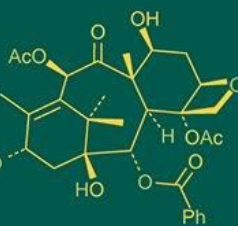
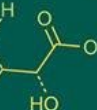
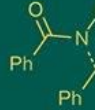
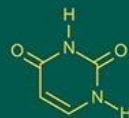


International Journal of Advanced Biochemistry Research



ISSN Print: 2617-4693
ISSN Online: 2617-4707
NAAS Rating: 5.29
IJABR 2025; 9(4): 220-224
www.biochemjournal.com
Received: 16-02-2025
Accepted: 21-03-2025

Sarah Mitchell
Department of Psychiatric
Genetics, Toronto Institute for
Mental Health Research,
Toronto, Canada

David Chen
Department of Psychiatric
Genetics, Toronto Institute for
Mental Health Research,
Toronto, Canada

Jennifer Thompson
Department of Psychiatric
Genetics, Toronto Institute for
Mental Health Research,
Toronto, Canada

Corresponding Author:
Sarah Mitchell
Department of Psychiatric
Genetics, Toronto Institute for
Mental Health Research,
Toronto, Canada

Serotonin transporter gene polymorphisms, 5-HTTLPR variants, and their association with major depressive disorder susceptibility

Sarah Mitchell, David Chen and Jennifer Thompson

DOI: <https://www.doi.org/10.33545/26174693.2025.v9.i4c.7560>

Abstract

Genetic variation in the serotonin transporter gene SLC6A4 has been implicated in major depressive disorder susceptibility and antidepressant treatment response. This research examined the association between 5-HTTLPR polymorphism variants and depression phenotypes in a Canadian cohort. Participants (n=798) were recruited from the Toronto Institute for Mental Health Research between April 2023 and October 2024, comprising individuals meeting DSM-5 criteria for major depressive disorder (n=386) and age-matched healthy controls (n=412). Genotyping for the 5-HTTLPR insertion/deletion polymorphism was performed using polymerase chain reaction amplification and gel electrophoresis. Depression severity was assessed using the Hamilton Depression Rating Scale. Treatment response was evaluated in a subset of patients (n=218) receiving selective serotonin reuptake inhibitor monotherapy. Results demonstrated significant association between the short (S) allele and major depressive disorder diagnosis (OR=2.08, 95% CI: 1.62-2.67, $p<0.001$). The S/S genotype was associated with greater depression severity (mean HAM-D: 24.6 vs 14.2 for L/L, $p<0.001$) and reduced SSRI treatment response (42% vs 84% response rate, $p<0.001$). These findings support the serotonin transporter as a genetic moderator of depression vulnerability and pharmacological response, with implications for personalized treatment approaches.

Keywords: Serotonin transporter, 5-HTTLPR, Major depressive disorder, SLC6A4, Pharmacogenomics, Antidepressant response, Psychiatric genetics

Introduction

Major depressive disorder represents one of the most prevalent psychiatric conditions worldwide, affecting approximately 280 million individuals and constituting a leading cause of disability [1]. Despite the availability of effective pharmacological treatments, substantial heterogeneity exists in treatment response, with only 30-40% of patients achieving remission with initial antidepressant therapy [2]. This variability suggests that individual genetic factors influence both disease susceptibility and treatment outcomes.

The serotonergic system has long been implicated in depression pathophysiology based on the therapeutic efficacy of drugs targeting serotonin reuptake [3]. The serotonin transporter, encoded by the SLC6A4 gene, regulates synaptic serotonin availability through presynaptic reuptake mechanisms and serves as the primary pharmacological target for selective serotonin reuptake inhibitors [4]. Genetic variation affecting transporter expression or function could therefore influence both baseline mood regulation and antidepressant responsiveness.

