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An examination of genes, stress and suicidal behavior in two First Nations communities: The role of the brain-derived neurotropic factor gene

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ABSTRACT

Suicide claims over 800,000 lives each year worldwide. Suicide rates in indigenous populations in Canada are about double that of the national average, making it a serious public health issue. Numerous factors are involved in suicide risk, including genetic factors, as well as various psychosocial stressors, such as historical experience with the Indian Residential School system for Indigenous populations, as well as protective variables such as social support. Here, we report the first genetic study of suicidal behaviors that includes multiple measures of stress and social supports. We investigated the role of the functional Val66Met marker (rs6265) in the Brain-Derived Neurotropic Factor (*BDNF*) gene in suicidal ideation and suicide attempt in a First Nations community sample ($N = 278$). We did not find a significant association between the *BDNF* rs6265 marker and suicidal behaviors. We found childhood adversities, recent life stress, chronic stress, perceived stress, difficulties, and hazardous alcohol use to be associated with both suicidal ideation and suicide attempt. Thus, while additional studies with larger samples are required to elucidate the genetic component of suicide, addressing environmental stressors may be important for suicide prevention.

1. Introduction

Suicide claims over 800,000 deaths worldwide a year (World Health Organization) and close to 4000 deaths per year in Canada (Statistics Canada CANSIM table 102–0551). In Canada, the rates of suicide in Indigenous populations are significantly higher than the national average and vary considerably across these populations. For example, the rate of First Nations suicide was twice that of the overall suicide rate in Canada, at 24 suicides per 100,000 individuals per year (Kirmayer et al., 2007b). A number of risk and protective factors have been identified in relation to suicide, including such risk factors as early life trauma and recent life stress, and protective factors like social support and religious affiliation (Wu et al., 2015; Turecki and Brent, 2016; Sinyor et al., 2017). The effects of colonization and oppression, including sendentarization or forced settlement, relocation, and forced assimilation through residential schooling, are amongst the most significant historical traumatic events that precipitated the ongoing stress and struggles in First Nations people (Kirmayer et al., 2007a; Bombay et al., 2011). These social factors may partly contribute to the heightened risk of suicide in this population (Lawson-Te Aho and Liu, 2010). A recent study examined the relationships between previous generational residential school attendance and the current physical and mental health of First Nations, Métis and Inuit Canadians living off reserve and detected strong associations for lower self-perceived mental health, higher risk of distress, suicidal ideation, and suicide attempt (Hackett et al., 2016). This evidence supports the significant role of historical intergenerational trauma on the risk of suicidal ideation, suicide attempt, and suicide (Eggertson, 2015). The transmission of the

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effects of oppression across generations – the historical aspect of colonization - needs to be delineated.

In addition to these effects, family and twin studies have supported a prominent genetic component in the risk of suicidal ideation, suicide attempt, and suicide completion (reviewed in (Zai et al., 2012a)). The interplay between gene variants and social environmental variables has been explored in a number of suicidal ideation/attempt studies (reviewed in (Mandelli and Serretti, 2013)), where suggestive findings were reported for genes in the serotonin (e.g., (Caspi et al., 2003; Wasserman et al., 2006; Brezo et al., 2010; Zhang et al., 2010; Murphy et al., 2011; Ben-Efraim et al., 2013)), dopamine (Haeffel et al., 2008), glutamate (Sokolowski et al., 2013), the stress response systems (Wasserman et al., 2008; Ben-Efraim et al., 2011; Roy, 2012), and the neurotrophin Brain-derived neurotropic factor (Perroud et al., 2008; Sarchiapone et al., 2008). It is important to note that no studies have explored gene variants in Indigenous populations.

Reduced brain-derived neurotropic factor (*BDNF*) expression has been found in suicide attempters and victims (reviewed in (Dwivedi, 2010); (Pinheiro et al., 2012; Banerjee et al., 2013; Grah et al., 2014; Chiou and Huang, 2016)). Increased plasma *BDNF* (Mansur et al., 2016) and no significantly different *BDNF* levels (da Graca Cantarelli et al., 2015; Eisen et al., 2016) have also been reported in suicide attempters. However, the relationship between *BDNF* gene expression and suicidal ideation/attempt, whether it is suicide attempt, suicide completion, or suicidal ideation, remains unclear (Eisen et al., 2015). The decrease in *BDNF* in suicide victims could be sex- and brain region-specific, with a decrease in the frontopolar prefrontal cortex observed in females and a decrease in the hippocampus observed in males (Hayley et al., 2015).

