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SPECIFICATION OF GENETIC-BASED SYSTEMIC MANIFESTATIONS OF HUMAN TENDENCY TO AGGRESSIVE, SUICIDAL AND ADDICTION BEHAVIOR

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A study was carried out on the genetic conditionality of the systemic manifestation of a person's tendency to aggressive, suicidal and addictive behavior. As a result of a study involving 150 men and 150 women, systemic connections between risk indicators of aggressive, suicidal and addictive behavior with the following SNPs were determined: rs1800497 (DRD2), rs6280 (DRD3), rs1851048 (CACNA2D3-1), rs6777055 (CACNA2D3-2), rs4680 (COMT), rs2562456 (ZNF-LD), rs6923492 (GRM1). An information table has been developed that specifically reflects the connections between the genotypes of the identified polymorphisms and the presence and direction of their influence on the studied vectors of deviant behavior.
Keywords: SNP, genotypes, genetics of aggressive behavior, genetics of suicidal behavior, genetics of addictive behavior.

INTRODUCTION

As is known, any forms of complex, including deviant, behavior are formed under the influence of a complex of biological, psychological, social, natural and man-made factors. Moreover, the entire set of endogenous factors is certainly determined by many genes that interact systematically and ensure stable manifestations of a person's phenotypic characteristics, potentially predetermining his tendency to certain forms of deviant behavior [1]. Individual sets of genetic and phenotypic characteristics demonstrate the stability of the propensity for certain deviations in a particular person throughout his life, despite the fact that the peak of behavioral deviations occurs in adolescence [2].

The current state of research into the genetic determination of individual sets of behavioral deviations confirms the advisability of further searching for the genetic foundations of the systemic formation of various vectors of deviant behavior. A number of works present systemic connections between sets of genetic and phenotypic factors in the complex manifestation of behavioral deviations. Thus, the studies of E.A.D. Clifton et al. (2018) and J. Tiebeek et al. (2022) substantiate the systematic genetic determination of indicators of social behavior, mental health, physical well-being, addictiveness, cognition,

level of education, reproductive characteristics [3, 4]. L. R. Karlsson et al. (2019) summarized evidence of shared genetic influences on measures of risk tolerance and risky behavior [5]. M. A. Spano et al. (2023) found a negative correlation between genetically determined risky behavior (smoking, drinking alcohol, lack of physical activity) and the desire for education [6].

Previously conducted own studies revealed stable combinations of phenotypic indicators (high level of general nonspecific reactivity of the organism, excitability, anxiety, depression, adventurousness, affectiveness, neuroticism, irritability), which are complexly correlated with aggressive, suicidal and addictive behavior. These behavioral deviations are the basis of social and criminal tension in society, which justifies the need for further study of their etiology.

As a result of summarizing our own research [7–11] and the latest data from the scientific literature [12–16], the following candidate genes and corresponding polymorphisms were identified, systemically associated with phenotypic signs of a person's tendency to aggression, auto-aggression and chemical addictions: DRD2 (rs1800497), DRD3 (rs6280), CACNA2D3-1 (rs1851048), CACNA2D3-2 (rs6777055), COMT (rs4680), ZNF-LD (rs2562456), GRM1 (rs6923492).

The purpose of our study was to characterize the genetic determination of the systemic manifestation of a person's tendency to aggressive, suicidal and addictive behavior.

MATERIALS AND METHODS

The study involved 300 clinically healthy men and women 18–25 years old, representatives of the Caucasian race, indigenous residents of three regions of the European part of Russia: Arkhangelsk region, Volgograd region, Republic of Crimea. For the study, we selected students from state universities who were brought up in a complete, socially prosperous family, without financial and everyday problems, and without chronic somatic and neurological diseases. Все работы проводили анонимно, в апреле-мае 2023 года. All studies were conducted anonymously in April-May 2023. The principles of the Universal Declaration of Bioethics and Human Rights (Articles 4 (benefit and harm), 5 (autonomy and individual responsibility), 6 (consent) and 9 (privacy and confidentiality) were observed [4].

The psychological status of the study participants was determined by assessing the Freiburg Multifactor Personality Inventory – FPI (I. Farenberg, H. Zarg, R. Gampel) [17]; character accentuations (K. Leonhard [18]); suggestibility, frustration, irritability and resentment (V. V. Kozlov et al. [19]); adventurousness (A. Chichin [20]); behavioral, social, professional, economic, political activity and social destructiveness (Yu.A. Shatyr et al. [21]); type of behavioral activity (cardiotype) A–B (V. V. Delarue and F. A. Tambieva [22]). The tendency to auto-aggression was determined according to the method of T.N. Razuvaeva, the severity of suicidal ideation was assessed using the suicidal ideation module of the Columbia Suicidal Severity Scale (C-SSRS) [23]. To assess the behavioral status associated with chemical addictions, the experience and frequency of alcohol consumption, smoking and drug use were identified through a survey.

Laboratory genetic research of biological material was carried out by real-time polymerase chain reaction (PCR) method using kits produced by Synthol (Russia) and a real-time amplifier RotorGene 6000 (Corbett Research, Australia). Genomic DNA was isolated from buccal epithelium by adsorption onto magnetic particles. The following polymorphisms were studied that are promising in relation to aggression, autoaggression and chemical addictions: rs1800497 (DRD2), rs6280 (DRD3), rs1851048 (CACNA2D3-1), rs6777055 (CACNA2D3-2), rs4680 (COMT), rs2562456 (ZNF-LD), rs6923492 (GRM1).

