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Posted Date: 8 November 2023

doi: 10.20944/preprints202311.0556.v1

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Genetic Psychophysiology and Markers of Resilience to Anxiety and Depression in Sports and Extreme Professions

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Abstract: Background: A personalized approach to occupational medicine allows specialists to prevent professional hazards such as stress-related depression and anxiety in extreme work environment. Objective: Herein, we aim to detect genetic markers of low resilience to stress. Methods: The study cohort included 97 elite athlete and 167 special forces personnel. The research team collected buccal mucosa samples and examined psychological status with the Hospital Anxiety and Depression Scale (HADS). We assessed 35 variants within selected genes that are most often associated with low resilience to stress, anxiety and depression. Fisher's Exact test was used to determine nonrandom associations between scores in HADS scale and the genetic variants. We also trained machine learning models to predict score values from genotyping findings and ranked genetic biomarkers according to their predictive power. Results: High-risk depression profiles included C/T genotype of *MTHF*R C677T and A/C variant of *MTHFR* A1298C. Susceptibility to anxiety was associated with several polymorphisms regulating neuroactive substances, immune response, and coagulation. The ML-models accurately detect depression or anxiety levels with MAE/ROV of 17.69±1.35 and 17.86±2.09% respectively. Conclusions: The study findings justify a polymorphic nature of anxiety and confirm the immune system involvement in regulating stress response.

Keywords: sports; psychogenetics; psychophysiology; elite athletes; stress-resistance; machine learning; extreme professions; depression; anxiety

1. Introduction

Genetic psychophysiology is a field of science with rapidly developing interdisciplinary research linking genetics, brain, and human behavior. Studies in this field can reveal stress-copying strategies and supply occupational medicine with markers of stress resistance which is an ability to manage work demands when individual psychological needs are not met within the profession [1]. Exposure to stressful events and failure to resist them is a primary causal factor of common mental disorders (CMDs) such as anxiety and depression [2]. Susceptibility to depression and anxiety reflects individual

 doi:10.20944/preprints202311.0556.v1

stress resistance. Studies on CMD management are challenging due to interpersonal variability in genes, environment and their impact on psychological traits. Identification of stress-resistance markers should include multifactorial analysis of gene-to-environment interaction in challenging conditions.

In extreme jobs, work-related stressors can provoke anxiety and depression [3]. Environmental stressors of professional sports include injuries, career dissatisfaction, physical overload, insecure employment and limited educational opportunities [4–11]. Therefore, nearly half of athletes seek for professional psychological help [10]. Injuries rate and severity correlate with CMD incidence among athletes [9,10]. After joint trauma, football players have a three times higher chance of developing distress [9]. A level of stress in sports is comparable to that in extreme professions, although stressors are different [12,13].

Commonly, mental disorders start from sport injuries and lead to mood disorders. Numerous studies confirmed a relationship between career dissatisfaction and CMD signs [11,14]. An increase in career satisfaction scores by one point notably reduces a chance of anxiety/depression (OR = 0.836) [11]. A multi-center study proved a link between anxiety/depression and stressors such as job dissatisfaction and adverse life events [14].

In military professionals, meaning in life is a strong predictor of depression and perceived stress. In the post 9/11 US veterans, higher life meaning after military service was predictive of lower stress at 6 months follow-up [15]. After combat, officers experienced shame and felt guilt, which led to depression and suicidal ideation [16]. A high incidence of suicidal ideation and attempts among military personnel justifies the importance of developing stress-preventive strategies.

Predisposition to depression and anxiety as well as low resilience to stress can be inherited. However, recent studies emphasize the importance of environment in developing certain psychological conditions [17]. Still, genetic mechanisms of stress resistance are not well understood due to its multifactorial nature, i.e., the detection of one mutation in one gene cannot explain the phenotypic plurality of CMD pathogenesis [18]. A one-to-one relationship between genotype and phenotype does not fully elucidate genetic modulation of the effect of stressors on mental status. Analysis of exogeneous factors may reveal gene-environment interaction which also impacts behavior [19,20].

The aim of this study was to identify genetic markers of stress resistance in athletes and people in extreme professions. Hypothetically, genetic polymorphisms attribute to the ability to manage work-related challenging conditions and one can predict compliance to psychological stress in the aforementioned professions.

To test the hypothesis, we focused on the following objectives:

- Identify biomarkers of depressed mood in athletes and people in extreme professions.
- Detect genetic determinants of elevated levels of anxiety in the studied population.
- Build models predicting scores in HADS subscales from genetic data.

2. Materials and Methods

2.1. Dataset Description

We recruited 97 high-performing athletes who practiced three categories of sports. The first category included complex coordination sports: acrobatics, gymnastics, fencing, freestyle, equestrian sports and pistol shooting. The cyclic sports based on the reviewing the stunt in a cycle comprised the second category: swimming, rowing, and athletics. Sports games were in the third group: football, field hockey, volleyball, and water polo. The mean age of male athletes was 24.77±4.28 years (n=56), and the everage age of female athletes was 27.95±6.31 years (n=41). We also recruited 167 male special forces employees of the same age group as the studied athletes.

 doi:10.20944/preprints202311.0556.v1

2.2. Methods

2.2.1. Psychological Assessment

Psychological status of athletes was assessed with *the Hospital Anxiety and Depression Scale* (HADS) - a short sensitive tool commonly used in occupational medicine for measuring anxiety and depression among workers who do not have any acute physical discomfort [21]. The HADS is a fourteen item scale, the total score is the sum of the 14 items. Each item on the questionnaire is scored from 0 to 3 and the total score ranges from 0 to 21. A cut-off point of 8/21 refers to depression or anxiety, which is mild if the score lies within the range of 8-10. In this scale, 11-14 points correspond to the moderate level of depression/anxiety and 15-21 points signal severe pathology [21].