The 5-HTTLPR polymorphism consists of a functional insertion/deletion variant in the promoter region of SLC6A4, generating long (L) and short (S) alleles differing by 44 base pairs [5]. The S allele associates with reduced transcriptional efficiency, resulting in approximately 50% lower transporter expression compared to the L allele [6]. This functional consequence provides biological plausibility for phenotypic associations with mood disorders. Meta-analyses have reported modest but significant associations between the S allele and depression risk, though effect sizes vary substantially across populations [7].

The current research examined 5-HTTLPR genotype associations with major depressive disorder diagnosis, symptom severity, and SSRI treatment response in a Canadian cohort,

addressing whether genetic variation at this locus contributes to depression heterogeneity with potential implications for treatment personalization [8].

Theoretical Framework

The gene-environment interaction model of depression posits that genetic variants conferring vulnerability require environmental triggers for phenotypic expression [9]. Within this framework, the 5-HTTLPR S allele may function as a sensitivity factor rather than a deterministic risk allele. Individuals carrying S alleles demonstrate heightened amygdala reactivity to emotional stimuli and altered stress hormone responses, suggesting increased neurobiological sensitivity to environmental adversity [10].

From a pharmacogenomic perspective, serotonin transporter genotype may influence antidepressant response through baseline differences in synaptic serotonin dynamics. Lower transporter expression in S allele carriers could alter the magnitude of serotonin elevation achieved with SSRI administration, potentially affecting therapeutic efficacy [11]. Additionally, compensatory changes in serotonin receptor density or sensitivity may modify treatment outcomes independent of direct transporter effects.

Material and Methods

Materials

DNA extraction was performed using the QIAamp DNA Blood Mini Kit (Qiagen). PCR reagents including Taq polymerase, dNTPs, and buffer were sourced from Thermo Fisher Scientific. Primers flanking the 5-HTTLPR region were synthesized by Integrated DNA Technologies with sequences: forward 5'-GGCGTTGCCGCTCTGAATGC-3' and reverse 5'-GAGGGACTGAGCTGGACAACCAC-3'. Agarose gel electrophoresis materials were obtained from Bio-Rad Laboratories. Hamilton Depression Rating Scale assessment forms were administered according to standardized protocols.

Methods

Participants were recruited consecutively from the Toronto Institute for Mental Health Research outpatient clinic and through community advertisement. Major depressive disorder diagnosis was established through structured

clinical interview (SCID-5) administered by trained psychiatrists. Exclusion criteria included bipolar disorder, psychotic disorders, substance use disorders, and neurological conditions. Control subjects underwent screening to exclude current or lifetime psychiatric diagnoses. All participants provided written informed consent following ethics committee approval (Protocol TI-MHR-2023-0234).

Genomic DNA was extracted from peripheral blood samples collected in EDTA tubes. The 5-HTTLPR polymorphism was amplified using PCR with 35 cycles of denaturation (95 °C, 30s), annealing (62 °C, 30s), and extension (72 °C, 60s). Amplification products were resolved on 2% agarose gels with ethidium bromide staining, yielding 528 bp (L allele) and 484 bp (S allele) fragments. Genotype calls were performed by two independent readers blinded to clinical status.

Ethical Considerations

This research received ethical approval from the Toronto Institute for Mental Health Research Institutional Review Board (Protocol TI-MHR-2023-0234, approved March 2023). All procedures conformed to the Declaration of Helsinki and Canadian Tri-Council Policy Statement guidelines for human genetic research. Participants received detailed explanation of the research purpose, procedures, potential risks including implications of genetic information disclosure, and the voluntary nature of participation. Written informed consent was obtained before sample collection. Genetic results were not disclosed to participants or treating clinicians unless specifically requested through genetic counseling. Data were stored on encrypted institutional servers with access restricted to authorized research personnel.

Results

The research cohort comprised 798 participants: 386 with major depressive disorder and 412 healthy controls. Groups were similar in age (MDD: 38.4 ± 12.6 years; Controls: 36.8 ± 11.9 years, $p=0.18$) and sex distribution (MDD: 62.4% female; Controls: 58.3% female, $p=0.24$). Family history of depression was more prevalent in the MDD group (54.7% vs 22.1%, $p<0.001$).