To perform statistical analysis, the pandas, matplotlib.pyplot, phik, numpy, seaborn, scipy packages of the Python programming language were used. Correlation analysis was performed using the Phi K Correlation and Global Correlations method with the calculation of coefficients ϕk and gk. Comparison of polymorphisms was performed using a nonparametric method – the Kruskal-Wallis test.

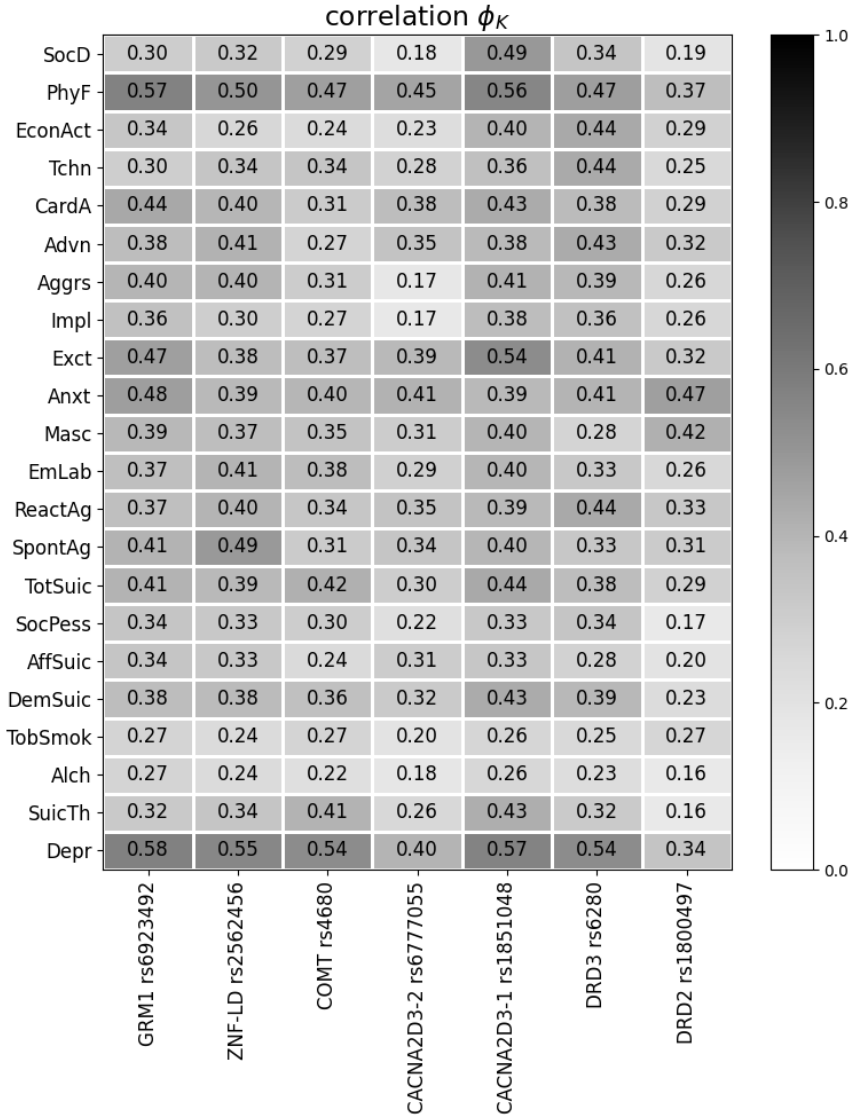
RESULTS AND DISCUSSION

To identify the main, most pronounced systemic connections between indicators of the risk of developing aggression, auto-aggression and chemical addictions with the analyzed polymorphisms, global correlation coefficients were calculated for the entire sample population of subjects. Only indicators that had a statistically significant relationship with at least one polymorphism under study were taken into account (Figure 1).

The next stage of the study was devoted to a comparative analysis of the severity of risk indicators for the development of aggression, auto-aggression and chemical addictions between groups of subjects with different genotypes for each polymorphism studied. Indicators that showed statistically significant differences or trends towards statistically significant differences ($p<0.1$) between the genotypes of the analyzed SNP were selected for the final accounting. The results of the study are presented in Figures 2, 3, 4, 5, 6, 7, 8.

It is known from the literature that the minor allele of the rs1800497 polymorphism (T allele) is associated with a reduced number of dopamine binding sites in the brain and presumably determines the presence of alcohol and nicotine addiction, as well as predisposition to a number of neuropsychiatric disorders, including eating disorders [24–26]. The highest risk of alcohol dependence was identified in the C/T genotype, along with the risk of obesity and suicidal tendencies [27]; the T/T genotype has a higher risk of developing attention deficit hyperactivity disorder, less pronounced pleasure reactions, and a higher likelihood of developing depression, while the C/C genotype, along with a high probability of developing alcohol dependence, has a risk of developing attention deficit hyperactivity disorder, along with a high level of emotional intelligence [14, 16].