2.2.2. Genotyping

We assessed 35 variants within selected genes that are most often associated with low resilience to stress, anxiety and depression. The targeted genotyping panel included genes regulating metabolism of neuroactive substances in the following brain systems:

- **Serotonergic system** regulates basic biological functions such as sleep, appetite, circadian rhythms, and cognition. Decreased serotonin activity is linked with depression, mania, anxiety disorders, suicidal ideantions and etc [22].
- **Dopaminergic system** spreads across the mesocortical, mesolimbic, and nigrostriatal pathways regulating multiple functions. The mesocortical pathway is involved in regulation of attention, executive function, and working memory. The mesolimbic pathway is important for motivation and reward processes. Planning and execution of motor function are processed in the nigrostriatal pathway [23].
- **Noradrenergic system** activates and facilitates cerebral blood flow, metabolism, and electroencephalographic activity. The system also improves adaptational plasticity, arousal, and vigilance. Noradrenergic dysfunctions are linked with a variety of psychiatric disorders including all forms of stress, addictions, anxiety, and depression [24].
- **Oxytocinergic system** regulates complex social cognition and behavior. Normal function of the system promotes healthy attachment, parental care, fear-reated bahaviour, social exploration and recognition [25]. A decreased level of oxytocin is commonly detected in patients with depression [26].
- **Gamma-aminobutyric acid-ergic (GABRA) system** consists of GABA receptors, GABA transporters , and glutamate decarboxylase which work as an inhibitory neurotransmitter and help in maintaining the normal functions of the central nervous system [27]. Alterations in this system are seen in patients with neurological diseases [28].
- **Neurotrophin family of growth factors** is a group of proteins responsible for development, survival and function of neurons in central and peripheral nervous systems [29].

We also studied several genetic variants that regulate two other systems:

- **Immune response**. Stress can exhaust the immune defense. For this reason, we also considered genes regulating cytokines as relevant to the study: strong immune protection increases stress resistance [30,31].
- **Blood coagulation**. Maladjustment to extreme physical exercises can disregulate the production and activation of coagulation factor, thus promoting microbleeding or thrombi formation [32–34].

2.2.3. Data Preprocessing

Categorical variables presenting allelic variants were converted into numbers with LabelEncoder function from Scikit-Learn framework, the encoding function prepared them for machine learning models [35]. The variables with less than 10% of missing values were replaced with median. We

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also trained an intermediate regression algorithm to predict the findings that were absent in a higher percentage of cases [36].

2.3. Study Methodology

Working on the first objective, we identified genetic biomarkers of susceptibility to depression in the studied group. We encoded allelic variants into a contingency matrix to investigate a relationship between genetic biomarkers and scores in HADS subscales [37]. The two-sided Fisher's exact probability test was used to claculate odds ratios for presence of a specific allele in people susceptible to depression [38]. Then, we resorted to The Fisher-Exact Hypothesis Test for determining a statistical significance of the results [39].

To address the second objective, we identified the effect of each genetic variant on developing anxiety. For this, we applied the same techniques as in the first objective.

To address the third objective we trained machine learning (ML) models to predict HADS scores from genetic biomarkers. At the time of the exploratory analysis, we revealed a non-linear relationship between genetic variants and results in HADS. For this reason, we decided to apply tree-like models to the study: Gradient Boosting Machine, CatBoost, LightGBM and XGBoost [40–42]. We trained the models in a cross-validation technique and retrieved performance metrics such as mean absolute error (MAE) and its proportion to the range of values (MAE/ROV %). The Kruskal-Wallis and Mann-Whitney tests were used to study statistical difference in the distributions of peformance among the models.

We applied a feature selection technique to show top informative predictors of depression and anxiety among the studied genetic polymorphisms. In this technique, the relative rank of predictors corresponds to nodes of the decision tree. The relative importance of each genetic polymorphism was assessed with respect to the predictability of the results in HADS [43].

3. Results

3.1. Genetic Susceptibility to Depression

The research did not show a strong association between the studied genetic variants and depression risk (see Tables 1–2). A chance of developing depression was higher in the carriers of *MTHFR* C677T C/T genotype and *MTHFR* A1298C A/C genotype: OR 0.29 and 0.33, respectively, p=0.05 (see Table 3). The *MTHFR* gene encodes a key regulatory enzyme in folate and homocysteine metabolism. A recent study also demonstrated a relationship between abnormal folate biosynthesis and risk for depressive disorders [44].

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Table 1. Relationship between scores in HADS subscalses and genetic variants responsible for neuroactive substances.

