ORIGINAL RESEARCH

Predicting PTSD using the New York Risk Score with genotype data: potential clinical and research opportunities

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Background: We previously developed a post-traumatic stress disorder (PTSD) screening instrument, ie, the New York PTSD Risk Score (NYPRS), that was effective in predicting PTSD. In the present study, we assessed a version of this risk score that also included genetic information.

Methods: Utilizing diagnostic testing methods, we hierarchically examined different prediction variables identified in previous NYPRS research, including genetic risk-allele information, to assess lifetime and current PTSD status among a population of trauma-exposed adults.

Results: We found that, in predicting lifetime PTSD, the area under the receiver operating characteristic curve (AUC) for the Primary Care PTSD Screen alone was 0.865. When we added psychosocial predictors from the original NYPRS to the model, including depression, sleep disturbance, and a measure of health care access, the AUC increased to 0.902, which was a significant improvement ($P = 0.0021$). When genetic information was added in the form of a count of PTSD risk alleles located within *FKBP5*, *COMT*, *CHRNA5*, and *CRHR1* genetic loci (coded 0–6), the AUC increased to 0.920, which was also a significant improvement ($P = 0.0178$). The results for current PTSD were similar. In the final model for current PTSD with the psychosocial risk factors included, genotype resulted in a prediction weight of 17 for each risk allele present, indicating that a person with six risk alleles or more would receive a PTSD risk score of $17 \times 6 = 102$, the highest risk score for any of the predictors studied.

Conclusion: Genetic information added to the NYPRS helped improve the accuracy of prediction results for a screening instrument that already had high AUC test results. This improvement was achieved by increasing PTSD prediction specificity. Further research validation is advised.

Keywords: post-traumatic stress disorder, psychological trauma, diagnostic screening, test development, genotype, single nucleotide polymorphism

Introduction

The goal of our original study was to identify brief risk assessment instruments for post-traumatic stress disorder (PTSD). To meet this objective, we used data from several trauma studies, including data related to mental health status, substance misuse, and other psychosocial measures.[1–3] In these studies, PTSD was assessed based on the full Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria.[4] As discussed, combining these original studies gave a population that included 3298 persons, 270 of whom were PTSD-positive cases.[1–3]

A number of brief PTSD screening tools are currently available. These include the Primary Care PTSD Screen (PCPS), the Short Screening Scale for PTSD, and

the Short PTSD Rating Interview, among others.[5–10] These screeners are relatively short, appear to have reasonable specificity and sensitivity, and are typically focused on core PTSD symptoms.[1]

When developing the original New York PTSD Risk Score (NYPRS), our primary goal was to create a simple screening instrument that was useful in different clinical settings and improved upon current screeners.[1] Our objective was to develop a PTSD assessment tool that could be used in different settings to plan treatment interventions and resource allocations. Consistent with this approach, we examined multiple risk factors that extended beyond single-dimension PTSD screeners in common use.[7] Our original approach was consistent with the method recently used by Marx et al in a study designed to predict combat PTSD among Vietnam veterans.[11] In our current study, we assess the utility of a psychosocial prediction model that also includes genetic risk information.[12]

Previous research regarding traumatic events guided our original study.[13–15] Although research suggests that most persons recover quickly from traumatic experiences,[16] reviews of existing studies suggest that exposure to traumatic events typically results in mental health impairments among a subgroup of individuals.[17,18] Research also suggests that PTSD is not only associated with neuroendocrine and immune system alterations,[19,20] but also with the onset of inflammatory-related health conditions,[21] pointing to the neurobiological foundation of this disorder.[22]

Based on this body of research, the focus of the current study was to assess diagnostic PTSD instruments for use in clinical practice that also incorporated genetic risk information. As previously noted, prediction of the onset and course of PTSD has been difficult.[23,24] Typically, variables related to predisposition, those occurring before the exposure to trauma, and variables occurring after the exposure to trauma are the best predictors of PTSD onset and course.[23,24]

To date, several genetic components for PTSD have been identified that may explain vulnerability to PTSD. These include biologic pathways involving the hypothalamic-pituitary-adrenal axis, locus coeruleus, and noradrenergic and limbic systems.[25–28] In the current study, risk factors for PTSD were assessed among outpatients with a high prevalence of PTSD, ie, patients seen for chronic noncancer pain in a large regional medical center.[29] Chronic noncancer pain is a condition often associated with a history of PTSD.[30]

In this study, we assessed four known genetic markers for PTSD using a cumulative risk allele model, similar to what has been done to predict genetic associations in other clinical areas.[31] Specifically, we completed diagnostic interviews and collected DNA samples among 412 pain patients to determine if *FKBP5* (rs9470080), *COMT* (rs4680), *CHRNA5* (rs16969968), and *CRHR1* (rs110402) single nucleotide polymorphisms were cumulatively associated with PTSD, after psychosocial predictors from the NYPRS were added to the prediction model.