The *BDNF* gene (HGNC: 1033) is 67.2 kb in length and is localized to chromosomal region 11p14.1. The functional single-nucleotide polymorphism rs6265 in the *BDNF* gene codes for an amino-acid change from Valine to Methionine at the 66th codon (196G > A; Val66Met), resulting in reduced packaging of the *BDNF* protein into secretary vesicles (Chiaruttini et al., 2009) and decreased secretion in the synapse (Egan et al., 2003). Genetic studies of *BDNF* rs6265 in suicide outcomes have yielded mixed results (Hong et al., 2003; Huang and Lee, 2007; Zarrilli et al., 2009; Spalletta et al., 2010; Nedic et al., 2013; Ratta-Apha et al., 2013). A number of research groups found that patients with the low-expression (Lotrich et al., 2013) Met allele were at increased risk of suicide in patients with various psychiatric disorders (Huang and Lee, 2007; Iga et al., 2007; Kim et al., 2008; Sarchiapone et al., 2008). The Val/Val genotype has also been associated with suicide attempt in the elderly subgroup of a rural Chinese sample (Wang et al., 2015) and in a sample from Mexico (Gonzalez-Castro et al., 2015). Findings of associations between other *BDNF* gene polymorphisms and suicide completion have also been reported (Ropret et al., 2015).

We previously analyzed 3352 subjects for association between the *BDNF* rs6265 marker and suicidal ideation/attempt, and found the Met allele to be associated with suicide attempt (Zai et al., 2012b). However, association of suicide attempt with the Val/Val genotype have also been reported; the mixed findings could be due in part to contributions from certain environmental stressors including childhood trauma (Perroud et al., 2008; Sarchiapone et al., 2008). Additional studies are needed to clarify these intriguing gene-environment interaction findings.

While most gene-environment interaction studies have focused on childhood maltreatment, there is a lack of studies that investigate the contribution of other stress variables and more importantly resilience factors including social support in suicidal behavior. Furthermore, the role of *BDNF* rs6265 has not been investigated for possible association with suicidal behavior in First Nations communities. In the current study, we aim to investigate the roles of various stressors, social support, and the *BDNF* rs6265 marker in suicidal behavior in a First Nations community.

2. Methods

2.1. Participants

Participants ($N = 464$) were recruited as part of the Researching Health in Ontario Communities (RHOC) study, which aims to investigate the inter-relationships among stress, mental health, substance use, and violence issues (Wells et al., 2011). Adults from two Ontario First Nations communities were recruited from (a) a random sample of members of the First Nation, (b) individuals who self-identified as having a mental health and/or substance use problem recruited via posters, community advertisements and by word of mouth, and (c) community volunteers who wished to participate (Spence et al., 2016). Two hundred and seventy-eight participants provided saliva samples for genetic analyses, and completed self-report computerized questionnaires, including the Perceived Stress Scale (Cohen et al., 1983), Chronic Stress Scale (Turner and Turner, 2005), the Alcohol Use Disorders Identification Test (AUDIT) which measures harmful or hazardous drinking (Saunders et al., 1993), childhood adversities (Turner et al., 1995), recent life stress (Avison and Turner, 1988; Turner and Avison, 1992a,b; Thoits, 1995), limitations in activities and daily functioning (i.e., disability) as assessed by the 12-item WHODAS 2.0 (Ustün et al., 2010b; Ustün et al., 2010a). Measures of resilience included a measure self-identification as First Nations (single item developed by research team in which respondents were asked the extent to which they identified themselves as First Nations with response options - not at all, a little, a moderate amount, a lot) and social supports (Statistics Canada, 2003) (see (Wells et al., 2014)). Lifetime suicide attempt and suicidal ideation were assessed as part of the Ontario Student Drug Use and Health Survey (Paglia-Boak et al., 2012). The study methods adhered to the Tri-Council Policy Statement on Ethics of Research Involving First Nations, Inuit, and Metis Peoples of Canada and the principles of Ownership, Control, Access, and Possession (CIHR, NSERC, SSHRC, 2010; National Aboriginal Health Organization, 2005). The study was approved by the Research Ethics Board at CAMH as well as the Band Chief and Council of the two First Nations. This article was reviewed by First Nations community representatives, comprising a Research Advisory Committee, for cultural relevance and accuracy.

