

# Childhood Dysregulation is Associated with Brain-Derived Neurotrophic Factor and the Serotonin 2A Receptor

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## Introduction

While the CBCL-Dysregulation Profile (CBCL-DP) is known to have high heritability, genomewide association studies of the phenotype to date have not revealed significant findings.<sup>1</sup> We undertook an *a priori* selection of 7 candidate genes from a 36 gene SNP chip along with analysis of 2 common VNTRs. (Table 1).

We used latent class analysis (LCA) to determine a profile of responses consistent with the CBCL-DP to allow for an empirical, data-driven manner of grouping individuals with high attention problems (AP), aggressive behavior (AGG), and anxious-depression (AD).<sup>2</sup>

**Table 1.** Candidate genes selected for analysis.

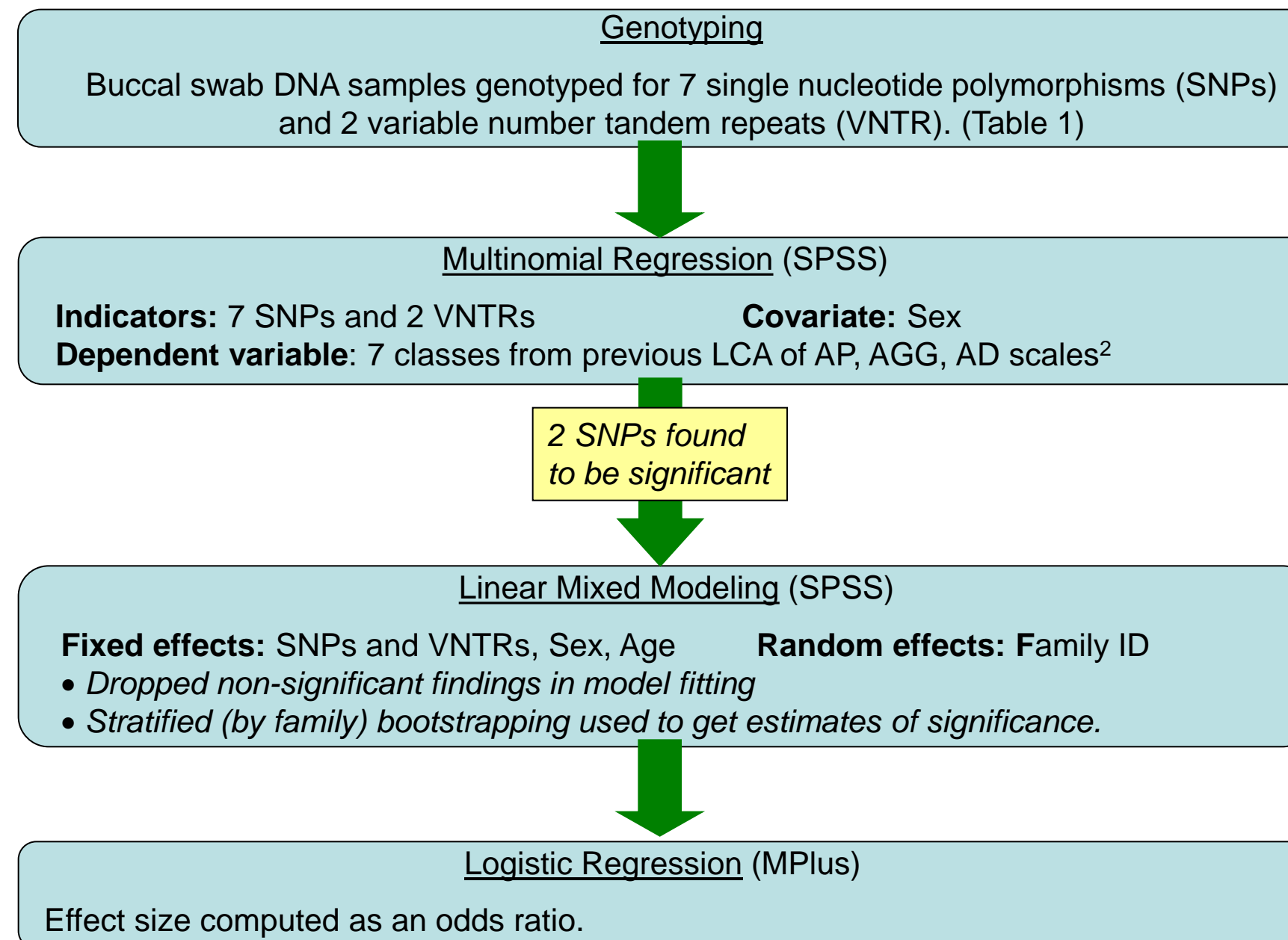
System	Gene	Polymorphism
<b>Adrenergic</b>	Steroid receptor co-activator-1 (SRC1)	SNP C>G rs11125744
	Adrenergic receptor alpha-2A (ADRA2A)	SNP C1291G rs1800544
<b>Serotonergic</b>	Serotonin 2A receptor (HTR2A)	SNP His452Tyr G>A rs6314
	Serotonin 1B receptor (HTR1B)	SNP rs6296
<b>Dopaminergic</b>	Dopamine D1 receptor (DRD1)	SNP A>G rs265981
	Dopamine transporter (DAT1)	VNTR
	Dopamine D4 receptor (DRD4)	VNTR
<b>Growth factor</b>	Brain-derived neurotrophic factor (BDNF)	SNP val66met rs6265
<b>Immunologic</b>	Complement component (3b/4b) receptor 1 (CR1)	SNP A>G rs6656401

