APOE**2 allele count", and "*APOE**4 allele count" as covariates, along with *DAT1*-VNTR *S allele count.

Subsequently, omnibus analyses using generalized linear models were performed to assess the association between NPI scores and the *DAT1*-VNTR *S allele count. In this case, only those dementia patients who were administered the questionnaire were considered. The NPI score under study was set as the dependent variable. At the same time, "age", "sex", "diagnosis", "*APOE**2 allele

count", "*APOE**4 alleles count", "education years" – available only for the subjects assessed for neuropsychiatric and cognitive tests –, "ADL (Activities of Daily Living) score" [51], "IADL (Instrumental Activities of Daily Living) score" [52] and "MMSE score" [53], were used as covariates. In this case, the *DAT1*-VNTR *S allele count was considered a covariate. All NPI scores were tested, as they could both show to be consistent with previously reported results, as for the association of *DAT1* with apathy in *APOE**4 carriers, and irritability/liability (henceforth referred to as irritability), but also provide novel findings for neuropsychiatric symptoms in dementia, as the subgroups of the NPI comprise a wide array of such profiles.

Further analyses were performed, stratifying the sample population by *APOE**4 allele count, using the same covariates as mentioned above, excluding *APOE**2 and *APOE**4 allele counts. This analysis was performed to explore the possible interaction between *APOE**4 and apathy in individuals with dementia, to further investigate a previously reported finding [22]. For the NPI subdomains that showed statistical significance in the omnibus analyses, we further performed linear regression analyses to assess group differences, using the same covariates as in the omnibus analyses.

In all the statistical analyses described, additive, dominant, and recessive genetic models for *DAT1*-VNTR were all tested. This means that, when performing the aforementioned analyses, each test was performed coding the *DAT1*-VNTR *S allele count as either 0/1/2 – additive model, based on the number of *S allele copies – or 0/1 – in the case of dominant model, 0 was assigned to *L/*L samples, while 1 was assigned *S/*S and *S/*L samples; in the case of recessive model, 0 was assigned to *S/*L and *L/*L samples, while 1 was assigned to *S/*S samples.

Because the NPI subdomains are not independent (showing correlated factor structures and clustering across neuropsychiatric syndromes), a Bonferroni correction was not applied across NPI domains, as per prior literature [54].

Statistical analyses were performed using IBM SPSS Statistics software (version 27.0) [55], considering a statistical significance cut-off of $P < 0.05$. Supplementary checks (regression diagnostics) on the results were performed using the stats R package, version 4.2.1.

Table 1 Demographics

Diagnosis	*N*	F (%)	Age (mean ± SD)	Age comparison *P*-value	Sex comparison *P*-value
AD	202	144 (71.3)	82.5 ± 6.2	< 0.001	0.001
naMCI	206	123 (59.7)	79.1 ± 6.0	< 0.001	0.339
aMCI	63	42 (66.7)	77.7 ± 6.3	0.150	0.105
Mix Dem	145	95 (65.5)	83.0 ± 5.2	< 0.001	0.058
Other	40	21 (52.5)	79.1 ± 6.7	0.031	0.820
CTRL	143	78 (54.5)	76.2 ± 7.6	---	---
Total	799	503 (63.0)	80.0 ± 6.8	---	---

Age and sex comparisons were tested, with the control group as the reference, using ANOVA comparisons of AD vs. CTRL, naMCI vs. CTRL, aMCI vs. CTRL, Mix Dem vs. CTRL, and Other vs. CTRL

AD Alzheimer's Disease, *naMCI* non-amnesic Mild Cognitive Impairment, *aMCI* amnesic Mild Cognitive Impairment, *Mix Dem* Mixed Dementia, *CTRL* Controls

Results

Demographics

As reported in Table 1, the 799 samples showed a mean age at examination of 80.0 years, with an overall standard deviation of 6.8 years; however, mixed dementia cases showed a slightly higher mean age, followed by AD, Other, and naMCI groups, and aMCI group second-last, while CTRLs showed the lowest mean age. The sample population was composed of 63.0% females.