We previously reported that a count of specific PTSD risk alleles located within *FKBP5*, *COMT*, *CHRNA5*, and *CRHR1* genetic loci (risk allele count range = 0–6, mean count = 2.92, standard deviation = 1.36) was associated with lifetime ($t[409] = 3.430$, $P = 0.001$) and early onset PTSD ($t[409] = 4.239$, $P = 0.000028$).[12] In logistic regression, controlling for demographic factors, personality traits, and exposures to trauma, this risk allele count remained associated with both lifetime (odds ratio = 1.49, $P = 0.00158$) and early-onset PTSD (odds ratio = 2.36, $P = 0.000093$).[12] Similar to other research,[32] our plan was to incorporate this genetic information into our original NYPRS model. Our specific research objective was to determine if a genotype-informed NYPRS model improved the diagnostic performance. If this information improved the accuracy of prediction, it might have future clinical and diagnostic implications.

Materials and methods
Conceptual approach

As noted, the research suggests that increased vulnerability to PTSD occurs among those with a history of mental health disorders and previous psychological trauma.[24,33–36] In addition, the psychobiological bases of these syndromes have also become more clear.[22,37] Consequently, we anticipated a number of behavioral-cognitive phenomena to emerge in traumatized persons, including sleep disturbances, substance misuse, and alterations in functional and mental health status.[1,21] Currently, PTSD is known to be associated with outcomes along several causal pathways that encompass cognitive, behavioral, and biological domains.[38] Accordingly, we used a multifactorial approach to guide our original model building, combined with agnostic (ie, atheoretical) examinations of statistical results to develop a new PTSD prediction model.[1] As briefly described below, the original NYPRS enabled the testing of specific models that were conceptually and empirically grounded and included a sample size adequate for data analysis.[1–3,39]

Development of risk score and statistical analysis

As we have described elsewhere,[1] we used a process of moving candidate variables in and out of prediction models, which

allowed for manipulation of specificity and sensitivity.[40] An initial model was developed using variables thought to be related to PTSD. This model was then extended to include the unique collection of candidate measurements of interest. These variables included mental health status, substance misuse, lifetime and current stress exposures, and community resource measures, among other psychosocial measures.[1–3,39] The goal of this model building was to estimate the area under the receiver operating characteristic curve (AUC), while using the fewest number of parameters.[1]

A nonparametric approach was used to compare the added effects of other variables above the contribution of the base model.[41] The results of the model were then used to construct a "risk score" for PTSD. The properties of the risk scores were examined in terms of sensitivity, specificity, AUC, and by use of a nomogram,[41] which is a graphical tool used to represent the model in terms of standardized weights.[1] These weights are the equivalent of standardized beta coefficients in linear regression, except that the base model coefficient is typically set to a score of 100 for the largest coefficient to aid in scoring.[1] One problem in estimating measures of diagnostic ability using the same dataset in which the model was derived is overestimation.[1] In the current study, this was corrected by estimating a bias-corrected version using a 1000-sample bootstrap procedure to provide a more accurate estimate of the AUC.[42] This procedure is considered superior to cross-validation using a training and validation dataset.[42] In addition to estimating the AUC, we also used Youden's index,[40] a summary measure of the receiver operating characteristic curve that provides a criterion for choosing a cutoff for which both sensitivity and specificity are maximized.[41,43] As a final step, PTSD genotype information identified in previous research, described below, was added to the prediction model in the form of risk alleles coded 0–6 (see Appendix).[12] The statistical software used in this study included SAS version 9.2 (SAS Institute Inc, Cary, NC, USA),[44] the RMS package in R version 2.15 (R Foundation for Statistical Computing, Vienna, Austria),[45] Stata version 12.1 (Stata Corporation, College Station, TX),[46] and Pepi software version 4.0 (Sagebrush Press, Salt Lake City, UT, USA).[47]