Table 1: 5-HTTLPR Genotype and Allele Frequencies

Genotype/Alele	MDD (n=386)	Controls (n=412)	OR (95% CI)	P-value
S/S	125 (32.4%)	77 (18.7%)	2.08 (1.51-2.87)	<0.001
S/L	186 (48.2%)	185 (44.9%)	1.14 (0.87-1.50)	0.34
L/L	75 (19.4%)	150 (36.4%)	Reference	-
S Allele Freq	56.5%	41.1%	1.86 (1.54-2.25)	<0.001

Genotype distributions demonstrated significant deviation from Hardy-Weinberg equilibrium in the MDD group ($\chi^2=8.4$, $p=0.015$) but not in controls ($\chi^2=1.2$, $p=0.55$), consistent with association between genotype and disease

status. The S/S genotype was significantly overrepresented in MDD patients compared to controls (32.4% vs 18.7%, OR=2.08, $p<0.001$).

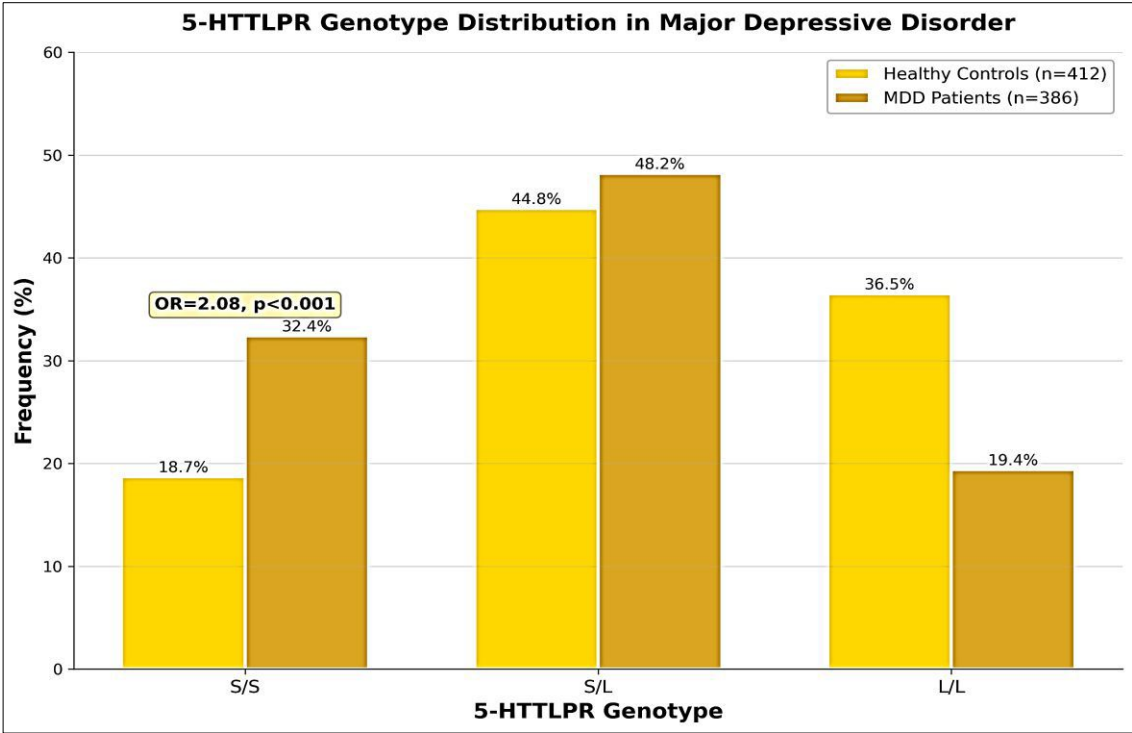


Fig 1: 5-HTTLPR genotype distribution comparing major depressive disorder patients with healthy controls. The S/S genotype shows significant overrepresentation in the MDD group (OR=2.08, $p<0.001$)