Genetic variant	Allele	HADS-D			HADS-A		
		OR	CI, 95%	p-value	OR	CI, 95%	p-value
SEROTONERGIC SYSTEM							
SLC6A4 5-HTTLPR	L/L	1.36	[0.53, 3.51]	0.64	1.06	[0.45, 2.51]	0.99
	L/S	0.60	[0.21, 1.72]	0.46	1.14	[0.48, 2.72]	0.82
	S/S	1.29	[0.37, 4.53]	0.72	0.62	[0.14, 2.70]	0.75
HTR2A rs6313	C/T	1.34	[0.52, 3.47]	0.64	0.39	[0.15, 0.98]	*0.05*
	C/C	0.78	[0.29, 2.13]	0.81	0.91	[0.37, 2.23]	0.99
	T/T	0.99	[0.19, 3.72]	0.72	4.82	[1.97, 11.78]	**0.001**
HTR2A rs7997012	A/G	0.69	[0.25, 1.89]	0.63	0.81	[0.33, 1.99]	0.82
	A/A	1.01	[0.37, 2.75]	0.99	1.45	[0.60, 3.50]	0.48
	G/G	1.46	[0.55, 3.85]	0.44	0.85	[0.32, 2.23]	0.81
HTR1A rs6295	C/G	0.92	[0.35, 2.40]	0.99	0.81	[0.33, 1.95]	0.67
	C/C	1.46	[0.55, 3.86]	0.44	1.33	[0.54, 3.28]	0.63
	G/G	0.71	[0.23, 2.21]	0.79	0.96	[0.36, 2.52]	0.99
DOPAMINERGIC SYSTEM							
COMT rs4680	A/G	0.83	[,0.32 2.17]	0.81	1.83	[0.71, 4.70]	0.27
	A/A	0.42	[0.09, 1.86]	0.38	0.15	[0.02, 1.17]	**0.04**
	G/G	2.22	[0.83, 5.91]	0.15	1.28	[0.48, 3.41]	0.60
COMT rs165599	A/G	0.52	[0.2, 1.38]	0.24	0.58	[0.24, 1.39]	0.28
	A/A	1.42	[0.56, 3.63]	0.47	1.46	[0.62, 3.44]	0.38
	G/G	2	[0.57, 7.02]	0.40	1.57	[0.46, 5.42]	0.45
DARPP-32 PPP1R rs3764352	T/T	0.73	[0.27, 2.01]	0.63	0.90	[0.35, 2.29]	0.83
	C/C	1.19	[0.26, 5.5]	0.69	0.43	[0.06, 3.35]	0.70
	C/T	1.3	[0.47, 3.58]	0.63	1.39	[0.55, 3.53]	0.50
DARPP-32 PPP1R rs879606	G/G	0.74	[0.25, 2.19]	0.62	1.29	[0.45, 3.7]	0.66
	A/A	0.99	[0.12, 8.01]	0.99	0.33	[0.02, 5.78]	0.45
	A/G	1.37	[0.46, 4.09]	0.61	1.01	[0.36, 2.85]	0.99
DARPP-32 PPP1R rs907094	A/A	0.89	[0.35, 2.27]	0.82	1.06	[0.45, 2.5]	0.99
	A/G	1.1	[0.42, 2.87]	0.81	1.22	[0.51, 2.92]	0.65
	G/G	1.08	[0.25, 4.74]	0.99	0.39	[0.05, 2.95]	0.71
DBH rs1108580	A/G	1.07	[0.41, 2.74]	0.99	0.9	[0.38, 2.16]	0.83
	A/A	1.31	[0.48, 3.58]	0.60	0.56	[0.18, 1.7]	0.46
	G/G	0.68	[0.22, 2.13]	0.60	1.78	[0.73, 4.3]	0.22
DBH rs1611115	C/C	1.35	[0.5, 3.67]	0.63	2.34	[0.84, 6.52]	0.12
	C/T	0.38	[0.11, 1.33]	0.13	0.57	[0.21, 1.57]	0.35
	T/T	3.35	[0.96, 11.68]	0.10	0.29	[0.017, 5]	0.39
DRD2 rs1800497	C/C	1.59	[0.51, 4.96]	0.60	0.34	[0.14, 0.81]	**0.02**
	C/T	0.72	[0.24, 2.22]	0.79	3.44	[1.48, 8]	**0.01**
	T/T	0.82	[0.04, 14.82]	0.89	0.67	[0.04, 12.02]	0.78
DRD2 rs6277	A/G	0.97	[0.38, 2.5]	0.99	0.99	[0.41, 2.36]	0.99
	A/A	1.93	[0.74, 5.01]	0.19	0.88	[0.33, 2.32]	0.99
	G/G	0.36	[0.08, 1.61]	0.26	1.17	[0.44, 3.08]	0.8
DRD2 rs6275	G/G	1.55	[0.59, 4.13]	0.48	1.22	[0.5, 2.97]	0.67
	A/A	0.59	[0.13, 2.63]	0.75	1.09	[0.35, 3.38]	0.77
	A/G	0.81	[0.29, 2.26]	0.81	0.76	[0.18, 3.42]	0.99
DRD4 rs1800955	C/T	2.04	[0.76, 5.43]	0.16	0.57	[0.23, 1.43]	0.28
	C/C	1.13	[0.39, 3.26]	0.79	0.45	[0.55, 3.6]	0.45
	T/T	0.27	[0.06, 1.21]	0.11	1.36	[0.21, 3.37]	0.48
NORADRENERGIC SYSTEM							
NET rs2242446	T/T	10.8	[0.29, 2.17]	0.64	0.55	[0.21, 1.43]	0.19
	C/C	0.51	[0.07, 4.00]	0.99	1.49	[0.41, 5.43]	0.47
	C/T	1.52	[0.56, 4.13]	0.46	1.57	[0.62, 3.98]	0.37
SLC6A2 rs5569	G/G	1.14	[0.43, 3.03]	0.82	0.92	[0.37, 2.28]	0.99
	A/A	1.20	[0.33, 4.36]	0.73	0.95	[0.27, 3.36]	0.99
	A/G	0.78	[0.28, 2.21]	0.81	1.12	[0.45, 2.8]	0.82
OXYTOCINERGIC SYSTEM							
OXTR rs53576	A/G	0.42	[0.14, 1.27]	0.15	0.52	[0.2, 1.38]	0.19
	A/A	1.99	[0.62, 6.39]	0.27	0.65	[0.14, 2.89]	0.75
	G/G	1.51	[0.56, 4.03]	0.47	2.19	[0.87, 5.52]	0.08
GAMMA-AMINOBUTYRIC ACID-ERGIC SYSTEM							
GABRA2 rs279858	C/T	0.5	[0.18, 1.39]	0.23	0.37	[0.14, 1]	*0.05*
	C/C	1.68	[0.57, 4.91]	0.36	2.68	[1.07, 6.74]	**0.04**
	T/T	1.39	[0.53, 3.68]	0.62	1.22	[0.49, 3.03]	0.65
GAD1 rs1978340	G/G	0.81	[0.3, 2.18]	0.81	0.7	[0.28, 1.77]	0.51
	A/A	1.25	[0.34, 4.52]	0.73	0.6	[0.13, 2.68]	0.75
	A/G	1.11	[0.41, 2.98]	0.81	1.74	[0.71, 4.27]	0.28
GAD1 rs3749034	G/G	0.86	[0.31, 2.43]	0.81	0.7	[0.26, 1.87]	0.51
	A/A	0.75	[0.09, 5.92]	0.99	3.41	[1.02, 11.4]	0.06
	A/G	1.25	[0.44, 3.54]	0.63	0.89	[0.32, 2.48]	0.89
NEUROTROPHIN FAMILY OF GROWTH FACTORS							
BDNF rs6265	C/C	0.85	[0.32, 2.23]	0.8	0.62	[0.26, 1.48]	0.35
	C/T	0.72	[0.24, 2.22]	0.79	1.9	[0.8, 4.5]	0.21
	T/T	2.88	[0.82, 10.03]	0.13	0.6	[0.08, 4.49]	0.99
TPH2 rs4570625	G/G	1.24	[0.47, 3.27]	0.81	1.38	[0.56, 3.37]	0.52
	G/T	0.99	[0.38, 2.58]	0.99	0.72	[0.29, 1.81]	0.65
	T/T	0.48	[0.03, 8.4]	0.61	0.95	[0.13, 7.13]	0.99