Use of existing PTSD screeners and other measures

As part of our original study, we reviewed existing PTSD screening instruments currently in clinical use.[7] In the initial New York PTSD Risk Score study,[1] we used two of these screener instruments, ie, the Short Screening Scale for PTSD

and the PCPS.[6,48] In the current study, we present the results only for the PCPS, because this instrument is more widely used than the Short Screening Scale for PTSD and generally produces better prediction results.[1] In addition, based on our previous study, we used core psychosocial measures identified in our earlier NYPRS research. This included a two-item measure of lifetime symptoms of depression, ie, the Patient Health Questionnaire-2.[1] Other assessments included a measure of current health care access and reported sleep disturbance.[1] For the lifetime PTSD model, we used a measure of lifetime sleeping problems. For current PTSD, we used a measure of sleeping problems in the past year. Altogether we examined more than 100 potential diagnostic predictors, however only a few proved significant in distinguishing cases from noncases using the diagnostic testing approach described.[1] Access to health care was assessed by a question related to having a regular doctor or access to health care. Difficulty sleeping was assessed by a question about ever experiencing sleeping problems in the past for two weeks or more or in the past 12 months. A measure of lifetime trauma exposure, which was included in previous NYPRS models,[1] was dropped from our analyses in the current study due to a lack of statistical significance. This trauma measure was based on reported lifetime exposure to traumatic events, including being in a serious accident, being physically/sexually assaulted, or being in a war zone, with a history of 4+ lifetime events defined as high exposure to trauma. The specific measures used in the final prediction models, including genotype information, are included in the study Appendix.

PTSD measure

Study interviewers administered diagnostic surveys using instruments deployed in past PTSD research, including the National Women's Study and the World Trade Center Study in New York.[24,49–52] To have PTSD in the current study, patients had to meet the full diagnostic criteria for lifetime PTSD, known as the "A through F" criteria.[24] These criteria include experiencing intense fear (criterion A), re-experiencing the event (criterion B), avoidance of stimuli associated with the event (criterion C), experiencing increased arousal (criterion D), experiencing symptoms for more than a month (criterion E), and experiencing psychological distress or impairment (criterion F). In the present study, we assessed both lifetime and current PTSD, with the latter defined as meeting the full DSM-IV PTSD criteria in the past 12 months. Data related to the validity of this PTSD measure have been previously published.[24,49–53]

Subjects

The study subjects were adult outpatients (18+ years of age) with chronic noncancer pain treated in a large health care system.[29,54] Patients with chronic noncancer pain typically have a high prevalence of PTSD.[55,56] The mean age of the patients studied was 55 ± 13.4 years and the prevalence of lifetime PTSD was 14.3% (95% confidence interval [CI] 11.1%–18.1%). The study sample was randomly selected from a population of chronic pain patients identified by query of electronic health records held at the Geisinger Clinic, an integrated health system that serves residents of 40 central and northeastern Pennsylvania counties.[29] Geisinger's ambulatory clinics have used the Epic outpatient electronic health record system (Epic System Corporation, Verona, WI, USA) since 2001. With patient consent, trained and supervised interviewers administered structured diagnostic telephone interviews from August, 2007 through November, 2008. This study was approved by the institutional review board at Geisinger Clinic.

