

Bridging Psychiatric Genomics and Translational Biological Insights: a Systematic Review of the Role of NMDA Receptor Subunits in Schizophrenia

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Introduction

- Schizophrenia (SCZ) is a complex neurodevelopmental disorder associated with severe behavioural and psychiatric symptoms with a strong genetic component (1).
- No diagnostic pathologies or biomarkers exist for SCZ, making diagnosis challenging and reliant on overlapping clinical symptoms (1, 2).
- Hypofunction of the N-methyl-D-aspartate receptors (NMDAR) has been implicated in driving glutamatergic dysfunction in SCZ pathophysiology in multiple studies (2).
- This downregulates glutamate signalling and disrupts downstream signalling pathways, impairing synaptic plasticity and long-term potentiation (2).
- Genetic variants of NMDAR may alter receptor function thus contribute to neuropsychiatric vulnerability (3, 4).

Aims

- To conduct a systematic review to determine whether certain NMDAR subunit genes are more liable than others for genetic disruption in individuals with SCZ.
- Carry out analysis of the location of the genetic variants within NMDAR functional domains within each *GRIN* gene.
- Identify any population differences within the genomic findings.

Methods

- In this systematic review; we searched Pubmed and Web of Science up to 3rd July 2025. PRISMA 2020 guidelines were followed.
- Eligibility was screened by title and abstract initially, with 20 full-text papers reviewed to identify the final 14 included.

References

(1) Owen MJ, Bray NJ, Walters JTR, O'Donovan MC. Genomics of schizophrenia, bipolar disorder and major depressive disorder. Nat Rev Genet 2025 December 01;26(12):862–877.

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(4) Singh T, Poterba T, Curtis D, Akil H, Al Eissa M, Barchas JD, et al. Rare coding variants in ten genes confer substantial risk for schizophrenia. Nature 2022 April 01;604(7906):509–516

Acknowledgements

Funding: Royal Society International Exchange grant (IES\R3\233206) (S.T., Z.H.), by the Higher Education Centre of Excellence (HICoE) special funding (304/CDADAH/4401009) (Z.H.), the International Research Collaboration Fund (1002/CDADAH/910410) (Z.H.), the Deutsche Forschungsgemeinschaft grant MU2789/20-1 and Interdisciplinary Center for Clinical Research (IZKF) Erlangen, Project E39 (C.P.M).

Risk of Bias was assessed using Newcastle-Ottawa Scale assessment being used for case-control studies and Joanna Briggs Institute Checklist for the family-based studies.

Search Terms

- (“Schizophrenia” AND “NMDA”) AND (“Genetic Variant” OR “Mutation”)

Inclusion/Exclusion Criteria

Inclusion	Exclusion
- NMDAR variants within human cohorts containing individuals with a confirmed Diagnosis of SCZ - Full-text in English	- Animal studies - Post-mortem tissue - Imaging studies - Signalling molecules - Pharmacology studies - Review articles

Statistical Analysis

A Chi-Squared Tests was performed to evaluate the distribution of genetic variants identified within the *GRIN* family of NMDAR subunit genes.

- Statistical Significance – $P < 0.05$.

Results

PRISMA 2020:

- Initial search -> 492 identified (304 – duplicates removed) with 20 full-text reviews to reach the final 14 studies

