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Relationship between maternal serotonin levels and autism-associated genetic variants

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Conflict of Interest

EHC has served on the Scientific Advisory Board for Impel Pharmaceuticals, anticipates research support from Jazz Pharmaceuticals, and receives an editorial stipend from Springer. JVV has consulted or served on advisory boards for Novartis, Roche Pharmaceuticals, and SynapDx; has received research funding from Novartis, Roche Pharmaceuticals, Forest, Seaside Therapeutics, Janssen, SynapDx, Yamo Pharmaceuticals, MapLight, and Acadia; and has received an editorial stipend from Springer and Wiley.

Introduction

The serotonin system is implicated in neurodevelopment. For example, maternal disruption of serotonin genes in rodents produces offspring neurodevelopmental changes (1). In humans, lower maternal WB5-HT associates with greater neurodevelopmental severity in autistic children (2). Family and twin data support the idea that multiple common genetic and non-genetic factors together contribute to autism. However, a subgroup (10-20%) carry a single rare, *de novo* genetic variant that contributes the vast majority of their autism risk (3). These rare autism-associated variants are most often found in autistic individuals with more severe neurodevelopmental phenotypes. Whether rare autism-associated genetic variants are associated with maternal serotonin levels has not previously been investigated. We therefore compared maternal WB5-HT levels in mothers of probands with rare autism-associated genetic variants to mothers whose autistic children did not harbor known rare genetic variants (**Figure 1a**).

Methods

Samples of autistic probands and their parents are from the University of Illinois at Chicago (UIC) Autism Center of Excellence (ACE) (4), and the UIC and Vanderbilt University sites of the Simons Simplex Collection (SSC) (5). Neither ACE nor SSC samples included non-autistic control probands or their parents.

WB5-HT was assayed using HPLC (2). Individuals taking medications known to affect 5-HT were excluded. Exome sequencing identified individuals with rare genetic variants.

Statistics

After identifying a difference in skewness (**Supplement 1**), we compared median maternal WB5-HT via a two-sample Wilcoxon rank sum test. We next compared maternal WB5-HT across groups at five quantiles (the 10th, 25th, 50th, 75th and 90th percentiles) using a percentile bootstrap method that accounts for multiple comparisons, in conjunction with the Harrell-Davis quantile comparison estimator (6).

Study approval

This study was approved by the Institutional Review Boards of the University of Illinois Chicago and Vanderbilt University. Informed consent was obtained from all participants.

Data availability

The accompanying Supporting Data Values file includes the values underlying the results presented here. Code is available at <https://github.com/amandeepjutla/2023-5ht-variants>. SSC and ACE data are respectively available from the Simons Foundation Autism Research Initiative and NIMH Data Archive.

Results

Our sample comprised 276 children with maternal WB5-HT data, 35 (13%) of whom had at least one rare autism-associated genetic variant (**Supplement 2**). Inheritance was *de novo* in 32 (91%), maternal in 2 (6%), and paternal in 1 (3%). Sample demographics (**Supplement 3**) were consistent with those typically reported in autism samples: most were male ($n = 229$, 86%), white ($n = 205$, 78%) and non-Latine (231, 88%).

We did not find a significant difference in median maternal WB5-HT between autistic children with and without a rare variant ($W = 4897.5$, $p = 0.12$); however, we did find that maternal WB5-HT was lower in rare variant carriers at the 75th (by 33.07, 95% CI = 5.55 – 64.40, $p = 0.02$) and 90th (by 64.60, 95% CI 26.65 – 101.44, $p < 0.01$) percentiles. (**Figure 1b, Supplement 4**). Similar analyses in ancillary samples of 301 children with paternal WB5-HT data ($n = 301$, 34 with a rare variant) and 346 with child WB5-HT data ($n = 346$, 38 with a rare variant) did not find median or quantile-level differences in WB5-HT between rare variant carriers and non-carriers (**Figure 1c, 1d**).

Conclusion

Even in this modest sample size we observed that WB5-HT extended into a higher range in mothers of autistic children without rare genetic variants as compared to mothers of children with variants. Although this aligns with our hypothesis of relatively lower WB5-HT in mothers of probands with rare variants, we did not see significant differences at a group median level. We observed no differences in fathers or autistic individuals themselves, indicating that these effects are not simply due to the heritability of WB5-HT.

The skewness of the maternal WB5-HT distribution in non-carriers indicates that the highest quantiles, where differences were observed, deviated from an expected normal distribution. This skewness in maternal WB5-HT parallels the elevated WB5-HT consistently observed in ~25% of autistic individuals. This may suggest that elevated maternal WB5-HT is associated with autism risk in a subset of individuals without rare genetic variants. We lacked control families that would have allowed us to evaluate maternal WB5-HT in comparison to general population WB5-HT (**Figure 1a**).