One-way ANOVA testing results – comparing each case group's mean age and sex with control one – are also summarized in Table 1. The tests showed a statistically significant difference ($P < 0.05$) in mean age between all groups and controls, except for the aMCI group. Furthermore, the AD group showed a statistically significant difference from controls, including in the sex distribution comparison.

Genotype and allele distribution of the *SLC6A3/DAT1* 40-bp VNTR and the APOE common polymorphism

The allele and genotype frequencies for the *DAT1* 40-bp VNTR, classified according to the number of VNTR repeats, are reported in Supplementary Table S1. The frequencies with the alleles classified as *S or *L are displayed in Table 2. No significant deviation from HWE was detected in the control group ($p = 0.491$)

The allele and genotype frequencies for *APOE* were also assessed in the sample population, as reported in Table 3. No significant deviation from HWE was detected for the control group ($p = 0.311$)

Association of *SLC6A3/DAT1* 40-bp VNTR with dementia pathologies

No significant association was observed when testing either group against CTRL using any of the models. A summary of the tests and their relative results is reported in Table 4.

However, an overall significant association was observed between *APOE**4 allele count and the risk of dementia development, as expected. We observed a 4-fold increase in risk for subjects with AD, a 2-fold increase for naMCI, a 3-fold increase for aMCI, and a 2-fold increase for Mix Dem individuals. All test results, regarding *APOE**2 and *APOE**4 allele count, are reported in Supplementary Table S2.

Table 2 *SLC6A3/DAT1* 40-bp VNTR genotype and allele frequencies in the whole sample under study

Diagnosis	Genotype frequency (%)				Allele frequency (%)		
	*S/*S	*S/*L	*L/*L	Total	*S	*L	Total
AD	23 (11.4)	88 (43.6)	91 (45.0)	202	134 (33.2)	270 (66.8)	404
naMCI	26 (12.6)	77 (37.4)	103 (50.0)	206	129 (31.3)	283 (68.7)	412
aMCI	10 (15.9)	29 (46.0)	24 (38.1)	63	49 (38.9)	77 (61.1)	126
Mix Dem	13 (9.0)	65 (44.8)	67 (46.2)	145	91 (31.3)	199 (68.7)	290
Other	5 (12.5)	12 (30.0)	23 (57.5)	40	22 (27.5)	58 (72.5)	80
CTRL	13 (9.1)	66 (46.2)	64 (44.8)	143	92 (32.2)	194 (67.8)	286
Total	90 (11.3)	337 (42.2)	372 (46.6)	799	517 (32.4)	1081 (67.6)	1598

The VNTR alleles were coded in the compact version

Table 3 *APOE* genotype and allele frequencies in the whole sample under study

Diagnosis	Genotype frequency (%)							Allele frequency (%)			
	*2/*2	*2/*3	*2/*4	*3/*3	*3/*4	*4/*4	Total	*2	*3	*4	Total
AD	2 (1.0)	14 (6.9)	1 (0.5)	134 (66.3)	50 (24.8)	1 (0.5)	202	19 (4.7)	332 (82.2)	53 (13.1)	404
naMCI	6 (2.9)	11 (5.4)	---	143 (69.4)	40 (19.4)	6 (2.9)	206	23 (5.6)	337 (81.8)	52 (12.6)	412
aMCI	3 (4.8)	1 (1.6)	---	41 (65.1)	14 (22.2)	4 (6.3)	63	7 (5.6)	97 (77.0)	22 (17.5)	126
Mix Dem	3 (2.1)	5 (3.5)	1 (0.7)	114 (78.6)	20 (13.8)	2 (1.4)	145	12 (4.1)	253 (87.2)	25 (8.6)	290
Other	3 (7.5)	1 (2.5)	---	29 (72.5)	5 (12.5)	2 (5.0)	40	7 (8.8)	64 (80.0)	9 (11.3)	80
CTRL	5 (3.5)	12 (8.4)	3 (2.1)	109 (76.2)	13 (9.1)	1 (0.7)	143	25 (8.7)	243 (85.0)	18 (6.3)	286
Total	22 (2.8)	44 (5.5)	5 (0.6)	570 (71.3)	142 (17.8)	16 (2.0)	799	93 (5.8)	1326 (83.0)	179 (11.2)	1598