## Sample and Measures

493 children from 195 families who were recruited from an outpatient child psychiatry clinic to participate in the Vermont Family Study (47.2% female; mean age = 10.9 years; age range = 5-18 years). Participation was voluntary and was approved by the University of Vermont IRB.

**Child Behavior Checklist (CBCL);**<sup>3</sup> 38 items from the Attention Problems (AP), Aggressive (AGG) and Anxious/Depressed (A/D) scales were used in the latent class analysis.

## Analyses

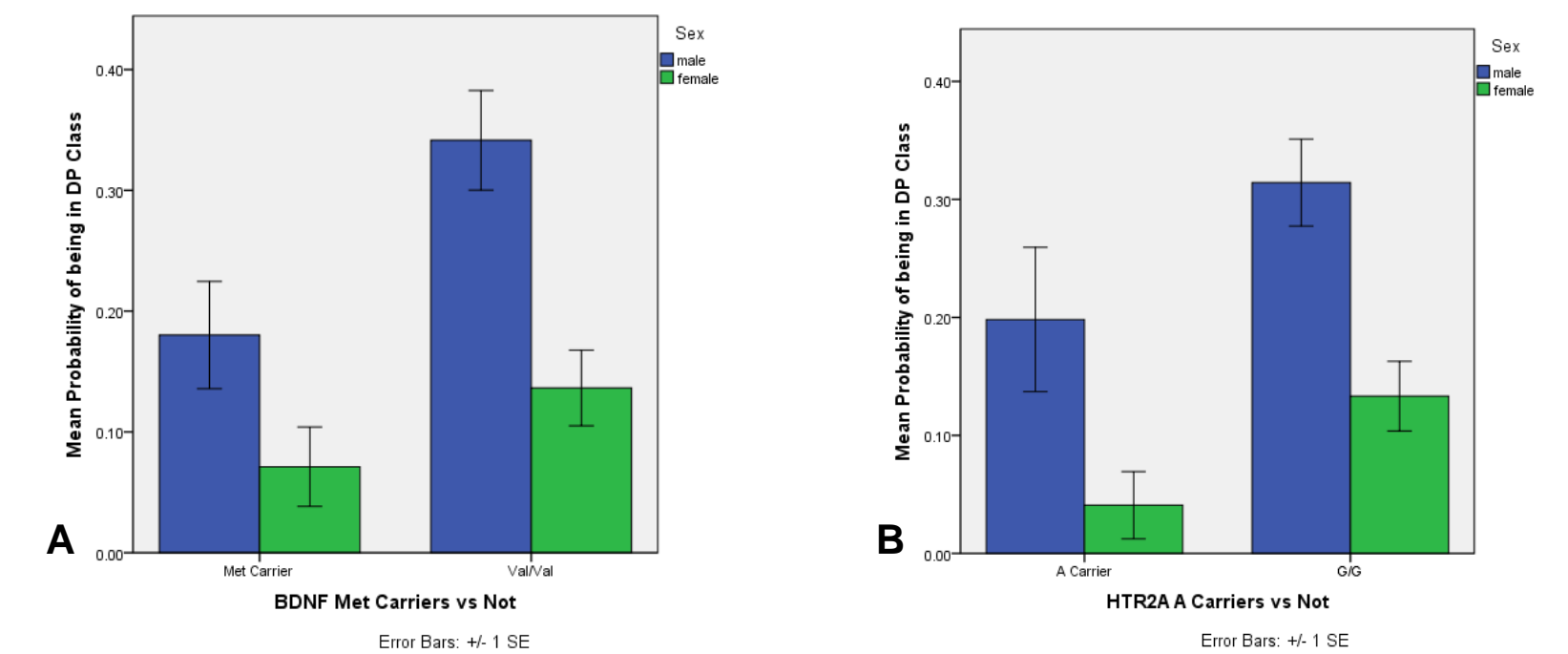


## Results

- 435 children had valid data for analysis of the BDNF genotype and 425 had valid data for the HTR2A genotype.
- The overall model did not require family random effects ( $p > 0.1$  when effects dropped) and demonstrated significant associations of being in the dysregulation class with BDNF and HTR2A ( $p < 1 \times 10^{-5}$ ) and sex ( $p < 1 \times 10^{-5}$ ).
- Associations held when dysregulation class data was analyzed using linear mixed modeling. (Figure 1a,1b).
- Effect size calculation showed Val homozygotes at BDNF have an increased likelihood of being in the dysregulation class [OR 2.602 (1.540-4.396)], G homozygotes at HTR2A were at increased risk [OR = 1.975 (1.080-3.611)], and having both risk genotypes also yielded a significantly increased risk [OR = 2.565 (1.579-4.165)] (Table 2).