The presented data from the experimental study (Figure 2) confirmed the connection of the T allele with nicotine addiction, but the connection of the C/C genotype with alcoholism was not determined. At the same time, in the C/C genotype variant (“major” or the most common in the European race) was revealed the minimal severity of systemic manifestations of indicators of aggressiveness, antisocial behavior and tobacco consumption in relation to the S/T variant.



Rice. 1. Correlation coefficients Phi K of the analyzed polymorphisms with risk indicators of developing aggression, auto-aggression and chemical addictions

A.M.F. Pego et al. (2020) found an association between the T/C and C/C rs6280 genotypes with drug addiction, as well as with a predisposition to risky behavior, including aggressive behavior [28]. C. Zhao et al. (2016) revealed a relationship between rs6280 and social conformity: it was found that in individuals with the genotype variant of the C/C polymorphism, which is characterized by increased release of dopamine in the striatum, susceptibility to social influence is more pronounced relative to individuals with genotypes C/T and T/T [29].

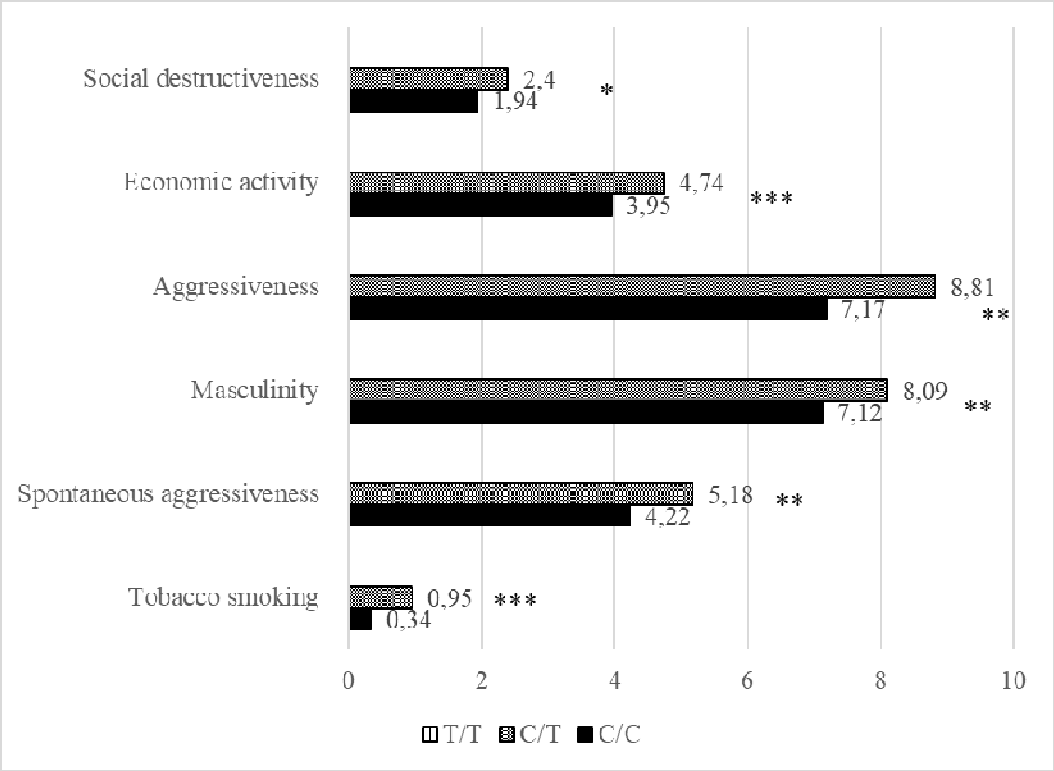
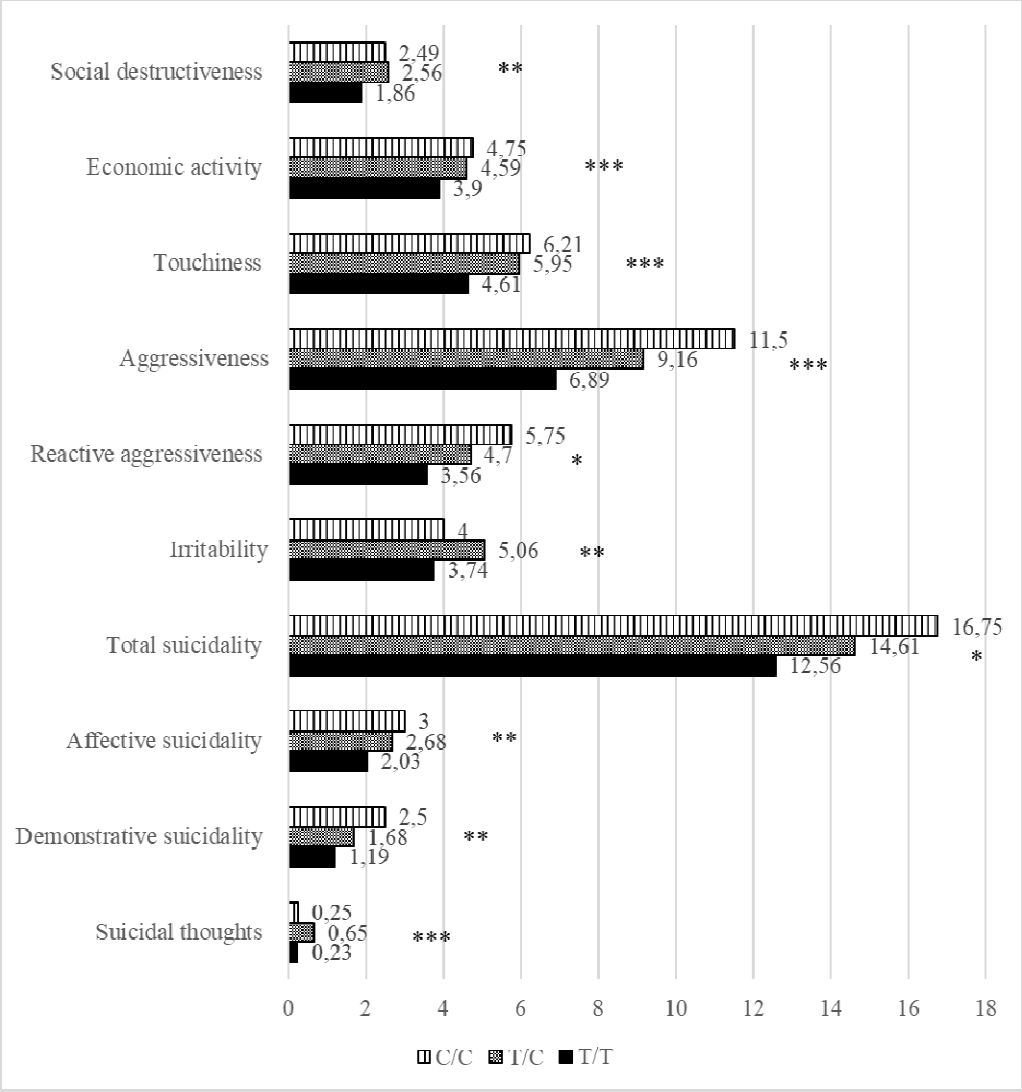