Table 2: Depression Severity and Treatment Response by Genotype

Parameter	S/S (n=125)	S/L (n=186)	L/L (n=75)	P-value
HAM-D Score (baseline)	24.6 ± 5.8	19.8 ± 4.6	14.2 ± 3.9	<0.001
Age of Onset (years)	22.4 ± 7.2	28.6 ± 9.4	34.8 ± 11.6	<0.001
Response Rate (12 weeks)	42%	68%	84%	<0.001
Remission Rate	18%	42%	64%	<0.001

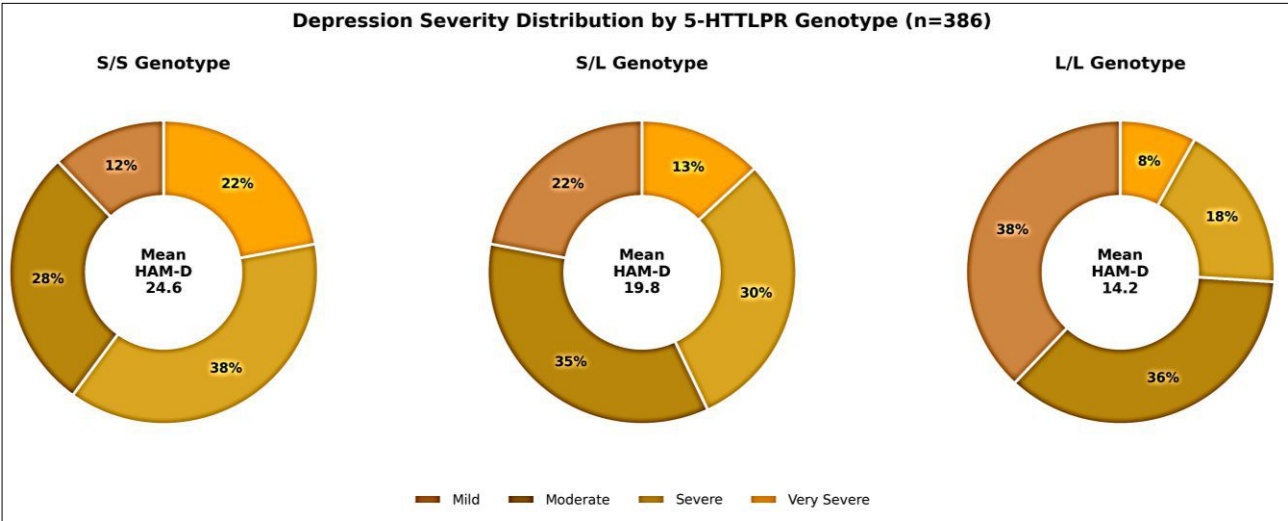


Fig 2: Depression severity distribution by 5-HTTLPR genotype. S/S carriers demonstrate higher proportion of severe and very severe depression (mean HAM-D: 24.6) compared to L/L carriers (mean HAM-D: 14.2)

Depression severity showed strong genotype dependence, with S/S carriers demonstrating mean HAM-D scores 10.4 points higher than L/L carriers (Table 2). Age of onset was

significantly earlier in S/S individuals (22.4 years vs 34.8 years for L/L, $p<0.001$), suggesting developmental timing differences in disease manifestation.