## Results (con't)

**Figure 1.** Analysis of dysregulation class using linear mixed modeling against BDNF (panel A) and HTR2A (panel B) genotypes



**Table 2.** Odds ratios from logistic regression

Gene	Genotype	OR	CI
BDNF	Val homozygotes	2.602	1.540-4.396
HTR2A	G homozygotes	1.975	1.080-3.611
BDNF/ HTR2A	BDNF Val homozygotes and HTR2A G homozygotes	2.565	1.579-4.165

## Conclusions

In this family study, there are associations with the Dysregulation Profile of the CBCL (CBCL-DP) and both BDNF and HTR2A. This association holds when the data were analyzed as continuous and when family clustering was included. Future research should be conducted in order to examine whether these findings can be replicated using the same models with a larger sample size in a different population.

## References

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2. Althoff RR, Ayer LA, Rettew DC, Hudziak JJ (2010b). Assessment of Dysregulated Children Using the Child Behavior Checklist: A Receiver Operating Characteristic Curve Analysis. *Psychological Assessment.* 22(3):609-17.
3. Achenbach, T. M., & Rescorla, L. A. (2001). Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont Research Center for Children, Youth, & Families.
4. Faraone SV, Doyle AE, Mick E, Biederman J (2001): Meta-analysis of the association between the 7-repeat allele of the dopamine d(4) receptor gene and attention deficit hyperactivity disorder. *Am J Psychiatry* 158:1052-1057.
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