Table 4 Association study results

Comparison	Model applied	OR	95% C.I. for OR		*P*-value
			Lower	Upper	
AD vs. CTRL	Additive	0.970	0.666	1.413	0.875
	Dominant	0.837	0.507	1.382	0.487
	Recessive	1.397	0.609	3.202	0.430
naMCI vs. CTRL	Additive	0.918	0.660	1.276	0.611
	Dominant	0.759	0.484	1.188	0.228
	Recessive	1.352	0.655	2.793	0.414
aMCI vs. CTRL	Additive	1.419	0.885	2.275	0.146
	Dominant	1.353	0.716	2.558	0.351
	Recessive	2.146	0.834	5.519	0.113
Mix Dem vs. CTRL	Additive	0.903	0.592	1.377	0.636
	Dominant	0.842	0.489	1.448	0.534
	Recessive	1.011	0.392	2.611	0.981
Other vs. CTRL	Additive	0.739	0.417	1.309	0.300
	Dominant	0.518	0.248	1.084	0.081
	Recessive	1.436	0.469	4.396	0.526

The model applied refers to the *DAT1**S copy number

Association of *SLC6A3/DAT1* 40-bp VNTR with neuropsychiatric scores in subjects with dementia

All NPI scores were analysed across the groups under study, as previously mentioned, using generalized linear models to test additive, dominant, and recessive models of the *DAT1*-VNTR *S allele. Data for non-significant scores are omitted for brevity (Supplementary Table S3).

No statistically significant association was observed between the total NPI score and the VNTR. However, the results revealed a novel association between *DAT1*-VNTR and apathy, as measured by NPI, across the whole dementia dataset. Indeed, although weak, the additive model for *DAT1*-VNTR showed an association in the omnibus analysis of the NPI apathy measure (P = 0.048; Fig. 1). When restricting the analysis to only *APOE**4 carriers (a test performed to further explore already reported the association of *DAT1* and apathy in *APOE**4 carriers [22]), we could see an association of both the additive model (P = 0.007, Fig. 2A) and the dominant one (P = 0.003, Fig. 2B) – results that seem consistent with previous studies when it comes to an association of *DAT1* and apathy in *APOE**4 carriers. However, when formally testing the interaction between *APOE**4 allele count and *DAT1*-VNTR by including an interaction term in the analyses for NPI apathy, no association could be seen for any of the models – additive, dominant, or recessive – tested.

In the recessive model, the *S/*S genotype resulted associated with the NPI irritability score (P = 0.034, Fig. 3).

A novel, although preliminary, association with NPI disinhibition score could be observed: indeed, both the additive model (P = 0.031, Fig. 4A) and the recessive one (P = 0.014, Fig. 4B) show an association with the aforementioned score.

These NPI scores, which yielded statistically significant outcomes in the omnibus generalised linear model analyses, were further analysed using linear regression, and the results were meta-analysed using a fixed-effect model. The results are reported in Table 5.