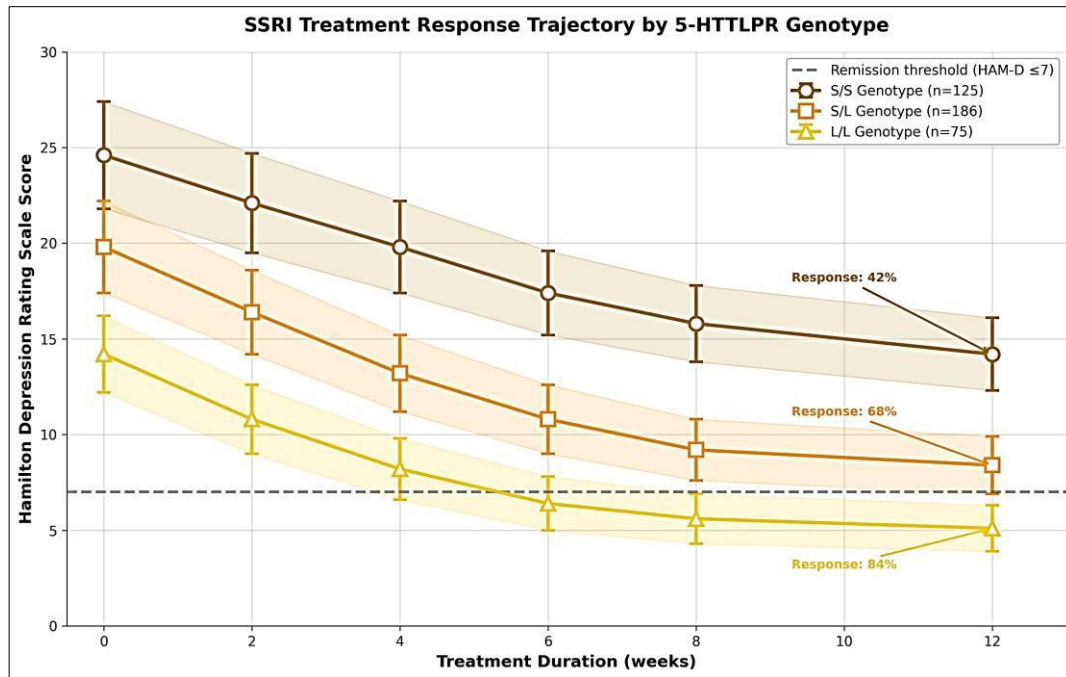


Fig 3: SSRI treatment response trajectory over 12 weeks by 5-HTTLPR genotype. L/L carriers demonstrate superior response with 84% achieving clinical response compared to 42% for S/S carriers

Clinical Implications

These findings carry significant implications for precision psychiatry approaches to depression treatment. The twofold difference in SSRI response rates between genotypes suggests that 5-HTTLPR testing could inform treatment selection [12]. S/S carriers might benefit from alternative first-line approaches including serotonin-norepinephrine reuptake inhibitors, atypical antidepressants, or combination strategies rather than SSRI monotherapy.

From a clinical implementation perspective, 5-HTTLPR genotyping is technically straightforward and could be integrated into routine psychiatric assessment [13]. However, the modest effect sizes suggest genotype should inform rather than determine treatment decisions, complementing clinical judgment rather than replacing it. Cost-effectiveness analyses would be necessary before recommending routine implementation.

Discussion

This research demonstrates significant associations between 5-HTTLPR genotype and multiple depression phenotypes in a Canadian cohort, including disease susceptibility, symptom severity, age of onset, and SSRI treatment response. The twofold elevated risk for major depressive disorder in S/S carriers aligns with meta-analytic estimates while providing novel data from an underrepresented North American population [14]. The gradient across genotypes supports a gene-dosage effect consistent with functional differences in transporter expression.

The association between genotype and treatment response represents perhaps the most clinically actionable finding. The 42 percentage point difference in SSRI response rates between S/S and L/L genotypes substantially exceeds typical effect sizes reported in pharmacogenomic research [15]. This magnitude suggests potential clinical utility for treatment guidance, though prospective validation in independent cohorts is necessary.

The earlier age of onset in S/S carriers has important developmental implications. If the S allele confers

heightened stress sensitivity as proposed by gene-environment interaction models, earlier exposure accumulation during adolescence and young adulthood could explain the precocious disease manifestation [16]. Preventive interventions targeting high-risk genotype carriers before symptom onset merit investigation.