Fig. 2. The severity of indicators of a person's propensity to aggression, suicide and chemical addictions in various genotypes SNP rs1800497 (DRD2)
Note: T/T genotype is not included in the sample; * – p ≤0,1;** – p≤0,05; *** – p≤0,001

The results of the experimental study (Figure 3) confirm the influence of the T/C and C/C genotypes on a person's tendency to aggressive behavior. Susceptibility to the social environment among representatives of the C/C genotype is high, the level of their demonstrative suicidality against the background of a low level of suicidal ideas. At the same time, in the variant of the T/T genotype ("major" or the most common in the European race) the minimum severity of the systemic manifestation of indicators of aggressiveness, suicidality, irritability and resentment is determined.

SNP rs1851048 of the CACNAD3-1 gene is the least studied in relation to the systemic connections of its genotypes with aggressive, suicidal and addictive behavior. Single studies in this direction demonstrate an indirect connection of rs1851048 with risky behavior [30–32].

The results of the undertaken experimental study (Figure 4) first demonstrated systematic relationships between risk indicators for the development of aggression, auto-aggression and chemical addictions with rs1851048 genotypes. In general, the positive influence of the major G/G genotype on the entire range of behavioral, functional and psychological grounds for the minimal risk of aggressive, suicidal and addictive actions in humans is confirmed.



Rice. 3. The severity of indicators of a person's propensity to aggression, suicide and chemical addictions in different genotypes SNP rs6280 (DRD3)
Note: * – p ≤0,1;** – p≤0,05; *** – p≤0,001

Based on the literature, SNP rs 6777055 CACNA2D3-2 is associated with depression, neuroticism, and emotional lability [33]. Однако, информация в отношении системных связей его генотипов с агрессивным, суицидальным и аддиктивным поведением в доступных источниках отсутствует. However, information regarding the systemic connections of its genotypes with aggressive, suicidal and addictive behavior is not available in available sources. Overall, CACNAD3-1 and CACNA2D3-2 are considered to be genes associated with a wide variety of neurological and neuropsychiatric disorders, including depressive disorders [34].