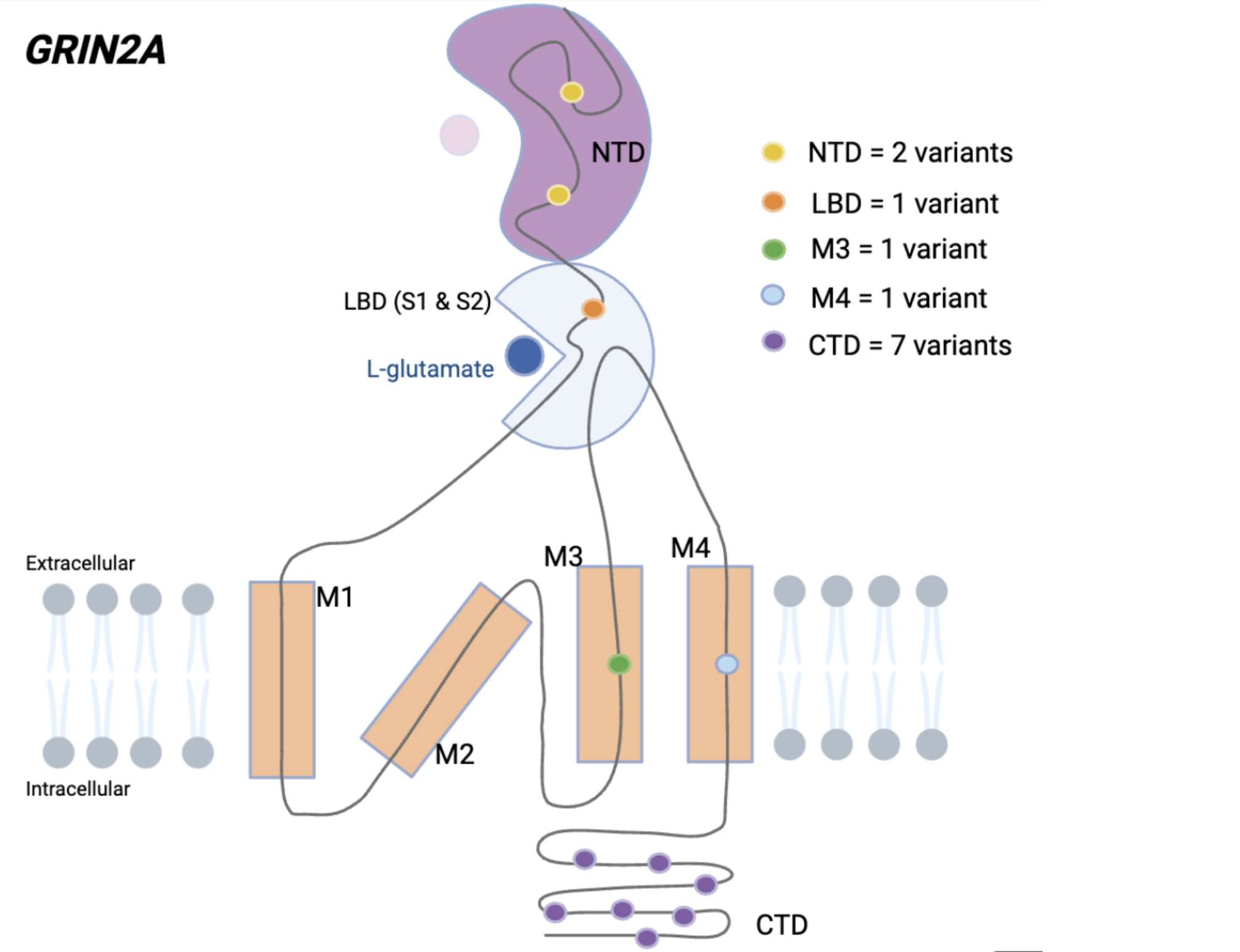


Figure 1: Structural representation of the variants identified in *GRIN2A* and their location within the subunit. Demonstrating a clustering of variants within the C-terminal domain with over half of the variants found in this region.

Risk of bias assessment showed a low risk for all studies.

Fourteen studies totalling 37,000 individuals with SCZ and 62,000 controls were included.

Key Findings

- 32/48 variants were located in *GRIN2A* and *GRIN2B*.
- The CTD with 17 variants had the highest concentration of variants within one functional domains.

GRIN Gene	No. Variants
<i>GRIN1</i>	4
<i>GRIN2A</i>	15
<i>GRIN2B</i>	17
<i>GRIN2C</i>	2
<i>GRIN2D</i>	0
<i>GRIN3A</i>	7
<i>GRIN3B</i>	3