Additional limitations include modest statistical power due to the small number of probands carrying a genetic variant. Further, maternal WB5-HT was assessed after autism diagnosis, rather than during pregnancy, which would presumably be the time point when maternal WB5-HT would have an impact on offspring neurodevelopment. Our sample's inclusion of only probands with an autism diagnosis also prevented the evaluation of a general impact of maternal WB5-HT on offspring development. Future work should include prospective studies of maternal WB5-HT during pregnancy with longitudinal follow-up in offspring, including in relation to autistic and other neurodevelopmental traits.

References

1. Muller CL, Anacker AM, Rogers TD, et al. Impact of maternal serotonin transporter genotype on placental serotonin, fetal forebrain serotonin, and neurodevelopment. *Neuropsychopharmacology*. 2017;42(2):427-436. doi:10.1038/npp.2016.166
2. Montgomery AK, Shuffrey LC, Guter SJ, et al. Maternal serotonin levels are associated with cognitive ability and core symptoms in autism spectrum disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2018;0(0). doi:10.1016/j.jaac.2018.06.025
3. Fu JM, Satterstrom FK, Peng M, et al. Rare coding variation provides insight into the genetic architecture and phenotypic context of autism. *Nat Genet*. 2022;54(9):1320-1331. doi:10.1038/s41588-022-01104-0
4. Chen R, Davis LK, Guter S, et al. Leveraging blood serotonin as an endophenotype to identify de novo and rare variants involved in autism. *Molecular Autism*. 2017;8:14. doi:10.1186/s13229-017-0130-3
5. Fischbach GD, Lord C. The Simons Simplex Collection: a resource for identification of autism genetic risk factors. *Neuron*. 2010;68(2):192-195. doi:10.1016/j.neuron.2010.10.006
6. Wilcox RR, Erceg-Hurn DM, Clark F, Carlson M. Comparing two independent groups via the lower and upper quantiles. *Journal of Statistical Computation and Simulation*. 2014;84(7):1543-1551. doi:10.1080/00949655.2012.754026