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Table 2. Relationship between scores in HADS subscalses and genetic variants responsible for coagulation.

Genetic variant	Allele	HADS-D			HADS-A		
		OR	CI, 95%	p-value	OR	CI, 95%	p-value
FGG rs2066865	C/C	0.94	[0.34, 2.56]	0.99	0.99	[0.39, 2.52]	0.99
	C/T	1.03	[0.36, 2.93]	0.99	0.78	[0.28, 2.16]	0.80
	T/T	1.18	[0.16, 8.94]	0.6	2.2	[0.51, 9.51]	0.28
FXI rs2036914	C/T	1.87	[0.64, 5.47]	0.33	3.31	[1.07, 10.23]	**0.03**
	C/C	0.7	[0.2, 2.48]	0.77	0.16	[0.02, 1.19]	0.06
	T/T	0.51	[0.11, 2.27]	0.54	0.65	[0.19, 2.28]	0.78
GP6 rs1613662	A/A	1.66	[0.37, 7.46]	0.75	4.51	[0.59, 34.41]	0.14
	A/G	0.68	[0.16, 2.99]	0.99	0.11	[0.01, 1.89]	0.13
	G/G	1.38	[0.07, 26.5]	3.61	0.33	[0.48, 26.99]	0.31

Table 3. Relationship between scores in HADS subscalses and genetic variants responsible for immune response.