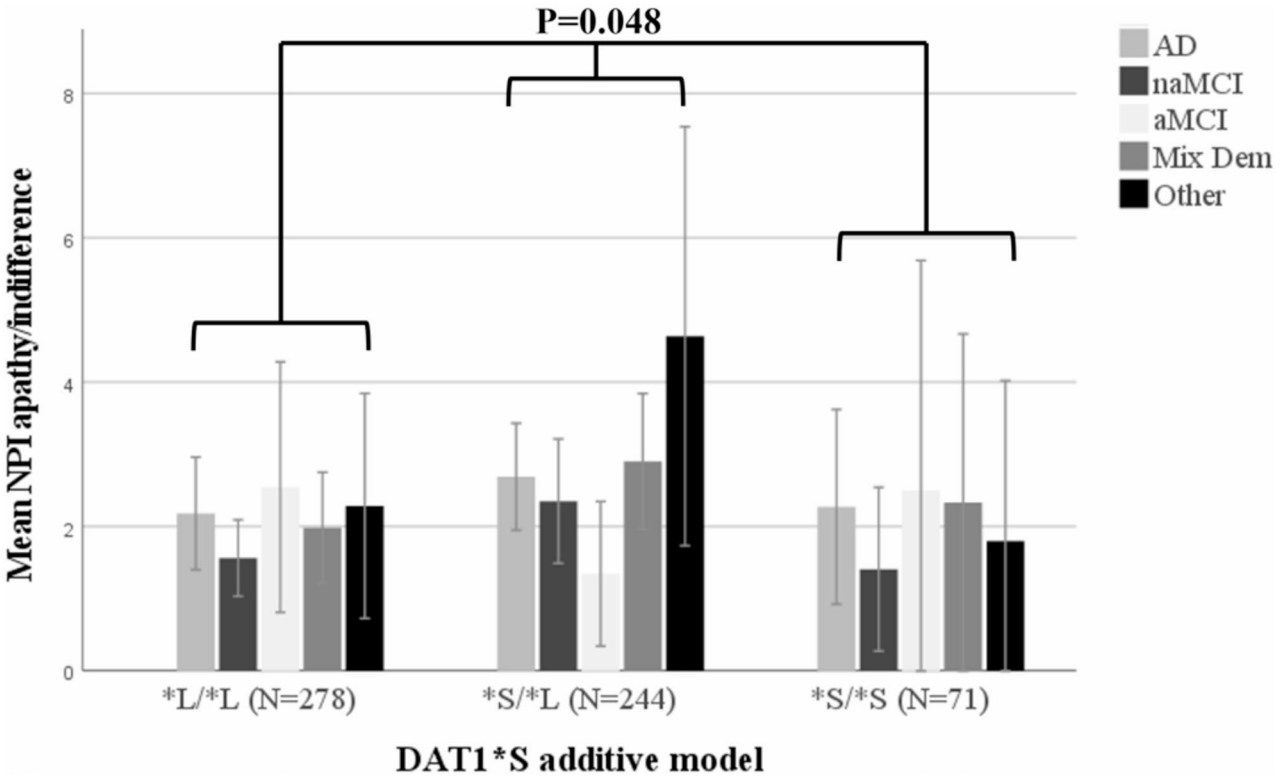

Fig. 1 NPI apathy/indifference score for *DAT1**S additive model in all dementia cases. AD=Alzheimer's Disease; naMCI = non-amnesic Mild Cognitive Impairment; aMCI=amnesic Mild Cognitive Impairment; Mix Dem=Mixed Dementia