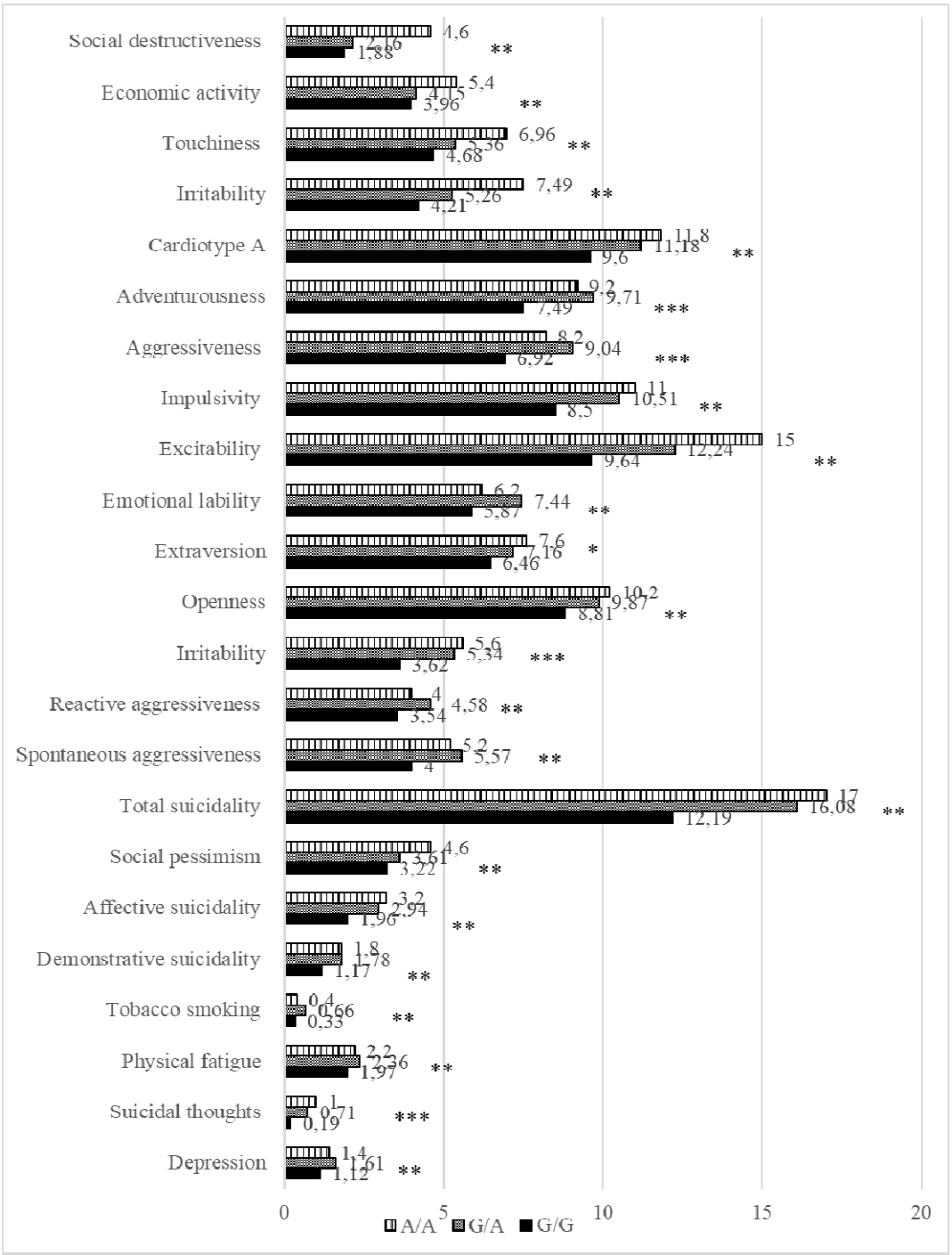


Fig. 4. The severity of indicators of a person's propensity for aggression, suicide and chemical addictions in various genotypes SNP rs1851048 (CACNA2D3-1)
Note: * – p ≤0,1;** – p≤0,05; *** – p≤0,001

The presented results of the experimental study (Figure 5) to a greater extent demonstrate the connection of the minor genotype C/C rs 6777055 with a pronounced tendency to aggressive behavior, against the background of a minimal risk of suicidality and manifestations of aggressiveness in representatives of the A/A genotype.

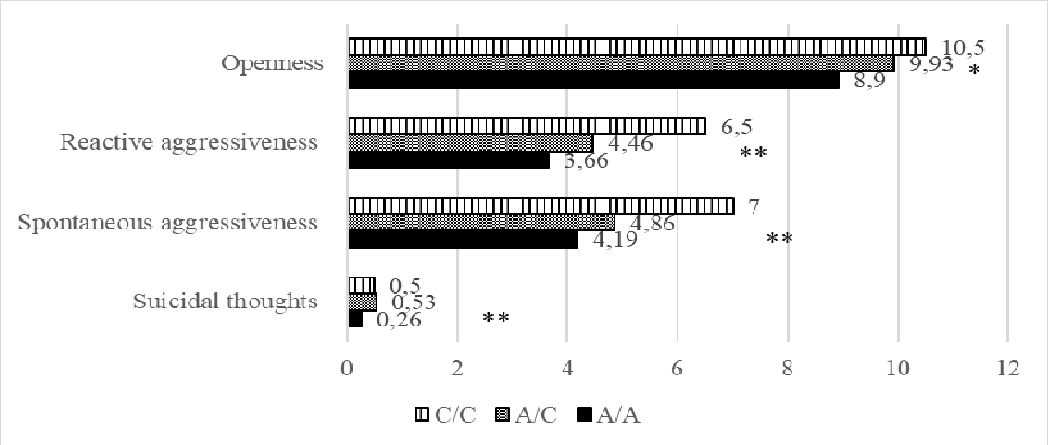


Fig. 5. The severity of indicators of a person's propensity to aggression, suicide and chemical addictions in various genotypes SNP rs6777055 (CACNA2D3-2)
Note: * – p ≤0,1;** – p≤0,05

M. Kaminskaite et al. (2020) found an association of rs4680 with the risk of alcohol dependence [35]. The G (Val) allele increases the risk of depression. Individuals with the G/G genotype are found to have a predisposition to risky behavior, higher levels of depression, a tendency to obesity and type 2 diabetes, as well as to consume foods rich in fat. For the G/A genotype (the most common heterozygous polymorphism in the population), an average level of predisposition to risky behavior was noted, and for the A/A genotype, more persistent associations with bulimia nervosa, anxiety, risk avoidance, as well as a higher level of emotional intelligence were noted [36–38].