2.2. Genomic DNA extraction and genotyping

Participants were asked to provide saliva samples which were collected using the Oragene 500 DNA kits (DNA Genotek Inc., Kanata, ON, Canada), with genomic DNA extracted according to manufacturer's instructions. DNA samples (20 ng) were genotyped for *BDNF* rs6265 using polymerase chain reaction-based TaqMan assay C_11592758_10 in 10-microlitre reaction volumes in Applied Biosystems 2720 Thermal Cyclers (Thermo Fisher Scientific Inc.), with the following cycling conditions: 95 °C for 10 min, followed by 40 cycles each of 95 °C for 15 s and 60 °C for 1 min. Genotypes were determined in the ViiA™ 7 real-time PCR system (Thermo Fisher Scientific Inc.).

2.3. Statistical analysis

Analyses were conducted on the sample with full genotype and questionnaire data ($N = 278$) using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY). Deviance from Hardy–Weinberg Equilibrium was examined using the chi-squared test (http://www.husdyr.kvl.dk/htm/kc/popgen/genetik/applets/kitest.htm). The questionnaire scores were inspected for normality (magnitudes of skewness and kurtosis of less than 2.0). AUDIT was used as a dichotomous variable, with scores of 8 or above being classified as reflecting hazardous or harmful drinking (Saunders et al., 1993). Table 1 shows the demographic information for the sample, with comparisons between individuals who have contemplated (i.e., suicidal ideation) or attempted suicide and those who have not. Analyses of sex,

Table 1
Comparison of demographic information, phenotype data, and *BDNF* rs6265 genotypes between individuals who have (A) considered and (B) attempted suicide and those who have not in the First Nations community sample.

(A) Variables	Considered suicide ($N = 67$)	Not considered suicide ($N = 211$)	t	Degree of freedom	p-value
Male/female	41/26	134/77			0.772
Identify as First Nations (a lot/moderate/a little/not at all)	51/9/5/2	140/51/16/4			0.279
Age	34.13 ± 13.23	40.06 ± 14.37	−2.994	276	0.003
Recent life events	4.46 ± 2.68	2.28 ± 2.30	6.500	276	<0.001
Childhood adversities	3.49 ± 2.07	2.35 ± 1.83	4.329	276	<0.001
Chronic stress	6.99 ± 4.43	4.21 ± 3.58	4.661	94.934	<0.001
Perceived stress	20.70 ± 7.43	16.31 ± 6.34	4.733	276	<0.001
Social supports	3.22 ± 2.18	3.42 ± 2.48	−0.571	276	0.569
Disabilities	23.84 ± 9.12	19.78 ± 8.63	3.740	276	0.001
AUDIT score ≥8 (Y/N)	38/29	77/134			0.004
Attempted suicide (Y/N)	34/33	0/211			<0.001
BDNF rs6265 genotypes (CC/CT/TT)(VV/VM/MM)	51/15/1	181/29/1			0.151[a]

(B) Variables	Attempted suicide ($N = 34$)	Not attempted suicide ($N = 244$)	t	Degree of freedom	p-value
Male/female	22/12	153/91			0.853
Identify as First Nations (a lot/moderate/a little/not at all)	27/4/2/1	164/56/19/5			0.461
Age	33.38 ± 11.91	39.36 ± 14.24	−2.300	276	0.022
Recent life events	5.03 ± 2.92	2.50 ± 2.36	5.688	276	<0.001
Childhood adversities	3.56 ± 2.16	2.49 ± 1.89	3.036	276	0.003
Chronic stress	7.71 ± 4.54	4.49 ± 3.73	4.579	276	<0.001
Perceived stress	21.74 ± 7.62	16.76 ± 6.54	4.068	276	<0.001
Social supports	3.29 ± 2.18	3.38 ± 2.44	−0.197	276	0.844
Disabilities	26.12 ± 9.75	20.01 ± 8.54	3.839	276	<0.001
AUDIT score ≥8 (Y/N)	20/14	95/149			0.040
BDNF rs6265 genotypes (CC/CT/TT)(VV/VM/MM)	25/8/1	207/36/1			0.090[b]

[a] Minor allele frequency (T) = 0.086; p-value for Hardy-Weinberg Equilibrium = 0.956; Odds ratio for minor allele (T)-carrying genotypes = 1.893 (95% confidence interval: 0.957–3.743).
[b] Minor allele frequency (T) = 0.086; p-value for Hardy-Weinberg Equilibrium = 0.956; Odds ratio for minor allele (T)-carrying genotypes = 2.014 (95% confidence interval: 0.871–4.658).

risky alcohol use, self-identity as First Nations, and genotypes with suicide attempt or suicidal ideation were conducted using Fisher's Exact Tests. Variables that were found to be significant in the individual tests were entered into the logistic regression models for suicide attempt and suicidal ideation in a backward stepwise approach to determine the set of variables for the final analysis with the *BDNF* rs6265 marker. Finally, we conducted stratified analyses to explore whether the association of *BDNF* rs6265 may be specific for individuals who had or had not experienced childhood adversities or recent life stress.

