

Problematic Sexual Behavior and Reward Deficiency Syndrome: A Genetic Association Analysis of an *SLC6A3* Variant

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Background

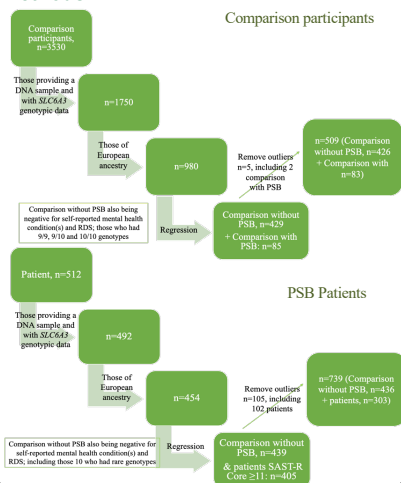
Problematic sexual behavior (PSB) refers to a number of similar terms, such as sex addiction,¹ compulsive sexual behavior² and hypersexuality.^{3,4} It affects 3-6% of the general population, with a higher prevalence in men than women.⁵ PSB can have a profound impact on personal life and may co-occur with other psychiatric conditions such as obsessive-compulsive disorder (OCD),⁴ reward deficiency syndrome (RDS),⁶ e.g., Attention-Deficit/Hyperactivity Disorder, personality disorders, and addictive disorders.^{4,7} Reward deficiency syndrome (RDS) has been referred to as an "octopus of behavioral dysfunction," encompassing a range of abnormal behaviors, due to disruptions in the reward neurotransmission cascade, that have a common endophenotype stemming from hypodopaminergia.⁸ The dopamine transporter is encoded by *SLC6A3* at chromosome 5p15.33. There is a variable number tandem repeat (VNTR) in the 3' untranslated region of *SLC6A3*, ranging from 3-13 repeats (9 and 10 being the most common) of a 40-base pair element.⁹ Multiple studies have shown that the 10/10 genotype of the *SLC6A3* 3' VNTR has been associated with RDS including family history of RDS,¹⁰ ADHD,^{11,12} and antisocial behavior.¹³

It is debatable whether PSB should be regarded as a compulsive behavior disorder, behavioral addiction, or impulse control disorder.^{14,15} PSB is not in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5,¹⁶ but is in the International Statistical Classification of Diseases (ICD)-11 as compulsive sexual behavior disorder.¹⁷ Currently, the evidence supporting treatment for PSB is weak (especially for pharmacological interventions).¹⁸ In addition, systematic data including non-treatment seekers is limited.¹⁷ Furthermore, research findings of the *SLC6A3* 3' VNTR and its association with psychiatric phenotypes such as RDS are varied, at least partly due to clinical heterogeneity, including differences by age,¹⁹ gender,¹⁹ and ethnicity.²⁰

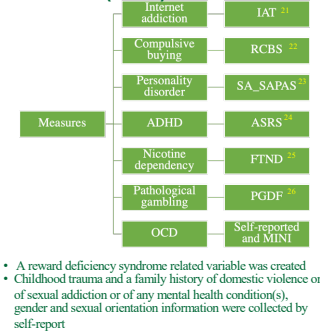
Hypotheses

1. Screening positive for factors previously associated with reward deficiency syndrome, having OCD, and childhood trauma are associated with PSB in a sample derived from a Canadian post-secondary education.
2. Individuals with the 10/10 genotype of the *SLC6A3* 3' VNTR may be at a higher risk of PSB in those of European ancestry, including PSB patients.

Methods



Methods (cont.)

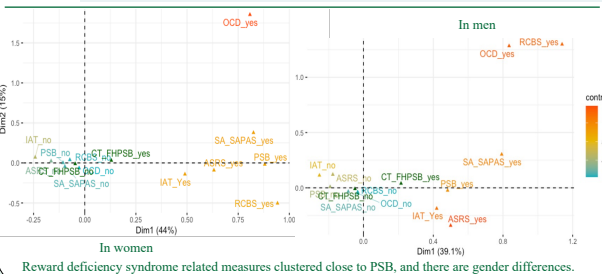
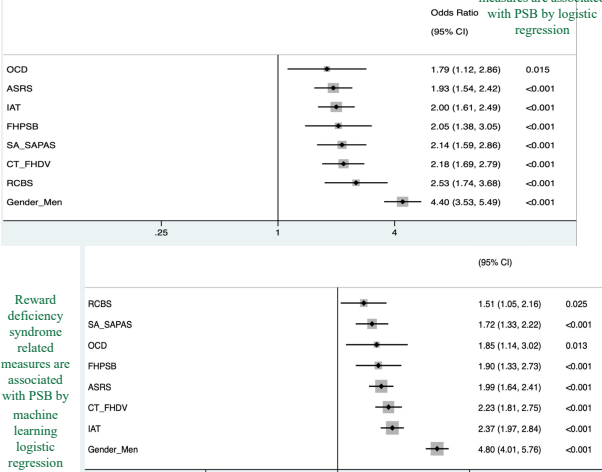


- Differences in data distributions: Pearson's χ^2 test
- Mean comparisons: non-parametric testing (Mann-Whitney U test and Kruskal-Wallis test, following by Dunn's test)
- Correlation: tetrachoric (for binary variables) and Kendall's τ (for categorical variables)
- Regression: backward stepwise logistic regression analyses and machine learning logistic regression with PSB as the dependent variable
- DNA samples were collected by buccal swabs and/or saliva. Genotyping was performed by polymerase chain reaction (PCR) with agarose gel electrophoresis.²¹

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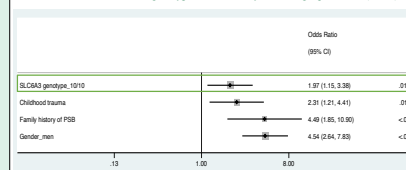
Results

The frequency of PSB was 16.5% (532/3219) in comparison participants.

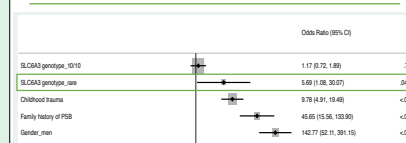


Results (cont.)

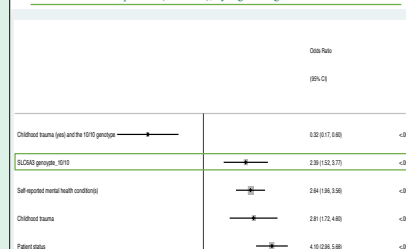
The distribution of *SLC6A3* genotypes was in Hardy-Weinberg equilibrium (HWE)



The 10/10 genotype is associated with PSB in comparison participants (P=0.013), by logistic regression



Rare genotypes are associated with clinical forms of PSB in PSB patients (P=0.041), by logistic regression



The 10/10 genotype and PSB is associated with RDS in all participants (P=1.73x10⁻⁴), by logistic regression

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ADDITION RESEARCH

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