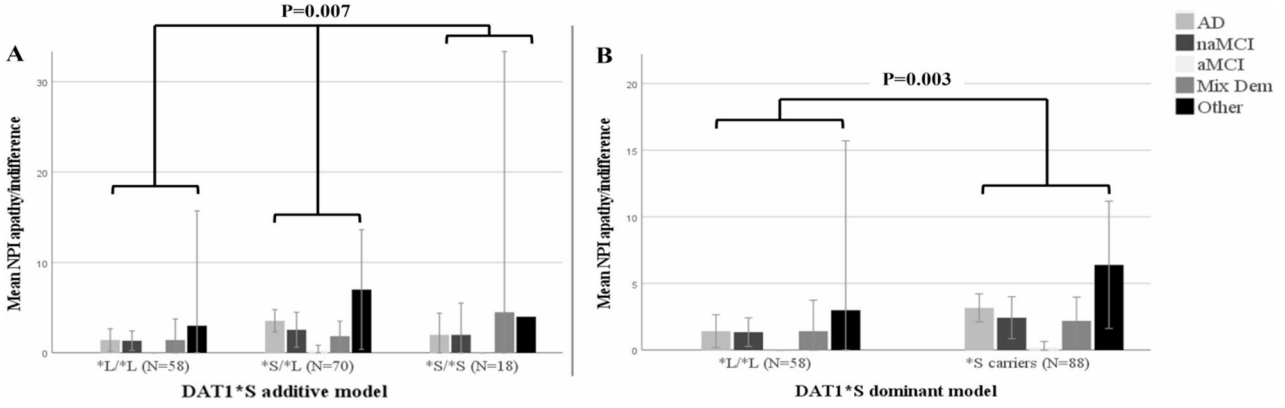

Fig. 2 NPI apathy/indifference score for *DAT1**S additive (**A**) and dominant (**B**) models in *APOE**4 carriers. AD=Alzheimer's Disease; naMCI = non-amnesic Mild Cognitive Impairment; aMCI=amnesic Mild Cognitive Impairment; Mix Dem=Mixed Dementia

Discussion

This study investigated the potential association between the 40-bp VNTR polymorphism in the 3'UTR of the *DAT1* gene and the development of dementia spectrum pathologies, as well as their neuropsychiatric and cognitive symptoms, in a Central-Italian elderly cohort. While previous research reported several associations between *DAT1* variants and diverse disorders, such as ADHD [9, 10], schizophrenia [11–13], and AD [19–26], especially concerning their specific neuropsychiatric endophenotypes, no prior study has examined the role of the VNTR in those pathologies belonging to the dementia spectrum. This gap could potentially expand understanding of dopaminergic contributions to a broader range of neurodegenerative diseases in the elderly population.

Although our data did not support a direct association between the *DAT1* 40-bp VNTR and any of the dementia spectrum disorders considered in the study, several notable findings emerged regarding the VNTR's influence on neuropsychiatric symptomatology. Indeed, we found that *DAT1*-VNTR is associated with apathy, especially when restricting the analysis to *APOE**4 carriers.