Genetic variant	Allele	HADS-D			HADS-A		
		OR	CI, 95%	p-value	OR	CI, 95%	p-value
BCR rs3761418	A/A	1.79	[0.68, 4.69]	1.34	1.1	[0.47, 2.59]	0.99
	A/G	0.36	[0.11, 1.1]	0.09	0.74	[0.3, 1.8]	0.66
	G/G	2.11	[0.6, 7.38]	0.22	1.66	[0.48, 5.69]	0.43
FKBP5 rs1360780	C/C	1.59	[0.61, 4.18]	0.48	0.44	[0.17, 1.16]	0.12
	C/T	0.76	[0.29, 2]	0.64	2.32	[0.88, 6.14]	0.09
	T/T	0.48	[0.03, 8.4]	0.61	0.95	[0.13, 7.14]	0.99
IL1B rs1143643	C/T	0.69	[0.26, 1.78]	0.48	1.92	[0.78, 4.73]	0.19
	C/C	1.42	[0.55, 3.66]	0.46	0.37	[0.12, 1.13]	0.11
	T/T	1.09	[0.31, 3.83]	0.99	1.24	[0.41, 3.75]	0.76
IL1B rs16944	A/G	0.94	[0.35, 2.51]	0.99	0.65	[0.26, 1.63]	0.39
	A/A	1.34	[0.37, 4.89]	0.72	0.13	[0.01, 2.23]	0.16
	G/G	0.92	[0.34,2.53]	0.99	2.7	[1.08, 6.77]	**0.03**
IL6 rs1800797	A/G	0.89	[0.34, 2.32]	0.99	1.1	[0.46, 2.65]	0.99
	A/A	0.2	[0.03, 1.54]	0.14	0.16	[0.02, 1.22]	0.06
	G/G	2.3	[0.89, 5.94]	0.11	1.96	[0.81, 4.72]	0.15
IL6R rs2228145	A/A	1.34	[0.52, 3.45]	0.64	2.34	[0.93, 5.9]	0.08
	A/C	0.94	[0.36, 2.45]	0.99	0.42	[0.15, 1.16]	0.12
	C/C	0.45	[0.06, 3.4]	0.7	0.79	[0.18, 3.42]	0.99
FOLATE SYSTEM							
MTHFR C677T	C/C	1.52	[0.58, 3.98]	0.48	1.13	[0.48, 2.67]	0.83
	C/T	0.29	[0.08, 1]	*0.05*	0.86	[0.35, 2.1]	0.83
	T/T	3.36	[1.09, 10.35]	0.06	1.05	[0.24, 4.56]	0.99
MTHFR A1298C	A/C	0.33	[0.11, 1.02]	*0.05*	1.23	[0.52, 2.89]	0.66
	A/A	2.53	[0.96, 6.65]	0.09	0.88	[0.37,2.1]	0.83
	C/C	1.09	[0.31, 3.82]	0.99	0.85	[0.25, 2.94]	0.99

3.2. Inherited Predisposition to Anxiety

Several genotypes were associated with increased scores in the HADS-A subscale. In the serotonergic system, the *HTR2A* rs6313 T/T genotype was associated with anxiety (OR 4.82, p=0.001). In the dopaminergic system, the *DRD2* rs1800497 C/T genotype indicated an increased risk of anxiety

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and C/C genotype signaled a reduced risk (OR 3.44, p=0.01 vs OR 0.34, p=0.02). Careers of the *COMT* rs4680 A/A genotype also had more chances to feel nervousness due to professional stress (OR 0.315, p=0.04). The subjects who were homozygous for the C allele of *GABRA2* rs279858 had greater odds of developing anxiety (OR 2.68, p=0.04). In neurotrophin family of growth factors, noradrenergic and oxytocinergic systems, we failed to detect genetic markers of anxiety.

Allelic variants of coagulatory system genes exhibited a pronounced relationship with scores in HADS-A subscale. The *FXI* rs2036914 C/T genotype promoted susceptibility to anxiety (OR 3.31, p=0.03). The *IL1B* rs16944 G/G homozygotes had a high probability of anxiety (OR 2.70, p=0.03) (see Table 3). The study results prove the polygenic nature of susceptibility to CMDs, in particular to anxiety.

3.3. Prediction of Depression and Anxiety Levels in Sports and Extreme Professions

In psychology, an estimator's prediction can deviate largely from the desired outcome (or true scores). In the current study, a regression model reliably predicted the depression level with MAE/ROV of 16.7% (see Table 4). Computations of scores in the HADS-A scale were slightly more precise: MAE/ROV of the top-performing model reached the level of 16.55%. On average, the performance of ML algorithms predicting scores in both HADS subscales was almost equal, although the number of significant genetic associations was higher for HADS-A (see Figure 1).

Genes encodings components of serotonergic system were among top three predictors of scores in HADS-D and HADS-A scales. *HTR2A* rs6313 also provided the greatest odds ratio for the risk of anxiety (OR 4.82,p=0.001). A high perdictive power of the serotonergic genes reflects an important role of serotonin in mood regulation.

For selecting optimal features, we ranked genetic predictors of HADS scores according to the information gain value (Figures 2– 3). *HTR1A* rs6295 polymorpshism demonstrated the highest relative importance in predicting the depression level. A genetic marker of coagulatory system, *FXI* rs2036914, also contributed to the accurate prognosis of the depression level. The strongest predictor of anxiety was *HTR2A* rs6313. A set of genetic markers of the immune system were top-informative predictors of the HADS-anxiety score (*IL1B* rs1143643 and rs16944, *IL6* rs1800797). The findings justify the importance of considering genetic markers of immune and coagulatory systems while predicting stress resistance in athletes and military employees.