DNA collection and genotyping

Following the diagnostic interviews, buccal swab kits were mailed to consenting adults. Altogether, 414 returned the buccal swab kit with adequate DNA for the current analyses. Two subjects were identified as non-Caucasian and were not included in the current study to avoid problems due to population stratification and the different allele frequencies found among different ethnic groups. The candidate genes studied and corresponding single nucleotide polymorphisms were: catechol-O-methyltransferase (*COMT*; rs4680), FK506 binding protein 51 (*FKBP5*; rs9470080), cholinergic receptor, nicotinic, alpha 5 (*CHRNA5*; rs16969968) and corticotropin-releasing hormone receptor-1 (*CRHR1*; rs110402). These four single nucleotide polymorphisms were found to be significant predictors of PTSD in the past.[12] The targeted single nucleotide polymorphisms were originally part of a broader behavioral health study related to the genetics of pain, stress, and addiction reported elsewhere.[54,57,58] The *COMT* gene is associated with anxiety disorders, psychosis, depression, and other conditions involving regulation of the catecholamine pathway and has been associated with PTSD. The *FKBP5* gene regulates sensitivity of the glucocorticoid receptor, is functionally involved in hypothalamic-pituitary-adrenal axis activity, and has also been associated with PTSD in several studies.[59–61] The *CHRNA* gene cluster, which encodes components of the nicotinic acetylcholine receptor, is associated with nicotine dependence and cigarette smoking,[62,63] substance misuse,[54] and, more recently, PTSD.[12,25] The *CRHR1* gene is associated with a polypeptide hormone and neurotransmitters involved in corticotropin-releasing hormone activity linked to the mammalian stress response.[22] Studies suggest this gene regulates function of the hypothalamic-pituitary-adrenal axis and is associated with the impact of exposure to stress and onset of PTSD.[61,64,65] Combined, these four genetic loci appear to be vital in regulation of mammalian fear circuitry and are also likely to interact with other key biologic pathways, including inflammatory ones.[22,66]

Genotyping was performed on a 7500 real-time polymerase chain reaction platform (Applied BioSystems, Foster City, CA, USA), using TaqMan kits following the manufacturer's protocols. Quality control measures included visual inspection of allelic discrimination plots, monitoring concordance of cross-plated duplicate pairs, monitoring the overall call rate, and monitoring agreement with Hardy-Weinberg expectations.[67]

Results

The demographic profile of the study subjects shows that 68.8% were female, 66.2% were 40–64 years of age, 62.0% were married, 49.6% had a high school diploma or less education, and 42.1% had an annual household income of $30,000 or less, as shown in Table 1. Further, 38.9% met criteria for lifetime major depressive disorder and 21.2% had a history of high lifetime exposure to traumatic events (ie, exposed to 4+ traumatic life events). Altogether, 65.7% reported ever having difficulty sleeping for two weeks or more and 1.9% reported that they did not have regular access to a medical doctor or health care services. Finally, as shown in Table 1, in this study population, the prevalence of lifetime PTSD was 14.3% (95% CI 11.1–18.1) and the prevalence of current PTSD was 10.7% (95% CI 7.9–14.1, Table 1). Bivariate analysis suggested that PTSD (both lifetime and current) was most strongly associated with high lifetime trauma exposure, history of major depression, and history of reported sleep problems ($P < 0.001$).

The results for lifetime and current PTSD are shown in Table 2. As can be seen, the PCPS used alone had a sensitivity of 94.9% and a specificity of 78.1% in predicting lifetime PTSD, resulting in an AUC of 0.865 (95% CI 0.822–0.908). Adding the psychosocial predictors from the original NYPRS, including lifetime sleep disturbance, symptoms of depression, and access to health care, resulted in a sensitivity of 94.9% and a specificity of 78.7%, with a corresponding AUC of 0.902 (95% CI 0.873–0.930, bias corrected AUC = 0.889). This represents a significant improvement in the prediction model over the base model that included only the

Table 1 Patient variables by PTSD status (n = 412)