3. Results

Genotype frequency distribution for the *BDNF* rs6265 marker did not deviate significantly from Hardy-Weinberg Equilibrium (data not shown; $p = 0.956$).

Suicidal ideation was negatively associated with age (Table 1A) and positively associated with recent life events, childhood adversities, chronic stress, perceived stress, disabilities, and harmful/hazardous drinking ($p < 0.05$). Self-identity as First Nations, sex, and social supports were not significantly associated with suicidal ideation ($p > 0.05$).

Similarly, participants who attempted suicide were younger than those who had not attempted suicide (Table 1B). Participants who attempted suicide scored higher in recent life events, childhood adversities, chronic stress, perceived stress, and disabilities compared to participants who had not attempted suicide ($p < 0.05$) (Table 1). Harmful/hazardous drinking was also over-represented in participants who attempted suicide ($p < 0.05$). Self-identity as First Nations, sex, and social supports were not significantly associated with suicide attempt ($p > 0.05$).

From the stepwise logistic regression analysis of suicidal ideation, age, risky alcohol use, recent life events, childhood adversities, and disabilities remained in the model (Table 2A). Similarly, significant results were found for the analysis of suicide attempt history. From the stepwise logistic regression analysis of suicide attempt, age, recent life events, and disabilities remained in the model (Table 2B). The genotypes for *BDNF* rs6265 were not associated with suicidal ideation ($p = 0.180$) or suicide attempt ($p = 0.173$) in the final regression models. When we conducted stratified analyses based on exposure to childhood or recent life stress, we did not find significant results ($p > 0.05$). Results from analyses of sex, identity as First Nations, and social supports were not significant.

4. Discussion

We report here the first study that incorporated the functional *BDNF* rs6265 variant as well as both stress and support measures in a First Nations community sample. The *BDNF* rs6265 was not significantly associated with suicidal ideation or attempt in our First Nations community sample. The Met allele has been previously associated with risk of suicide attempt (Zai et al., 2012b). The effect of *BDNF* rs6265 may be specific for individuals who had not experienced life stresses, the results which may explain the different findings of the other allele (Val) being the risk allele in individuals with childhood trauma (Perroud et al., 2008; Sarchiapone et al., 2008). In other words, the rs6265 Met allele may play a role in suicidal ideation/attempt in individuals without any history of childhood trauma, while the Val allele may play a role in suicidal ideation/attempt in individuals who have experienced childhood trauma. It should be noted that our moderate sample size with an observed minor allele frequency for rs6265 of less than 10% was underpowered to detect a statistically significant effect. Including childhood trauma in future analyses of *BDNF* with suicidal ideation/attempt in larger samples may resolve some of the mixed findings and clarify the role of *BDNF* in the various suicidal ideation/attempt. Nonetheless, the lack of significant influence of childhood adversities to our *BDNF* rs6265 results raised the possibility that the type of childhood adversities may need to be considered. For example, in previous research the Val/Val genotype was associated with self-harm in the context of

Table 2
Results from backward stepwise logistic regression analyses of (A) suicide consideration and (B) suicide attempt in our First Nations community sample.

(A) Considered suicide	B	Standard error of B	Wald	Degree of freedom	*p*-value	Exp(B)	95% Confidence interval of Exp(B)
Age	−0.025	0.013	3.900	1	0.048	0.975	0.951–1.000
AUDIT score ≥8 (Y/N)	0.551	0.327	2.844	1	0.092	1.735	0.915–3.290
Recent life events	0.237	0.065	13.134	1	<0.001	1.267	1.115–1.440
Childhood adversities	0.180	0.085	4.453	1	0.035	1.198	1.013–1.416
Disabilities	0.053	0.017	9.103	1	0.003	1.054	1.019–1.091
BDNF rs6265 genotypes	0.497	0.371	1.795	1	0.180	1.643	0.795–3.399
(B) Attempted suicide	B	Standard error of B	Wald	Degree of freedom	*p*-value	Exp(B)	95% Confidence interval of Exp(B)
Age	−0.032	0.016	3.919	1	0.048	0.968	0.938–1.000
Recent life events	0.307	0.076	16.341	1	<0.001	1.360	1.172–1.578
Disabilities	0.073	0.021	11.707	1	0.001	1.076	1.032–1.122
BDNF rs6265 genotypes	0.612	0.449	1.857	1	0.173	1.844	0.765–4.445