Statistical Analysis

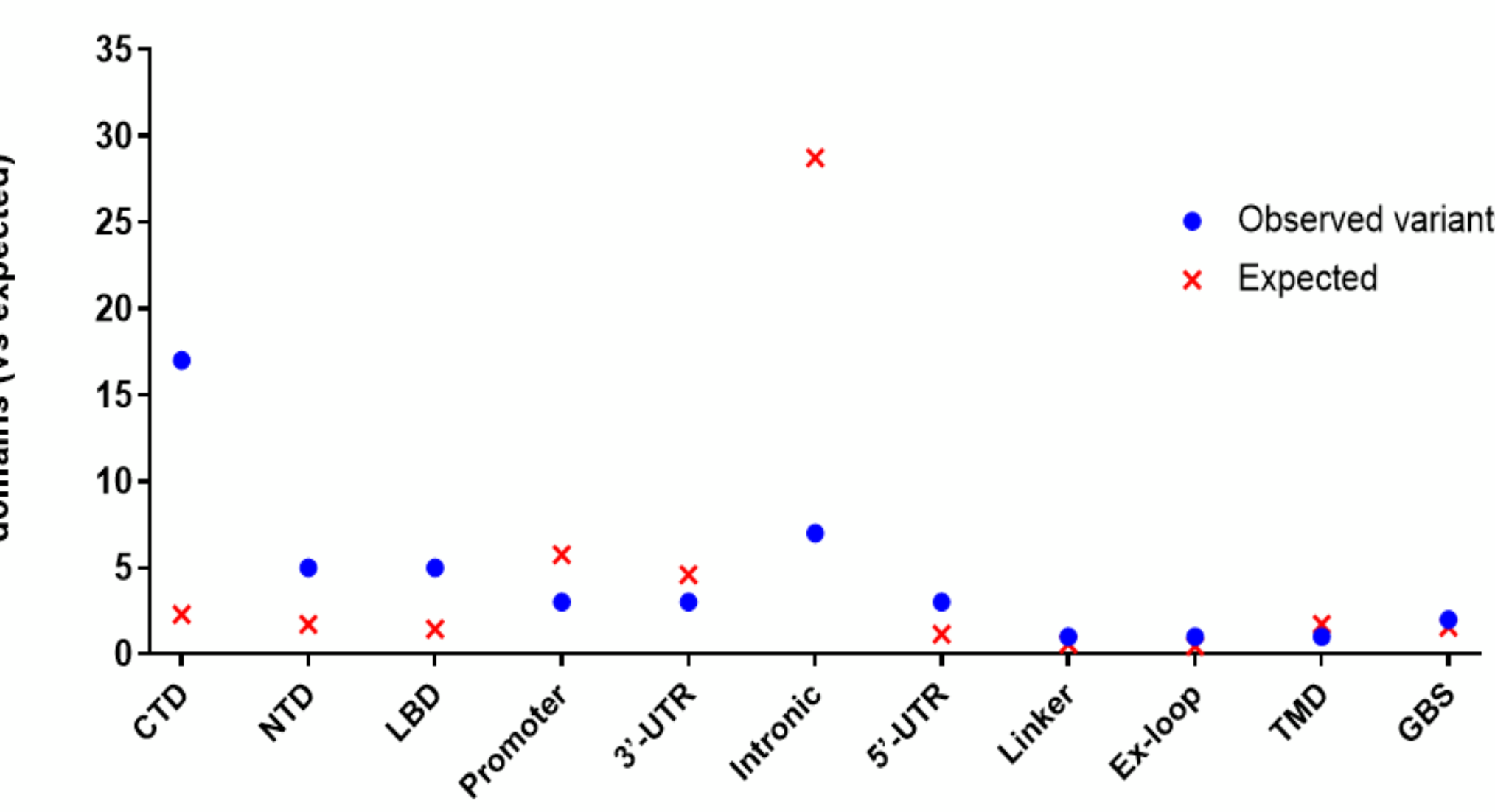
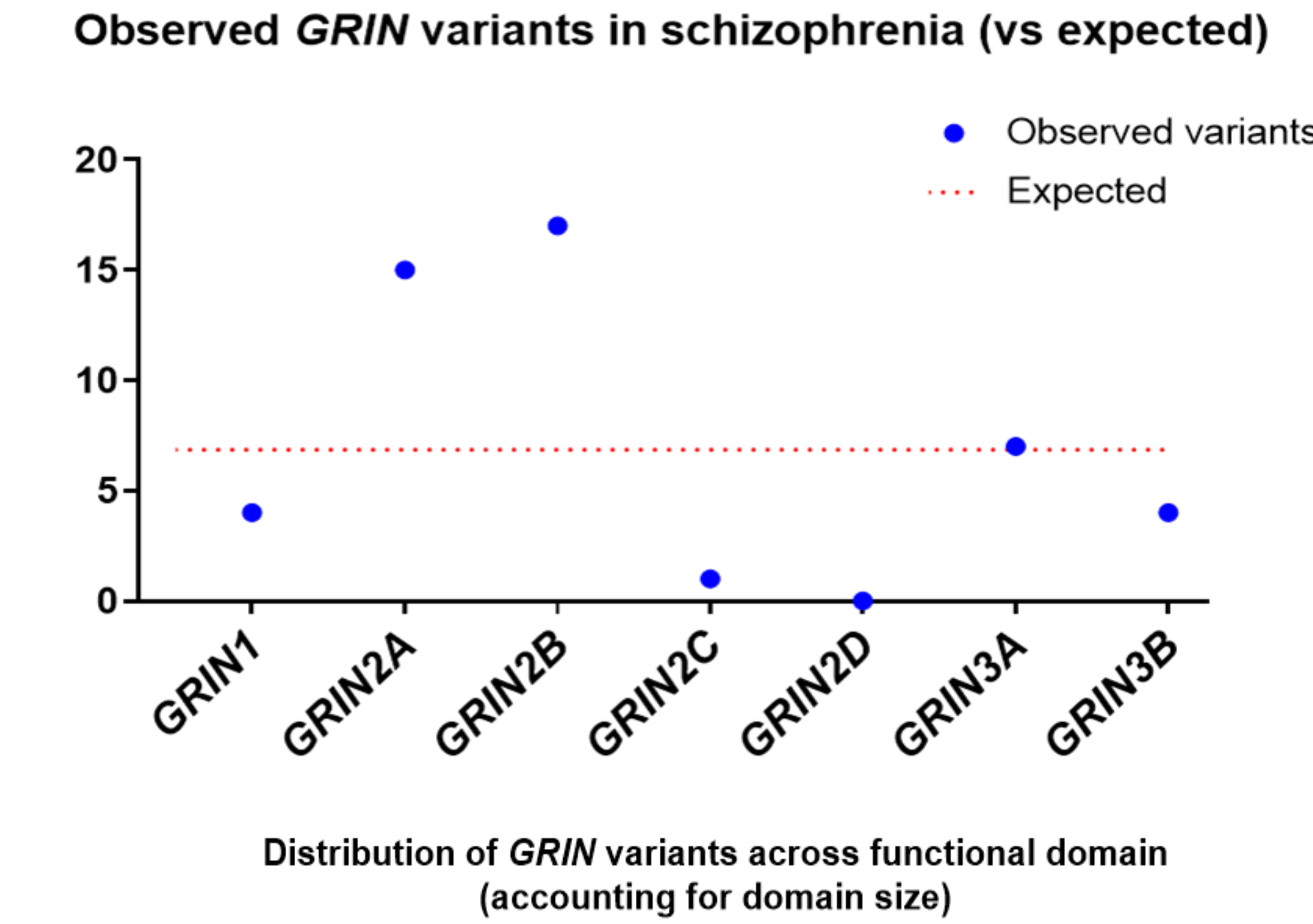