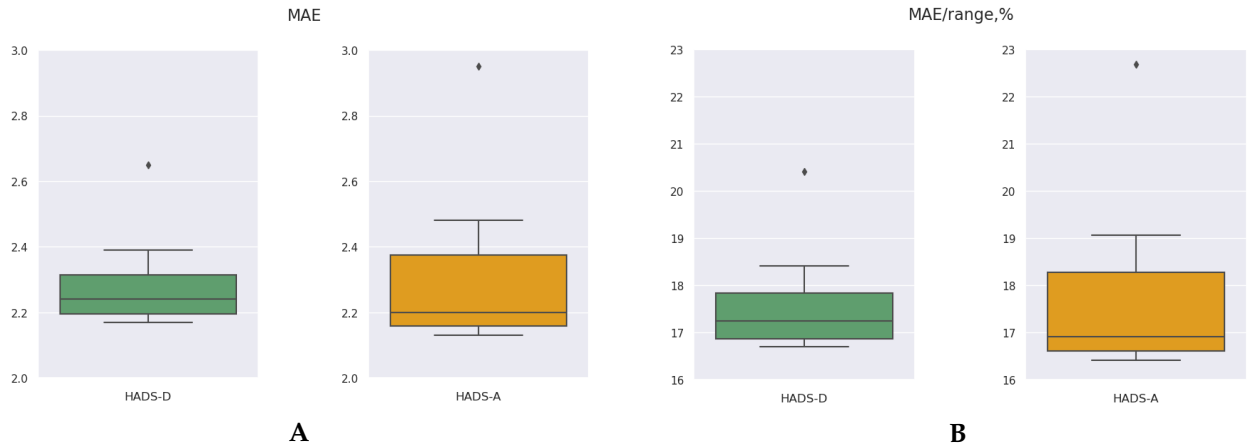

Figure 1. Metrics of models predicting HADS scores (**A**) and mean absolute error; (**B**) MAE/*ROV*,%

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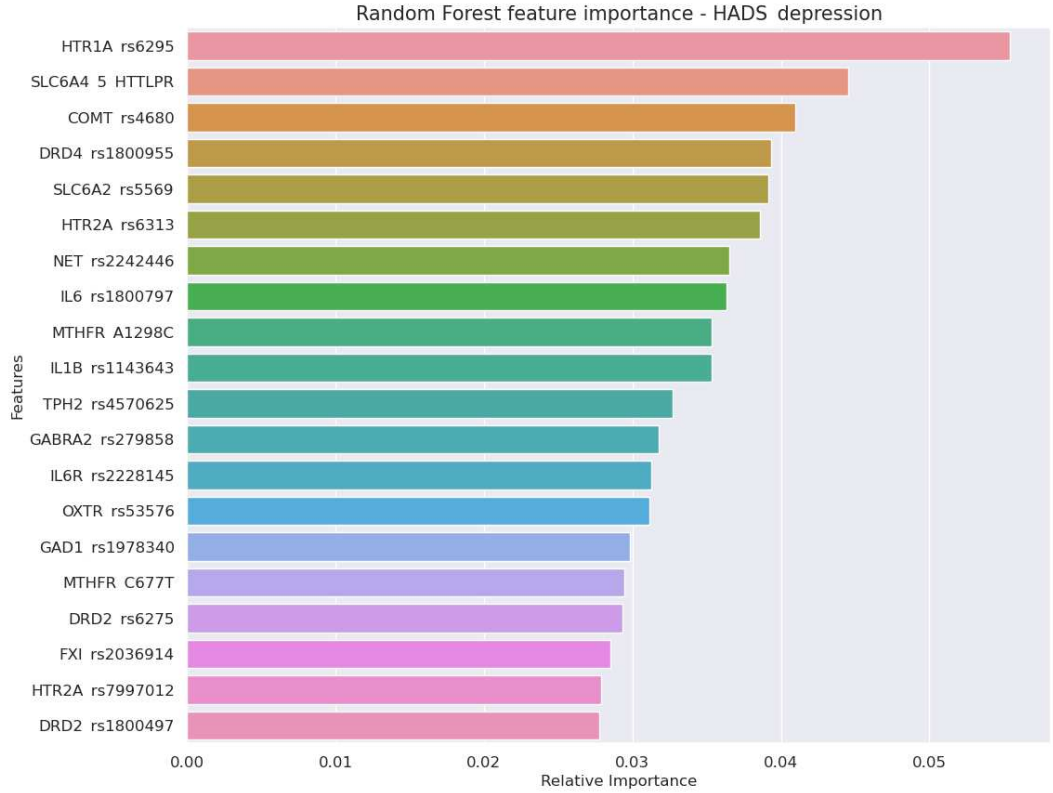

Figure 2. Feature importance in the Random forest model predicting scores in HADS-Depression