The results of the experimental study (Figure 6) confirm the influence of the G/G genotype on a person's tendency to engage in risky behavior, due to a high level of social destructiveness, irritability, aggressiveness and suicidality. The role of the A/A genotype in the formation of anxiety and minimization of risk behavior, including those caused by low levels of psychoactive substance consumption, has been confirmed.

As follows from the literature data, among the possible rs2562456 genotypes, the A/A genotype in men has a statistically significant connection with such indicators of psychological status as balance and masculinity. In women with the G/G genotype, a statistically significant relationship with the pain sensitivity threshold was revealed [32, 39]. This indirectly indicates the positive impact of these genotypes (A/A and G/G) on a person's psycho-emotional state and minimization of risky behavior factors.

The presented results of the experimental study (Figure 7) do not confirm the positive relationship of the A/A genotype with masculinity in the general sample of men and women. For the first time, in relation to representatives of the A/G genotype, the

maximum severity of irritability, impulsivity, as well as affective, demonstrative and general suicidality was revealed. Against this background, the minimum values of the systemic manifestation of indicators of aggressiveness and suicidality are characterized by persons with the A/A genotype.

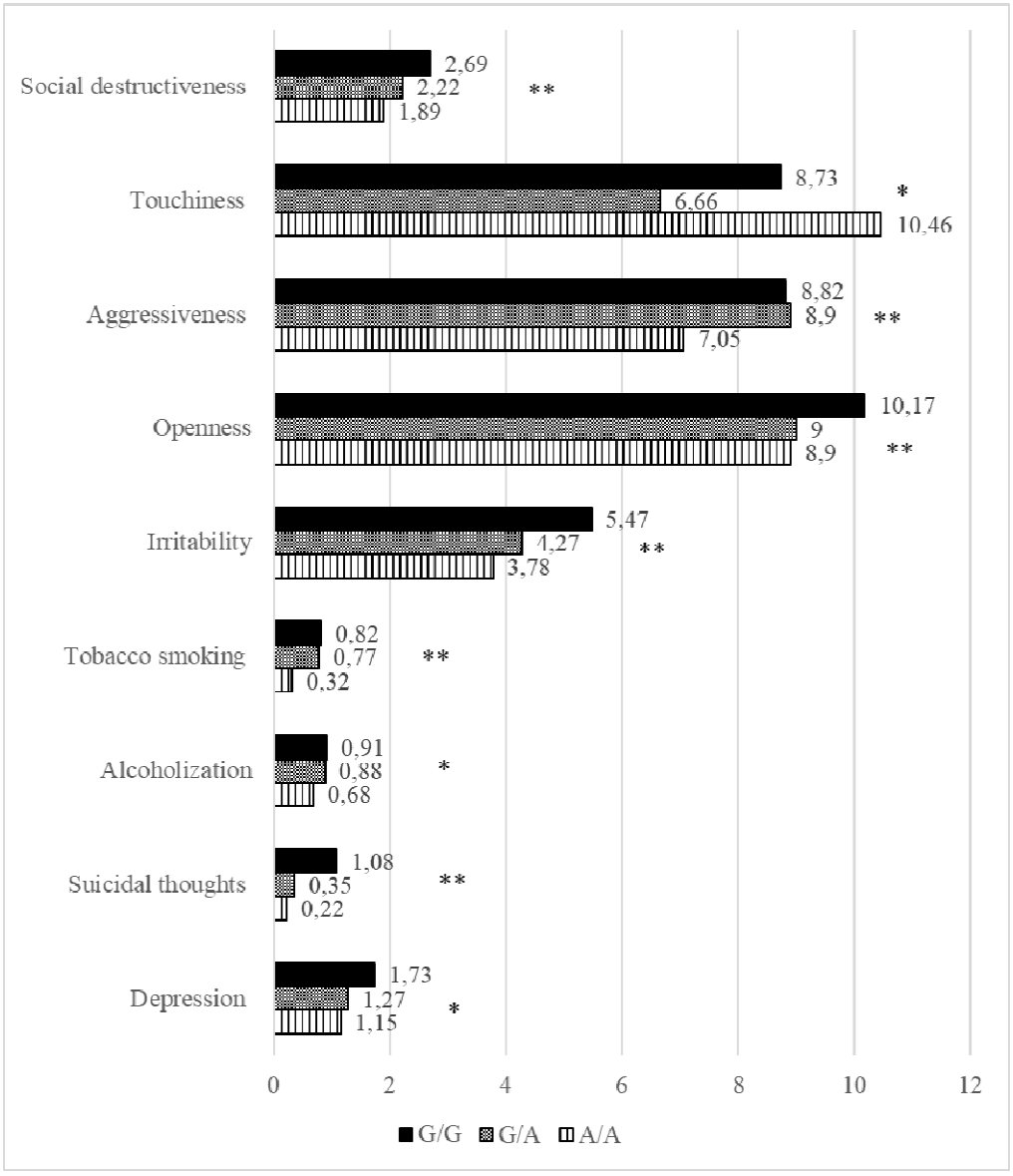


Fig. 6. Expression of indicators of human propensity to aggression, suicide and chemical addiction in various genotypes of SNP rs4680 (COMT)
Note: * – p ≤0,1;** – p≤0,05