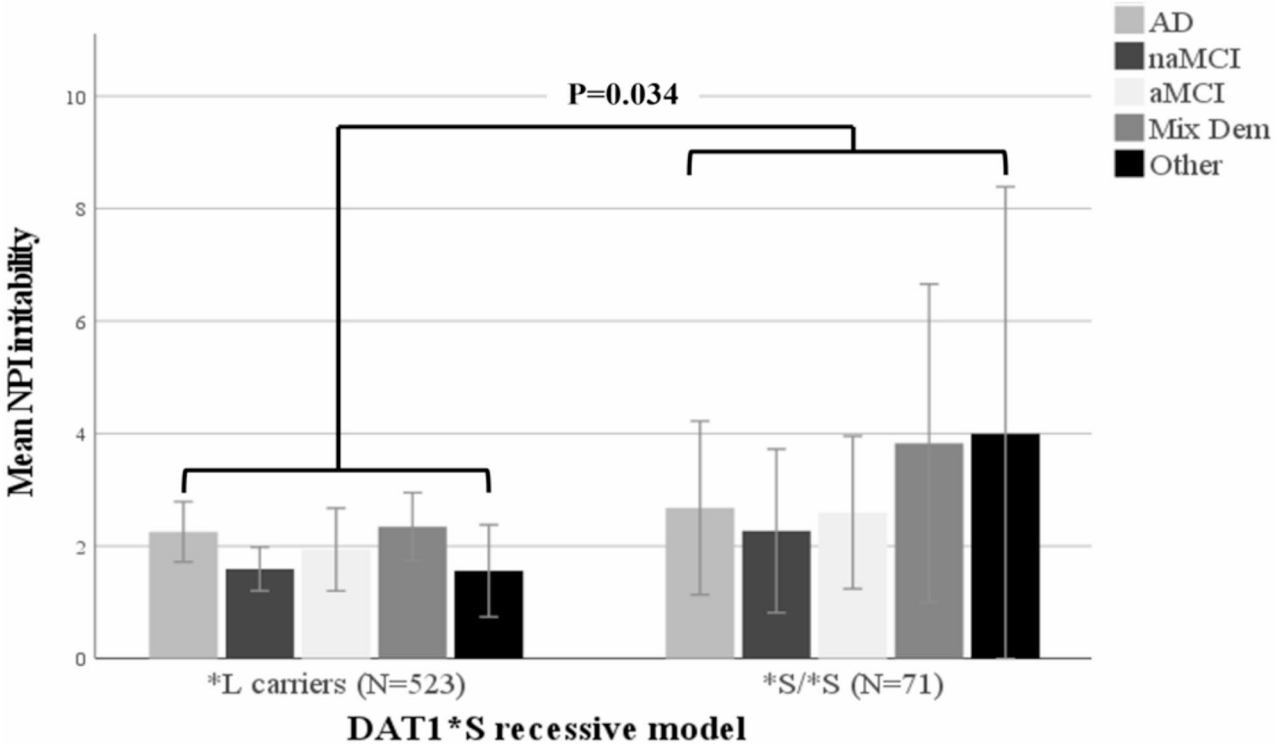

Fig. 3 NPI irritability score for *DAT1**S recessive model in all dementia cases. AD=Alzheimer's Disease; naMCI = non-amnesic Mild Cognitive Impairment; aMCI=amnesic Mild Cognitive Impairment; Mix Dem=Mixed Dementia

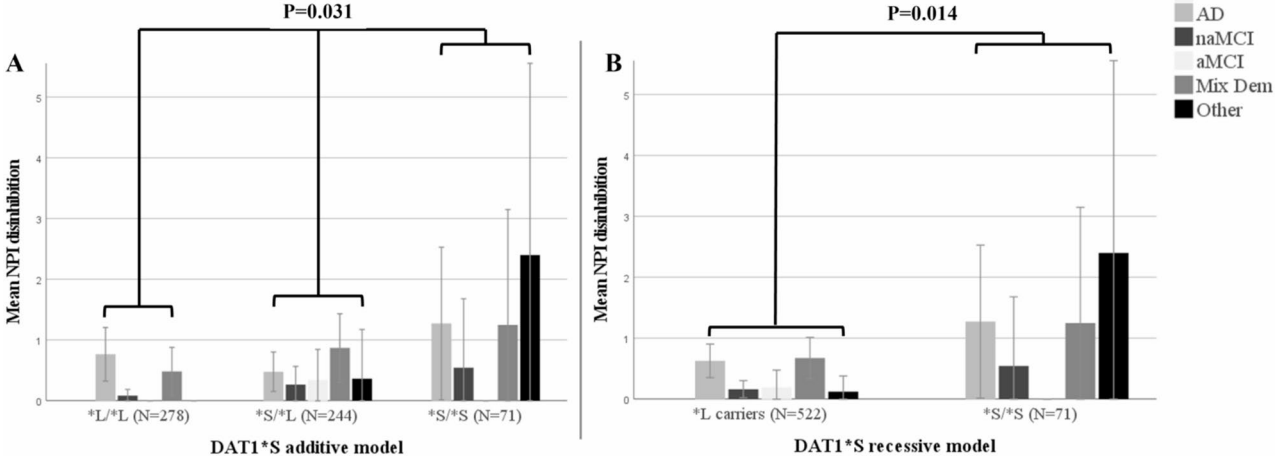

Fig. 4 NPI disinhibition score for *DAT1**S additive model (**A**) and *DAT1**S recessive model (**B**) in all dementia cases. AD=Alzheimer's Disease; naMCI = non-amnesic Mild Cognitive Impairment; aMCI=amnesic Mild Cognitive Impairment; Mix Dem=Mixed Dementia