Study variables	% total (n)	Lifetime PTSD*			Current PTSD**		
		% yes (n)	% no (n)	*P* value	% yes (n)	% no (n)	*P* value
Gender							
Male	31.2 (128)	10.2 (13)	89.8 (115)	0.103	7.0 (9)	93.0 (119)	0.105
Female	68.8 (283)	16.3 (46)	83.7 (237)		12.4 (35)	87.6 (248)	
Age, years							
18–39	8.5 (35)	22.9 (8)	77.1 (27)	0.021	20.0 (7)	80.0 (28)	0.051
40–64	66.2 (272)	16.2 (44)	83.8 (228)		11.4 (32)	88.6 (241)	
65+	25.3 (104)	6.7 (7)	93.3 (97)		5.8 (6)	94.2 (98)	
Married							
No	38.0 (156)	19.9 (31)	80.1 (125)	0.013	14.1 (22)	85.9 (134)	0.081
Yes	62.0 (255)	11.0 (28)	89.0 (227)		8.6 (22)	91.4 (233)	
High school or less education							
No	50.4 (207)	14.5 (30)	85.5 (213)	0.936	9.2 (19)	90.8 (188)	0.313
Yes	49.6 (204)	14.2 (29)	85.8 (216)		12.3 (25)	87.7 (179)	
Income less than $30,000							
No	57.9 (238)	11.3 (27)	88.7 (211)	0.041	7.6 (18)	92.4 (220)	0.016
Yes	42.1 (173)	18.5 (32)	81.5 (141)		15.0 (26)	85.0 (147)	
Limited access to health care							
No	98.1 (403)	14.4 (58)	85.6 (345)	0.880	10.7 (43)	89.3 (360)	0.868
Yes	1.9 (8)	12.5 (1)	87.5 (7)		12.5 (1)	87.5 (7)	
High trauma exposure, ever							
No	78.8 (324)	10.8 (35)	89.2 (289)	<0.001	8.0 (26)	92.0 (298)	<0.001
Yes	21.2 (87)	27.6 (24)	73.4 (63)		20.7 (18)	79.3 (69)	
Major depression, ever							
No	61.1 (251)	2.0 (5)	98.0 (246)	<0.001	1.6 (4)	98.4 (247)	<0.001
Yes	38.9 (160)	33.8 (54)	66.2 (106)		25.0 (40)	75.0 (120)	
Sleep problems, ever							
No	34.3 (141)	2.1 (3)	97.9 (138)	<0.001	0.7 (1)	99.3 (140)	<0.001
Yes	65.7 (270)	20.7 (56)	79.3 (214)		15.9 (43)	84.1 (227)	

Notes: *Lifetime PTSD = 14.3% (95% confidence interval 11.1–18.1); **current PTSD = 10.7% (95% confidence interval 7.9–14.1).
Abbreviation: PTSD, post-traumatic stress disorder.

PCPS ($P < 0.0021$). Adding genotype resulted in a sensitivity of 94.9% and a specificity of 81.5%, with an AUC of 0.920 (95% CI 0.897–0.951, bias corrected AUC = 0.901). This also represents a significant improvement over the previous model that included the PCPS and the original NYPRS factors ($P = 0.0178$).

In predicting current PTSD, the PCPS alone had a sensitivity of 95.4% and a specificity of 95.4%, resulting in an AUC of 0.954 (95% CI 0.916–0.992). Adding key predictors from the original NYPRS, including sleep disturbance, depression symptoms, and access to health care, resulted in a sensitivity of 100.0% and a specificity of 93.2%, with an AUC of 0.982 (95% CI 0.972–0.992, bias corrected AUC = 0.975). This represents a nonsignificant improvement in the prediction model over the base model that included only the PCPS ($P < 0.0674$). Next, adding genotype to the prediction,

Table 2 Results using NYPRS prediction model with genotype added (n = 412)

	Cutoff score	% specificity	% sensitivity	PV+	PV−	AUC	AUC 95% CI	*P* value
Prediction model used: lifetime PTSD								
PCPS only	100	78.1	94.9	42.2	98.9	0.865	0.822–0.908	–
PCPS + NYPRS	166	78.7	94.9	42.8	98.9	0.902	0.873–0.930	0.0021
PCPS + NYPRS + genotype	219	81.5	94.9	46.4	99.0	0.920	0.897–0.951	0.0178
Prediction model used: current PTSD								
PCPS only	100	95.4	95.4	71.2	99.4	0.954	0.916–0.992	–
PCPS + NYPRS	192	93.2	100.0	63.8	100.0	0.982	0.972–0.992	0.0674
PCPS + NYPRS + genotype	215	95.6	100.0	73.3	100.0	0.989	0.981–0.997	0.0194

Abbreviations: NYPRS, New York PTSD Risk Score; AUC, area under receiver operating characteristic curve; PV+, predictive value of positive test; PV−, predictive value of negative test; PCPS, Primary Care PTSD Screener.

results in a sensitivity of 100.0% and a specificity of 95.6%, with an AUC of 0.989 (95% CI 0.981–0.997, bias corrected AUC = 0.984). This represents a significant improvement over the previous model that included the PCPS and the original NYPRS predictors ($P = 0.0194$).

Table 3 shows the PTSD risk score results in the form of regression-derived weights used to generate the classification results shown in Table 2. As seen, for lifetime PTSD, a positive score on the PCPS (ie, three or more positive items) is given a base score of 100 (otherwise 0) and the psychosocial measures are given weights relative to these results. These weights are then used to calculate a PTSD risk score. The last row of Table 3 shows the cutoff scores for a lifetime PTSD classification based on these risk score weights, ie, 100 for PCPS used alone, 166 for PCPS + NYPRS factors, and 219 for PCPS + NYPRS + genotype.