emotional maltreatment (Bresin et al., 2013) and not with physical abuse (Serretti et al., 2013). Thus, more detailed studies on the role of specific types of trauma in suicidal ideation/attempt are warranted (Stein et al., 2010). Furthermore, the inclusion of multiple stress measures besides childhood adversities, including chronic stress, recent life stress, and perceived stress, as well as other suicide-relevant variables, including harmful/hazardous drinking and social supports sets our study apart from most previous genetic studies of suicidal ideation/attempt.

The findings in the current study are based on two First Nations communities and may not be generalizable to other First Nations, Métis, and Inuit communities, as well as other Indigenous communities in Canada and elsewhere. The cross-sectional design of the study also limits interpretations about cause and effect. Other risk and protective factors not included in the present analysis may be important, especially those relevant to First Nations communities, including cultural resilience (Spence et al., 2016); however, a larger sample size would be needed to have sufficient power to assess the role of these additional variables. The moderate sample size in the current study might have limited the power to detect an effect of the *BDNF* gene marker and other variables in suicidal ideation/attempt. Our sample has 80% power to detect an effect size (Genotype Odds Ratio or R_G) of 2.80 for the analysis of suicide attempt, and R_G of 2.30 for the analysis of suicidal ideation (alpha 0.05, 2-tailed, additive model, minor allele frequency 0.0863) (QUANTO: Gauderman and Morrison, 2006). Moreover, other genetic markers, including the often studied serotonin-transporter-linked polymorphic region (HTTLPR) (Li and He, 2007), the Monoamine Oxidase A promoter variable number tandem repeat (*MAOA* uVNTR) (Hung CF et al., 2012), and the Trytophan Hydroxylase 1 (*TPH1*) rs1800532 markers (González-Castro et al., 2014), need to be explored to better understand the role of genes in suicidal ideation/attempt (reviewed in Zai et al., 2012a,b). Several studies have examined both genetic and environmental risk factors for suicidal ideation/attempt (reviewed in Mandelli and Serretti, 2013; Brodsky, 2016). Many of these studies focused on childhood trauma, but only a few have also considered social support, life stressors, and alcohol use disorders (e.g., Kim et al., 2014; Choi et al., 2018). Our findings are in line with the literature showing that childhood trauma is associated with suicidal ideation (Bahk et al., 2017) and suicide attempt (Zatti et al., 2017). Similarly, our findings support a role for recent life stressors in suicidal ideation and suicide attempt, although further examinations of various types of stressors, especially those of an interpersonal nature, as well as better characterization of the timeframe between the stressors and suicidal events may further clarify these associations (Liu and Miller, 2014). We did not find social support to be associated with suicidal ideation/attempt. These findings are in agreement with some studies (Yen et al., 2005; Arie et al., 2008), but not other studies reporting a protective effect (Yen et al., 2005; King et al., 1990). Assessments for both actual and perceived social supports (e.g., Kleiman et al., 2014; Carpenter et al., 2015), as well as separate analyses for males and females, will likely clarify the mixed findings in the literature. Investigations of the interaction between social supports and stressors in larger samples (e.g., Kleiman et al., 2014; Lim et al., 2018) will provide additional insights into their interplay in risk of suicidal ideation/attempt. Finally, similar to our study, alcohol use disorders have been found previously to be associated with an increased risk for suicidal ideation and suicide attempt across different study designs (Darvishi et al., 2015). Our findings of disabilities being associated with suicidal ideation/attempt agree with the positive findings on suicidal ideation from the literature (e.g., Schulberg et al., 2005; Park et al., 2014; Adewuya et al., 2016). Overall, in support of previous research (Devries et al., 2014; Hung et al., 2015; Oyesanya et al., 2015), the current findings suggest that environmental factors such as adverse childhood experiences, recent life stressors, and hazardous drinking are associated with this distressing outcome; thus, addressing these issues is important for suicide prevention programming in these communities.

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Conflicts of interest

J.L.K. and C.C.Z. with patent applications.

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