However, the formal interaction term between *APOE**4 allele count and *DAT1*-VNTR was not statistically significant. This discrepancy likely reflects the lower statistical power of interaction tests and indicates that the observed stratified associations may not represent a true multiplicative gene–gene interaction, but rather additive or parallel effects. Nevertheless, this link between *DAT1*, *APOE*, and apathy is consistent with previous findings [22]. Notably, we extended these findings by identifying a broader association between the *DAT1**S allele and apathy, independent of *APOE* genotype; indeed, in our case, the association between *DAT1**S allele of the VNTR and the NPI apathy can be seen across our whole dementia cohort, in an additive genetic model, suggesting a preliminary association of the allele with the apathy endophenotype in subjects with dementia. This is in line with earlier studies suggesting reduced expression of the dopamine transporter associated with the *DAT1**S allele [14, 48–50], which may lead to increased synaptic dopamine levels and altered dopaminergic tone due

Table 5 Results of linear regression on subdomains significant in omnibus analysis

NPI subdomain	Model	Group	Linear regression results			Meta results		
			beta	SE	P	beta	SE	P
Apathy	Additive	AD	0.036	0.366	0.647	0.023	0.197	0.907
		naMCI	0.013	0.319	0.836			
		aMCI	-0.078	0.549	0.490			
		Mix Dem	0.101	0.465	0.251			
		Other	-0.032	1.504	0.880			
Apathy (*APOE**4 carriers)	Additive	AD	0.183	0.609	0.237	0.200	0.184	0.275
		naMCI	0.096	0.912	0.638			
		aMCI	0.209	0.199	0.486			
		Mix Dem	0.108	1.409	0.715			
		Other	---	---	---			
	Dominant	AD	0.284	0.863	0.070	0.236	0.246	0.338
		naMCI	0.192	1.238	0.343			
		aMCI	0.236	0.265	0.430			
		Mix Dem	0.104	1.824	0.729			
		Other	---	---	---			
Disinhibition	Additive	AD	0.050	0.206	0.508	0.074	0.099	0.452
		naMCI	0.120	0.181	0.109			
		aMCI	-0.001	0.179	0.993			
		Mix Dem	0.109	0.277	0.216			
		Other	0.379	0.529	0.053			
	Recessive	AD	0.120	0.423	0.115	0.052	0.181	0.772
		naMCI	0.122	0.280	0.103			
		aMCI	-0.145	0.337	0.296			
		Mix Dem	0.072	0.630	0.411			
		Other	0.478	1.002	0.008			
Irritability	Recessive	AD	0.059	0.768	0.454	0.101	0.377	0.789
		naMCI	0.092	0.595	0.212			
		aMCI	0.090	0.921	0.514			
		Mix Dem	0.093	1.062	0.270			
		Other	0.351	1.465	0.088			

to diminished reuptake. In regions where *DAT1* is most densely expressed – the striatum and nucleus accumbens, areas involved in motor control and reward pathways [56] – its dysregulation, leading to regional dysfunction, may cause apathetic symptomatology, especially in neurodegenerative diseases [57].

Additional associations observed in our data included the one with NPI irritability in *S/*S individuals.

Notably, our results also point to a preliminary association between the *S/*S genotype and disinhibition across the dementia spectrum. Disinhibition is, indeed, a common behavioural symptom in dementia [58], particularly in FTD [59], thought to arise from orbitofrontal cortex dysfunction [60]. Thus, the association in our cohort between the *DAT1*-VNTR *S/*S genotype and disinhibition in subjects with dementia is consistent with the hypothesis that the dopaminergic system modulates prefrontal cortical inhibition [61].

Conclusions

Although promising, these preliminary results highlight the need for a larger sample to increase statistical power and strengthen the robustness of these associations. To better understand how dopamine transporter function influences behaviour in neurodegenerative diseases, future research will be mandatory to confirm present findings and should employ larger, possibly longitudinal samples to better represent the frequent, moderately sudden changes in NPI scores of dementia spectrum disorders and incorporate multimodal approaches, such as PET imaging, environmental modifiers, and transcriptomic profiling. If these results are confirmed in larger datasets, they may pave the way for genotype-informed interventions in clinical practice.