Examination of the specific weights for the lifetime model is informative. In the final lifetime PTSD model, a weight of 100 is given for screening positive on the PCPS. However, when combined with the NYPRS factors, a weight of 29 is given for having one symptom of depression and a weight

Table 3 Primary Care PTSD Screener and NYPRS weights without and with genotype risk information added

	PCPS only	PCPS + NYPRS	PCPS + NYPRS + genotype
Predictor variables*: lifetime PTSD			
Positive PCPS results	100	100	100
Psychosocial measures from NYPRS			
PHQ-2 = one symptom	–	29	33
PHQ-2 = two symptoms	–	40	50
Sleep disturbance (lifetime)	–	35	33
No regular health care	–	37	30
Genotype			
Risk allele score (0–6)	–	–	14
PTSD cutoff score	100	166	219
Predictor variables*: current PTSD			
Positive PCPS results	100	96	68
Psychosocial measures from NYPRS			
PHQ-2 = one symptom	–	53	38
PHQ-2 = two symptom	–	24	25
Sleep disturbance (current)	–	100	75
No regular health care	–	72	51
Genotype			
Risk allele score (0–6)	–	–	17
PTSD cutoff score	100	192	215

Notes: *PCPS with three positive items results in a score = 100, otherwise = 0 for lifetime PTSD for all prediction models. For current PTSD, a positive PCPS (ie, three items positive) results in a score of 100, 96, and 68, respectively, for the PCPS used alone, PCPS + NYPRS, and the PCPS + NYPRS + genotype, otherwise = 0.
Abbreviations: PHQ-2, Patient Health Questionnaire, 2-item version; PCPS, Primary Care PTSD Screener; PTSD, post-traumatic stress disorder; NYPRS, New York PTSD Risk Score.

of 40 is given for having two symptoms of depression (having no symptoms results in a weight of 0). Having a history of lifetime sleep disturbance, with a positive PCPS screen, results in a weight of 35, and not having a regular health care provider or access to health results in a weight of 37. As seen, in the final model with the PCPS and NYPRS factors, genotype results in a prediction weight of 14 for each risk allele present. Thus, a person with six risk alleles or more would receive a PTSD score of $14 \times 6 = 84$, the second highest score.

For current PTSD, the results are similar. Based on prediction results, a weight of 100 was given for the PCPS used alone, 192 for the PCPS + NYPRS factors, and 215 for the PCPS + NYPRS factors + genotype. Examination of the specific weights for the current PTSD prediction is also informative. In the final model, a weight of 100 is given for screening positive on the PCPS. However, when combined with the NYPRS factors, a weight of 96 is now given to the PCPS, 53 is given for having one depression symptom, and a weight of 24 is given for having two depression symptoms (no depression symptoms = 0). In addition, having current sleep disturbance, with a positive PCPS screen together with other NYPRS factors included, results in a weight of 100 for sleep disturbance, and not having a regular health care provider results in a weight of 72 (Table 3). As seen, in the final model with the PCPS and the psychosocial risk factors from the NYPRS, the genotype score results in a prediction weight of 17 for each risk allele present. Thus, a person with six risk alleles or more would receive a PTSD score of $17 \times 6 = 102$, the highest score for any of the predictors assessed.

Table 4 shows the classification improvements that are achieved by adding genotype risk information to the NYPRS prediction model. As can be seen, for lifetime PTSD, improvement in prediction is achieved by increased specificity. In the NYPRS model with the PCPS, 10 cases were reclassified as noncases when genotype was added to the model ($75 – 65 = 10$). For current PTSD, the results were similar, with a small but significant ($P = 0.0194$) improvement in prediction specificity detected ($25 – 16 = 9$). It is important to note that Pearson r correlations suggested that the genotype risk scores used were not associated with NYPRS measures ($P > 0.50$), indicating that the genotype assessed tends to add unique prediction information to the NYPRS measure.