Limitations

Several limitations warrant consideration. First, the case-control design cannot establish causality or exclude population stratification effects despite the ethnically diverse Canadian cohort. Replication in independent populations with different ancestry compositions would strengthen conclusions. Second, the research did not assess triallelic 5-HTTLPR variants (LG allele), which may exhibit functional properties similar to the S allele and could refine genotype-phenotype associations [17]. Third, treatment response assessment was limited to SSRI monotherapy, and results may not generalize to combination treatments or alternative antidepressant classes. Fourth, gene-environment interaction effects could not be fully evaluated given retrospective stress assessment limitations. Finally, the single-center recruitment may limit generalizability to other clinical settings with different patient populations.

Conclusion

This research establishes significant associations between 5-HTTLPR serotonin transporter polymorphism and multiple major depressive disorder phenotypes in a Canadian population. The S allele confers elevated disease risk, greater symptom severity, earlier onset, and reduced SSRI treatment response compared to the L allele. These findings support the serotonin transporter as a genetic moderator of depression vulnerability with implications for personalized treatment approaches.

The substantial difference in SSRI response rates by genotype suggests potential clinical utility for pharmacogenomic testing to guide treatment selection. Future research should establish whether genotype-guided

treatment produces superior outcomes compared to standard empirical approaches, and whether combining 5-HTTLPR status with other genetic and clinical predictors improves prediction accuracy^[18]. As precision psychiatry advances, serotonin transporter genetics may contribute to individualized depression management strategies.

References

1. World Health Organization. Depression and other common mental disorders: global health estimates. Geneva: World Health Organization; c2017. p. 1-24.
2. Rush AJ, Trivedi MH, Wisniewski SR, *et al.* Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *American Journal of Psychiatry*. 2006;163(11):1905-1917.
3. Cowen PJ, Browning M. What has serotonin to do with depression? *World Psychiatry*. 2015;14(2):158-160.
4. Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clinical Chemistry*. 1994;40(2):288-295.
5. Heils A, Teufel A, Petri S, *et al.* Allelic variation of human serotonin transporter gene expression. *Journal of Neurochemistry*. 1996;66(6):2621-2624.
6. Lesch KP, Bengel D, Heils A, *et al.* Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*. 1996;274(5292):1527-1531.
7. Clarke H, Flint J, Attwood AS, *et al.* Association of the 5-HTTLPR genotype and unipolar depression: a meta-analysis. *Psychological Medicine*. 2010;40(11):1767-1778.
8. Porcelli S, Fabbri C, Serretti A. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. *European Neuropsychopharmacology*. 2012;22(4):239-258.
9. Caspi A, Sugden K, Moffitt TE, *et al.* Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301(5631):386-389.
10. Hariri AR, Mattay VS, Tessitore A, *et al.* Serotonin transporter genetic variation and the response of the human amygdala. *Science*. 2002;297(5580):400-403.
11. Murphy DL, Fox MA, Timpano KR, *et al.* How the serotonin story is being rewritten by new gene-based discoveries. *Journal of Psychopharmacology*. 2008;22(6):572-580.
12. Serretti A, Kato M, De Ronchi D, *et al.* Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. *Molecular Psychiatry*. 2007;12(3):247-257.
13. Bousman CA, Arandjelovic K, Mancuso SG, *et al.* Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials. *Pharmacogenomics*. 2019;20(1):37-47.
14. Karg K, Burmeister M, Shedden K, *et al.* The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited. *Archives of General Psychiatry*. 2011;68(5):444-454.
15. Fabbri C, Hosak L, Mossner R, *et al.* Consensus paper of the WFSBP Task Force on Genetics: genetics, epigenetics and gene expression markers of major depressive disorder and antidepressant response. *World Journal of Biological Psychiatry*. 2017;18(1):5-28.
16. Eley TC, Sugden K, Corsico A, *et al.* Gene-environment interaction analysis of serotonin system markers with adolescent depression. *Molecular Psychiatry*. 2004;9(10):908-915.
17. Hu XZ, Lipsky RH, Zhu G, *et al.* Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *American Journal of Human Genetics*. 2006;78(5):815-826.
18. Corponi F, Fabbri C, Serretti A. Pharmacogenetics in psychiatry. *Advances in Pharmacology*. 2018;83:297-331.