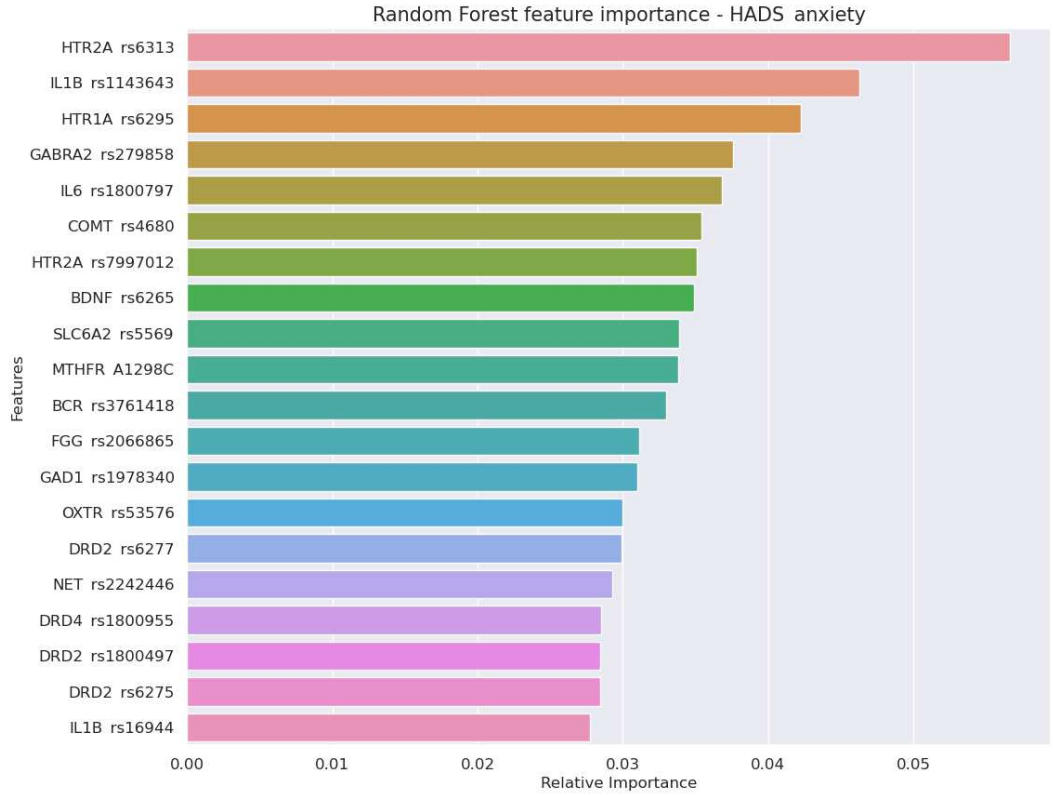

Figure 3. Feature importance in the Random forest model predicting scores in HADS-Anxiety

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Table 4. Performance of regression models predicting scores in HADS subscales

Model	HADS-Depression		HADS-Anxiety		p_{2-4}
	MAE (1)	MAE/ROV,% (2)	MAE (3)	MAE/ROV,% (4)	
CatBoost Regressor	2.26	17.37	2.18	16.76	
Random Forest	2.22	17.1	2.15	16.55	
LGBM Regressor	2.25	17.28	2.23	17.17	
Gradient Boosting	2.66	20.44	2.97	22.85	
XGB Regressor	2.37	18.23	2.38	18.28	
Theil-Sen Regression	2.29	17.64	2.48	19.06	
Lasso Regression	2.18	16.75	2.15	16.57	
Support Vector Regression	2.17	16.7	2.17	16.68	
Mean ± SD	2.30±0.18	17.69 ±1.35	2.32 ±0.27	17.86±2.09	0.5054

4. Discussion

4.1. Role of Genes and Environment in Liability to Stress

CMDs result from a complex interplay between genetic and environmental factors with a small contribution of each cofounder to disease development. Genes involved in CMD pathogenesis regulate sensory, affective and executive functioning as well as memory [45]. Although specific genetic variants has been considered as putative biomarkers for CMDs, the exact role of genes in developing these disorders has not been discovered yet [46].

Besides gene structure, researchers should also take into account gene expressions and epigenetic modifications. No consensus was reached on the association between common variants within the gene and CMDs [47], but scientists found that a change in *BDNF* expression may lead to depression or anxiety [47]. In adulthood, normal functioning of *BDNF* can minimize the risk for depression and lessen the effect of stressful life events. But the gene does not moderate the influence of childhood maltreatment [17]. This fact confirms a prominent role of environment in the disease occurrence.

Genetic factors can modulate physiologic response to stressful conditions in sports and extreme professions [48]. In an athletic career, occupation hazards include non-accidental violence [49], frequent injuries [50], discrimination [51], and low accessibility of mental healthcare. In military service, an increased stress level is associated with involvement in combat, witness of death, serious accidents, commitment to military service, demands for mental toughness, duty and honor [52]. Resilience to these environmental stressors depends on psychological, physiological, neurobiological, and genetic characteristics of an individual.

4.2. Association between Immune System and Stress-Resistance

Chronic stress damages the immune system and triggers CMDs [53]. A strong immune response can protect military employees and athletes against anxiety and depression. This stays in line with the current study. We explored genes responsible for the production of Interleukin-1β which regulates the interaction between the immune and central nervous systems. *IL1B* rs1143643 and *IL6* rs1800797 polymorphisms were the top predictors of anxiety in ML models constructed by us. Other researchers also showed that specific polymorphisms of *IL1B* gene may alter levels of the interleukin, and the dysfunction in cytokine synthesis induces anxiety, depression, and cognitive impairment [54].

Psychological response to stressors depends on the genotype and environment-genotype interaction. For example, the A allele of *IL1B* rs1143643 prevents anxiety in adults after a childhood trauma but it does not protect them against the development of low mood after recent negative life events [55]. A stressful environment is linked with epigenetic changes in the gene. The upregulation of *IL1B* was observed in military personnel suffering from post-traumatic stress disorder and in underage soldiers of the People's War in Nepal [56,57]. The *IL6* gene can influence the treatment effect of insomnia by antidepressants in military officers [58]. According to Milaneschi et al., stress duration and type determine the immune response to physical and mental pressure [59]. For instance, chronic

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anxiety and results in HADS-A subscale were associated with high global DNA methylation levels in the *IL6* gene. In contrast, another experimental study did not find any relationship between stress and changes in the *IL6* gene [60]. These findings reflect a complex interaction between environment, gemetic markers of immune system and stress-resistance.