Finally, using cross-tabular analyses, we assessed whether risk allele count (coded 0–6) was associated with being in the high trauma exposure category (coded yes = 1, no = 0) and found that these were not associated ($\chi^2 = 5.97$, df = 6,

$P = 0.427$, linear trend $P = 0.658$). Next, we cross-tabulated the allele count by PTSD status and found that this was significant ($\chi^2 = 12.93$, df = 6, $P = 0.044$, linear trend $P = 0.001$). Close examination of allele count by PTSD status suggested that a lower risk allele count was protective against onset of PTSD, given that the prevalence of PTSD among those with fewer than two risk alleles was very low (0%–4%) for both lifetime and current PTSD. Conversely, the prevalence of PTSD for those with 4+ risk alleles was typically 20% or higher.[12]

Discussion

We examined different clinical domains to evaluate prediction models that could be useful in predicting PTSD. Our overall goal was to develop a better PTSD prediction tool that was effective and could guide clinical interventions in different settings.[1] As suggested, based on extensive previous investigations, several prediction domains were identified, including core PTSD symptoms and psychosocial risk factors from the original NYPRS measure. Overall, the NYPRS alone also appeared to work very well in the current study. However, adding information on genotype risk to the NYPRS improved the prediction results.

Table 4 NYPRS classification without and with genotype information

	Gold standard		
	PTSD	**Non-PTSD**	**Total**
NYPRS model without genotype information – lifetime PTSD			
NYPRS ≥ 166	PTSD	56	75	131
(Table 3)	Non-PTSD	3	277	280
	Total	59	352	411
Sensitivity = (56/59) = 94.9%; specificity = (277/352) = 78.7%			
NYPRS model with genotype information – lifetime PTSD			
NYPRS ≥ 219	PTSD	56	65 ↓	121
(Table 3)	Non-PTSD	3	287	290
	Total	59	352	411
Sensitivity = (56/59) = 94.9%; specificity = (287/352) = 81.5%			
NYPRS model without genotype information – current PTSD			
NYPRS ≥ 192	PTSD	44	25	69
(Table 3)	Non-PTSD	0	342	342
	Total	44	367	411
Sensitivity = (44/44) = 100.0%; specificity = (342/367) = 93.2%			
NYPRS model with genotype information – current PTSD			
NYPRS ≥ 215	PTSD	44	16 ↓	60
(Table 3)	Non-PTSD	0	351	351
	Total	44	367	411
Sensitivity = (44/44) = 100.0%; specificity = (351/367) = 95.6%			

Abbreviations: NYPRS, New York PTSD Risk Score; PTSD, post-traumatic stress disorder.

Use of PTSD screeners in different health care settings has increased over the years.[1] Currently, the Department of Veterans Affairs and the Department of Defense are routinely using the PCPS in clinical practice to assess veterans and active duty personnel.[68] As has been noted, use of the NYPRS in clinical practice would likely require about 5 minutes or less for administration in most settings.[1] Given our current findings, clinicians might consider collecting genotype information in the future to confirm positive screening results, if further research supports our current findings. As shown, this genetic information appears to increase diagnostic specificity, which may be important before initiating treatment interventions. While this diagnostic improvement was small and more work needs to be done, as Table 2 shows, there was about a 10% improvement in the positive predictive value of the NYPRS when genotype was added to the prediction model. As noted, in the current PTSD model, with the PCPS and NYPRS psychosocial factors included, genotype results in a prediction weight of 17 for each PTSD risk allele present. Therefore, a person with six risk alleles or more would receive a PTSD score of $17 \times 6 = 102$, which is a relatively high prediction score. Noteworthy is that the prevalence of PTSD in our study sample was relatively low (<15%). For example, if the prevalence of current PTSD was closer to 20%, the predictive value of a positive test would be greater than 80%. Given the increasing convenience of genotyping and its decreasing cost, the NYPRS administered by a primary care provider with genotyping may be cost-effective in the future. This might be true following large-scale traumatic events or in more remote geographic regions where access to providers of mental health care is limited.