Figure 2a: Chi-Squared comparison of *GRIN* gene variant counts, comparing observed vs expected to a uniform distribution. *GRIN2A* (15 variants; contribution = 9.66, $X^2 = 38.90$ df = 6, $p < 0.0001$) and *GRIN2B* (17 variants; contribution = 14.99, $X^2 = 38.90$ df = 6, $p < 0.0001$) show marked enrichment relative to expectation.

Figure 2b: Chi-Squared comparison of observed vs expected numbers of variants within each functional domain accounting for domain size. 17 variants were located in the CTD (Contribution 94.01; $X^2 = 131.75$), substantially more than expected.

- rs890; *GRIN2B* 3'UTR was found in two studies. Chinese Han SCZ and European controls.
- 7 intronic variants were found within *GRIN2A/2B* with a link to early onset/first-episode SCZ.

Discussion

- Increased frequency of *GRIN2A/GRIN2B* variants in individuals with SCZ.
- Heritable and sporadic *GRIN2A* variants**, such as R1169W found across all affected members of a multiplex family, highlights combined genetic and environmental risk.
- GRIN2A/2B* are developmentally regulated subunits disproportionately disrupted in SCZ**, with CTD-clustered variants impairing Glu2N localisation/function and driving NMDAR hypofunction linked to cognitive deficits.
- Glu2N variants also occur in individuals with ASD and epilepsy**, indicating broader neurodevelopmental variant impact.
- Population-dependent variant patterns** highlight biological vulnerability and emphasise these subunits' key roles in receptor signalling and cognitive function

Limitations and Clinical Implications

- Insufficient large, diverse cohorts** limit understanding of population-level variant patterns and reduce statistical power for robust association analyses.
- Limited functional mapping and mechanistic validation** of *GRIN* variants restricts progress toward developing NMDAR-targeted therapies.

Future Direction

- Conduct large-scale GWAS/WES studies** including underrepresented populations.
- Map and validate functional effects of *GRIN* variants across NMDAR domains** to advance pharmacogenetic approaches
- Expand research on NMDAR hypofunction**, its impact on cognition, learning, and memory in SCZ and related neurodevelopmental disorders.

Conclusion

GRIN2A and *GRIN2B* are key developmentally regulated NMDAR subunits that are disproportionately affected in schizophrenia, underscoring the need for functional studies linking these variants to receptor biology and clinical outcomes.