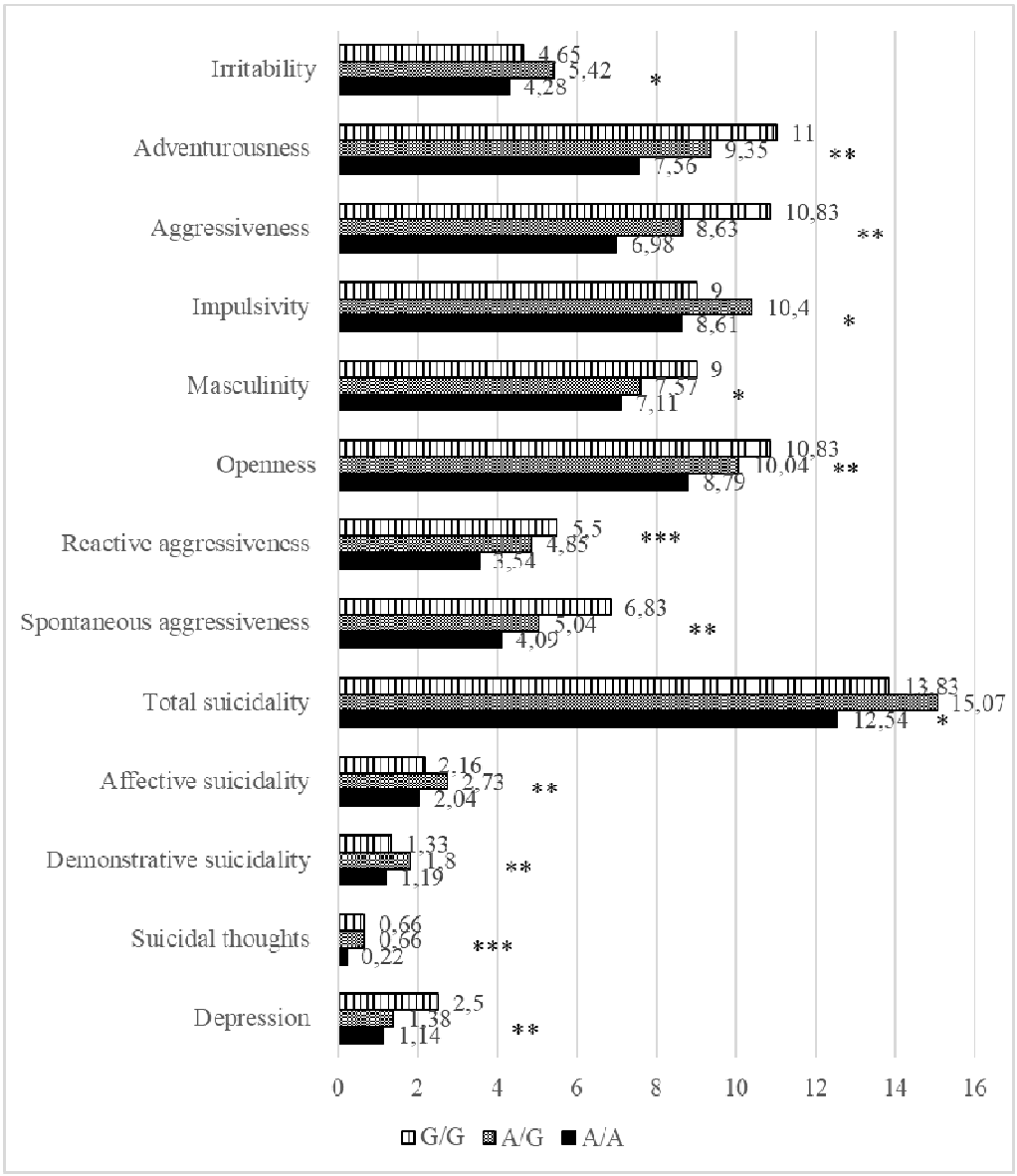


Fig. 7. The severity of indicators of a person's propensity to aggression, suicide and chemical addictions in various genotypes SNP rs2562456 (ZNF-LD)
Note: * – p ≤0,1;** – p≤0,05; *** – p≤0,001

There is limited data on SNP rs6923492 of the GRM1 gene that substantiates its association with prenatal risk factors for the development of attention deficit disorder and autism spectrum disorders [40, 41]. Its influence on the development of externalizing behavior (challenging behavior), on learning disorders, and in adult life on mood

disorders, the development of anxiety, and the demand for psychoactive substances has been shown [15, 42, 43].