The current study has several strengths and limitations. A major strength was that our original psychometric validation study involved a large survey population and three validation studies, which included a total combined sample of 3298 subjects.[1] We also assessed a broad range of psychological and interpersonal risk factors using standardized instruments and medical testing methods in our original study.[1] Another strength of the study was that the interviewer neither knew the status of the PCPS screener nor any details of the PTSD interview for the patient. These data were coded at the end of the interview by study analysts. Thus, interviewer bias was limited. Potential study limitations include omission of individuals without a telephone and those who were institutionalized. Moreover, nonresponse bias could have affected our survey results.[1] In addition, in the current study, we did not predict future PTSD, which is often difficult.[39] Nevertheless, we have conducted prospective predictions of

PTSD using the NYPRS in the past and these models have worked well.[3] However, these prospective PTSD predictions did not include genetic information. This research is planned as part of a future study. Also, the study sample size in the current analysis was limited (n = 412) and drawn from a single region of the US, ie, central Pennsylvania. The current study was also comprised of Caucasians of European lineage. All these factors may have biased our findings. Finally, the genetic variants studied were limited to four candidate single nucleotide polymorphisms and, while statistically significant, their contribution to the NYPRS model was modest (eg, about 3% improvement in specificity). Given the complexity of behavioral genetics,[69] clearly more work is needed before clinical implementation can be recommended.

Despite these limitations, our study suggests that a screening instrument, the NYPRS (Genetic Version) may have utility in PTSD screening in the future. This screening instrument has good sensitivity and specificity. Adding genetic information appeared to improve PTSD specificity and, thus, reduced the inaccuracy of this screening. It is also noted that the genotype count assessed and the NYPRS score results without the genotype were not associated, based on examination of Pearson r correlations ($P > 0.5$). This suggests that the genotype measure adds unique information on prediction. Also, as noted above, our analyses indicated that individuals with fewer than two PTSD risk alleles appear resilient to PTSD, regardless of exposure to trauma, given that the risk allele count examined was not associated with exposure to trauma but was linearly associated with PTSD.[12] The fact that the genotype added anything at all to our PTSD prediction model, given the impact of the PCPS and the NYPRS alone, we think suggests that further research is warranted.

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Disclosure

The preliminary results of this study were presented at the 31st Annual Meeting of the Anxiety Disorders Association of America, New Orleans, LA, on March 26, 2011. Otherwise, the authors report no conflicts of interest in this work.

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Appendix
New York PTSD Risk Score (Genetic Version)

Primary Care PTSD Screener (asked for lifetime and previous 12 months)

1. Have you had repeated bad dreams or nightmares or had disturbing or unpleasant memories, thoughts, or images that kept coming into your mind whether you wanted to think of them or not?
2. Have you deliberately tried hard not to think about something that happened to you or went out of your way to avoid certain places or activities that might remind you of something that happened in the past?
3. Have you felt you had to stay on guard much of the time or unexpected noises startled you more than usual?
4. Have you felt cut off from other people, or found it difficult to feel close to other people, or you could not feel things anymore or you had much less emotion than you used to have?

Symptoms of depression (asked for lifetime)

5. Have you ever had a period of two weeks or longer when you were feeling depressed or down most of the day or nearly every day?
6. Have you ever had a period of two weeks or longer when you were uninterested in most things or unable to enjoy things you used to do?

Sleep disturbance (asked for lifetime and previous 12 months)

7. Have you had difficulty falling asleep or staying asleep?

Source of health care/regular doctor (asked for previous 12 months)

8. Do you have a regular doctor or a usual source of care that you can go to for routine medical care?
9. Count of PTSD risk-alleles located within *FKBP5*, *COMT*, *CHRNA5*, and *CRHR1* genetic loci (coded 0–6, see Table A).

Table A Single nucleotide polymorphisms in NYPRS risk allele prediction model

SNP	Gene	Chromosome (map location)	MAF (minor/common)	Functional annotation	PTSD risk allele counted
Marker specifications (NCBI build 37.1)					
rs16969968*	*CHRNA5*	15 (78882925)	35.0% (A/G)	Missense (D⇔N)	A
rs9470080**	*FKBP5*	6 (35646435)	33.0% (T/C)	Intron	T
rs4680*	*COMT*	22 (19951271)	49.5% (G/A)	Missense (V⇔M)	A
rs110402*	*CRHR1*	17 (43880047)	42.4% (A/G)	Intron	G

Notes: *Additive model code 0, 1, 2 for risk allele; **dominant model coded 0, 1 for the risk allele. Risk alleles counted were coded 0-6 from observed values 0–7, to normalize these data for analysis.
For additional specifications, see Boscarino et al.[12]
Abbreviations: PTSD, post-traumatic stress disorder; NYPRS, New York PTSD Risk Score; MAF, minor allele frequency.