In summary, this study provides novel evidence that the *DAT1*-VNTR affects neuropsychiatric profiles, especially those related to apathy, irritability, AMB, and disinhibition, even if not directly associated with dementia diagnosis. These findings deepen our knowledge of the genetic underpinnings of behavioural symptomatology in

dementia spectrum and could lead to genotype-informed interventions targeting specific symptom domains in clinical practice.

Limitations

In presenting this novel study, we also acknowledge its limitations. For instance, although large, the cohort under study is composed solely of Caucasian participants from specialized clinical settings, which may limit the generalizability of the findings to more diverse populations and community-based samples.

At the same time, the inclusion of diagnostically diverse categories may attenuate group-specific effects, and results should therefore be interpreted with caution.

The cross-sectional design limits causal inference about the direction of association between the *DAT1*-VNTR variant and NPS.

Abbreviations

3'-UTR	3'-untranslated region
AD	Alzheimer's disease
ADHD	Attention-deficit/hyperactivity disorder
AMB	Aberrant motor behaviour
aMCI	Amnesic Mild Cognitive Impairment
CBD	Corticobasal degeneration
CDCD	Center for cognitive disorders and dementia
CDR	Clinical Dementia Rating
CJD	Creutzefeldt-Jakob disease
CTRL	Controls
DSM-5	Diagnostic and statistical manual of mental disorders
FTD	Frontotemporal dementia
GCTA	Genome-wide complex trait analysis
GERICO	Geriatric cognitive evaluation
GWAS	Genome-wide association study
HWE	Hardy-Weinberg equilibrium
LBD	Lewy body dementia
LOAD	Late-onset Alzheimer's disease
MCI	Mild cognitive impairment
naMCI	Non-amnesic Mild cognitive impairment
Mix Dem	Mixed dementia
MMSE	Mini-mental state examination
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and
NINDS-AIREN	National Institute of Neurological Disorders and Stroke and
NPH	Normal pressure hydrocephalus
NPI	Neuropsychiatric inventory
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PSP	Progressive subnuclear palsy
RFLP	Restriction fragment length polymorphism
SNP	Single nucleotide polymorphism
VaD	Vascular dementia
VNTR	Variable number of tandem repeats

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12920-026-02341-6.

Supplementary Material 1. Supplementary Table S1 (.xls). *SLC6A3/DAT1* 40-bp VNTR genotype and allele frequencies in the whole sample under study. AD=Alzheimer's Disease; naMCI=non-amnesic Mild Cognitive Impairment; aMCI=amnesic Mild Cognitive Impairment; Mix Dem=Mixed Dementia.

Supplementary Material 2. Supplementary Table S2 (.xls). Association study results for APOE*2 and APOE*4 covariates; each diagnosis group was compared with the controls one. AD=Alzheimer's Disease; naMCI=non-amnesic Mild Cognitive Impairment; aMCI=amnesic Mild Cognitive Impairment; Mix Dem=Mixed Dementia.

Supplementary Material 3. Supplementary Table S3 (.xls). Results for generalized linear model analyses performed on neuropsychiatric scores.

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Authors' contributions

B.T.B.: data curation, formal analysis, methodology, writing – original draft, writing – review and editing; A.G.G.: data curation, writing – original draft, writing – review and editing; G.R.: data curation, methodology; PB: data curation; R.C.: data curation; P.M.: data curation, resources, supervision, writing – original draft, writing – review and editing; V.N.: conceptualization, data curation, formal analysis, methodology, resources, supervision, writing – original draft, writing – review and editing.

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Data availability

The datasets generated and/or analysed during the current study are available in the FigShare (https://figshare.com/) repository, (https://doi.org/10.6084/m9.figshare.29980297).

Declarations

Ethics approval and consent to participate

Ethical approval for the GERICO study was granted by Umbria CER (Comitato Etico Regionale), Umbria Regional Ethics Committee Prot. N. CE-2078/25 del 16/04/2025.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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