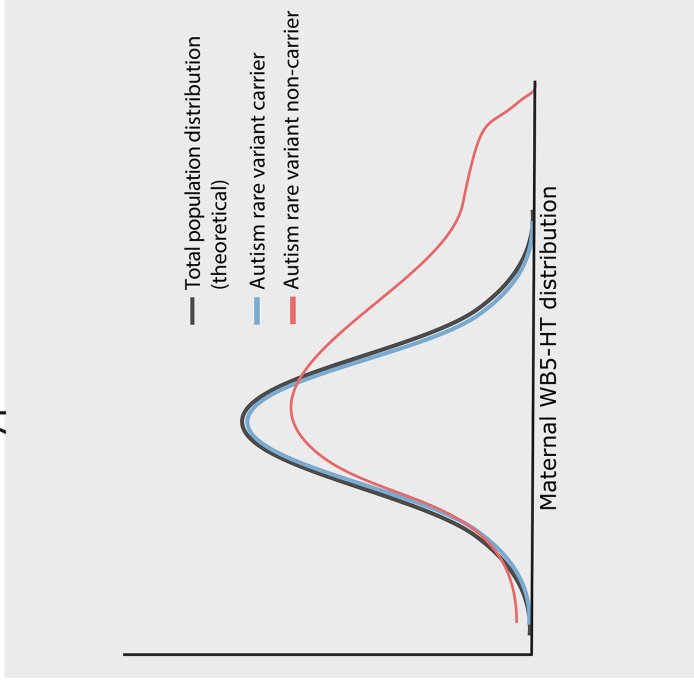
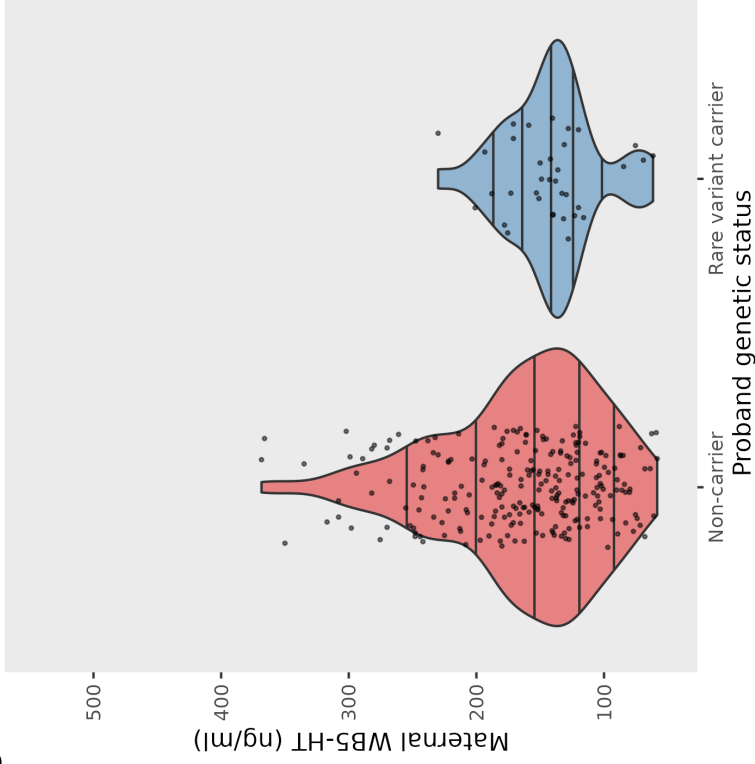
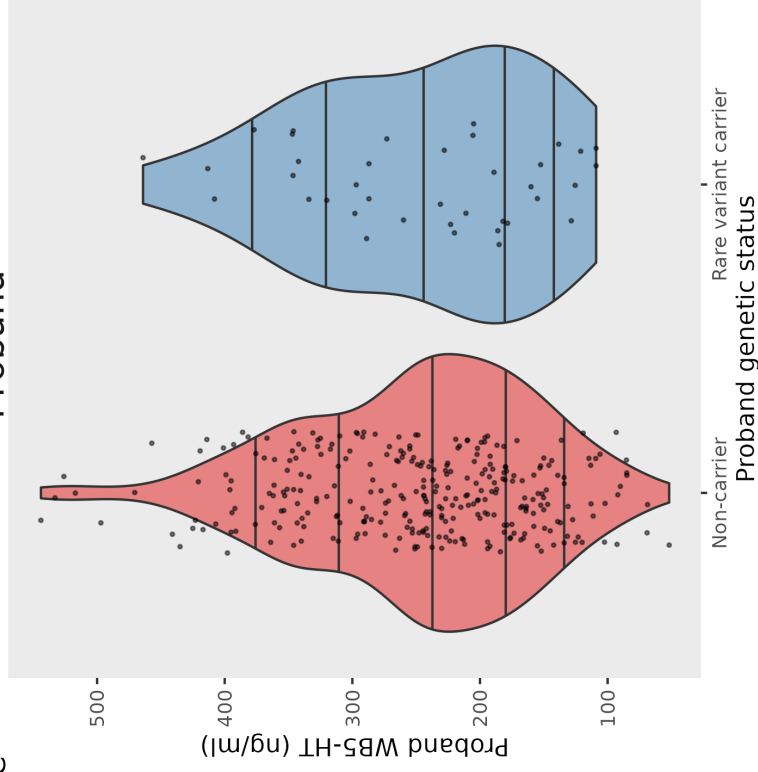
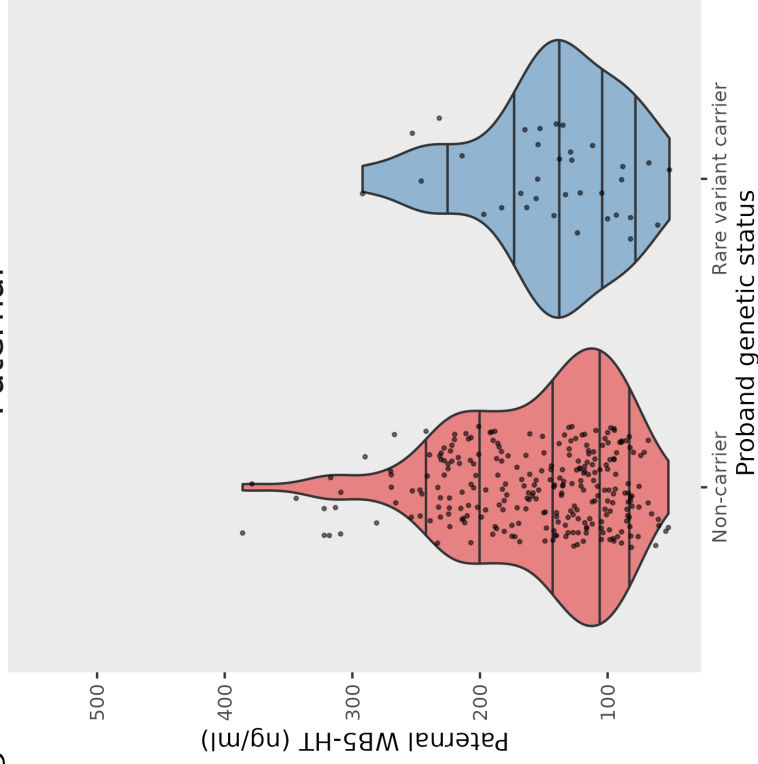
A**Hypothesized****B****Maternal****C****Proband****D****Paternal**

Figure Legend

We predicted that the mothers of probands carrying rare autism-associated variants would have lower WB5-HT than mothers of non-carrier probands. With the observation that 5-HT levels in mothers of ASD probands show an upward skew (2), we hypothesized that the mothers of non-carrier probands would not show this skew and instead show a normal distribution that would largely overlap with the theoretical distribution of the general population (A). Although median maternal WB5-HT did not differ across groups, the distribution was significantly upward-shifted in the autism rare variant non-carriers (B). We observed no significant differences in proband (C) or paternal (D) WB5-HT.