4.3. Polygenic Nature of Stress Resistance

Several studies advocate that various psychological conditions are partially inherited and partly developed due to life experience [61]. Researchers managed to find genotypes responsible for such diseases. In line with these studies, the current article describes molecular mechanisms of resilience to stress and provides knowledge of inherited liability to CMDs.

CMDs occur due to metabolic and immunologic shifts induced by chemical imbalance at the synaptic, cellular, receptor, and molecular levels [62]. The changes are triggered by genetic disturbances which can be inherited [63,64]. The predisposition to mental disease is highly polygenic with impossibility to identify a single polymorphism responsible for a systemic damage or disease [65]. Numerous genetic variants contribute to molecular pathogenesis of CMDs, and genetic studies in psychology and psychiatry should cover a variety of SNPs. For this reason, we also targeted the genes coding regulation of the nervous system at different levels.

At the molecular level, we studied the genes involved in ligand biosynthesis, transport, degradation, transmission and transduction. Ligand is a general term for signaling molecules that bind specifically to other molecules, i.e., receptors. Molecular transformation and interaction can explain complex behavioral changes [66]. For example, a low expression of *COMT* gene can lead to psychological disorders because of hyperdopaminergic and hypercatecholestrogenic state [67]. A neurotransmitter imbalance may cause a range of mental diseases, including depression and anxiety. A change in *DRD4* gene controling the expression of the domamine receptor can lead to depression [68]. A mutation of *DBH* gene disrupts catecholamine synthesis and results in mental disorders due to a dysregulation of dopamine beta-hydroxylase, the enzyme that catalyzes the conversion of dopamine to norepinephrine [69].

At the cellular level, we investigated genes regulating neuronal development and plasticity. Brain plasticity is dependant on longevity of neurons and the growth of dendrites. The response to a stressful environment may be modulated by *BDNF* which is vital for neuronal survival [70].

At the systemic level, we targeted transporter genes maintaining healthy neuronal network activity. A hyperactivation of sympathetic system may promote fear and anxiety [71]. Serotonin release into the hypothalamus stimulates sympathetic nerves, therefore specific polymorphisms of serotonin transporter *SLC6A2* are associated with depression and suicidal ideations [72]. Future advances in genetic psychophysiology may explain how the molecules that make up cells and systems determine individual behavior.

Conclusions

- Study findings justified a polygenic nature of stress resistance among people in extreme professions. Elevated levels of anxiety were associated with genes regulating the serotonergic, dopaminergic, GABRA-ergic systems, coagulation, and immune response. A chance of developing depression was higher in the carriers of *MTHFR* C677T C/T and *MTHFR* A1298C A/C genotypes.
- We found almost equal performance of ML algorithms predicting scores in HADS-Depression and in HADS-Anxiety subscales (17.69$\pm$1.35 vs 17.86$\pm$0.27 respectively), although the number of significant genetic associations was higher for HADS-Anxiety.
- Genes encoding serotonergic system - textitHTR1A and *HTR2A* - were among top three predictors of scores in HADS-D and HADS-A scales. *HTR2A* rs6313 also provided the greatest odds ratio for the risk of anxiety (OR 4.82,p=0.001). A high perdictive power of the serotonergic genes reflects an important role of serotonin in mood regulation.

 doi:10.20944/preprints202311.0556.v1

- A set of genetic markers of the immune system were top-informative predictors of the HADS-anxiety score (*IL1B* rs1143643 and rs16944, *IL6* rs1800797). The findings justify the importance of considering genetic markers of immune and coagulatory systems while predicting stress resistance in athletes and military employees.

Author Contributions: Conceptualization, I.M. and Y.S.; Methodology, Y.S.; Software, A.R.; Validation, I.M., N.S., D.S. and Y.S.; formal analysis, A.R.; investigation, T.T. and D.S.; data aquisition and curation, I.C., E.S. and N.S.; writing—original draft preparation, D.S.; writing—review and editing, Y.S.; visualization, A.R.; supervision, M.L.; project administration, I.M.; funding acquisition, M.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research is supported by ASPIRE, the technology program management pillar of Abu Dhabi's Advanced Technology Research Council (ATRC), via the ASPIRE Precision Medicine Research Institute Abu Dhabi (ASPIREPMRIAD) award grant number VRI-20-10.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of The Republican Scientific-Practical Center for Sports in Minsk (protocol code 20171886, year 2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ACE	angiotensin I converting enzyme
ACTN3	actinin alpha 3
AST	attention study technique
BCR	breakpoint cluster region
BDNF	brain-derived neurotrophic factor
CMD	common mental disorders
CNS	central nervous system
DARPP-32	dopamine- and cAMP-regulated phosphoprotein with an apparent Mr of 32,000
DRD2	dopamine receptor
FKBP51	FK506-binding Protein 51
GABRA2	gamma-aminobutyric acid type A receptor subunit alpha 2
HADS	hospital anxiety and depression scale
HTR1A	5-hydroxytryptamine receptor 1A
HTR2A	5-hydroxytryptamine receptor 2A
MAE	mean absolute error
MAE/ROV	mean absolute error / range of values
ML	machine learning
MTHFR	methylenetetrahydrofolate reductase
NET	norepinephrine transporter
SLC6A2	solute carrier family 6 member 2
SNP	single nucleotie polymorphysm
TPH2	tryptophan hydroxylase-2

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 doi:10.20944/preprints202311.0556.v1

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