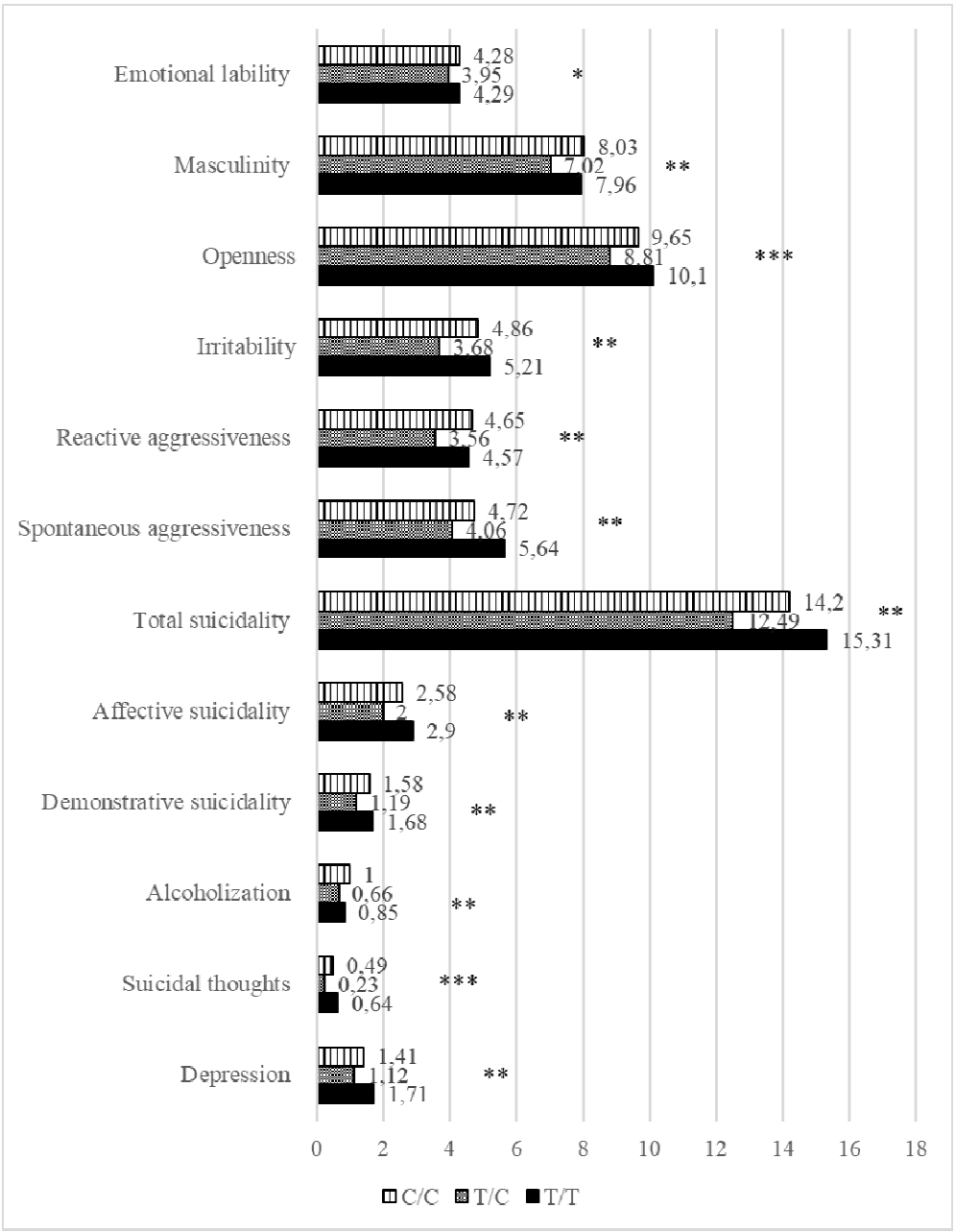


Fig. 8. The severity of indicators of a person's propensity for aggression, suicide and chemical addictions in various genotypes SNP rs6923492 (GRM1)
Note: * – p ≤0,1;** – p≤0,05; *** – p≤0,001

The presented data from the experimental study (Figure 8) for the first time shows the systematic relationships between risk indicators for the development of aggression, auto-aggression and chemical addictions with rs923492 genotypes. In general, the positive influence of the heterozygous T/S genotype on the entire range of behavioral, functional and psychological grounds for the minimal risk of aggressive, suicidal and addictive actions in humans has been proven.

Based on the results of the analysis of the potential role of the identified single nucleotide polymorphisms in the formation of the phenotypic prerequisites for a person's systemic tendency to aggressive, suicidal and addictive behavior, the genotypes of the presented SNPs were characterized by the presence and direction of their influence on the studied vectors of deviant behavior (Table).

Table

Genotypic characteristics of the systemic manifestation of a person's tendency to aggressive, suicidal and addictive behavior

SNP (gene)	Genotype	Deviations		
		Aggressiveness	Suicidalness	Addictiveness
1800497 (DRD2)	C/T	(+)	(0)	(+)
	T/T	no data	no data	no data
	C/C	(-)	(0)	(-)
6280 (DRD3)	T/C	(0)	(0)	(0)
	C/C	(+)	(+)	(0)
	T/T	(-)	(-)	(0)
1851048 (CACNAD3-1)	A/A	(0)	(+)	(0)
	G/G	(-)	(-)	(-)
	G/A	(+)	(0)	(+)
6777055 (CACNA2D3-2)	A/A	(-)	(-)	(0)
	C//C	(+)	(0)	(0)
	A/C	(0)	(+)	(0)
4680 (COMT)	G/A	(+)	(0)	(+)
	G/G	(0)	(+)	(+)
	A/A	(-)	(-)	(-)
2562456 (ZNF-LD)	A/A	(-)	(-)	(0)
	G/G	(+)	(0)	(0)
	A/G	(0)	(+)	(0)
6923492 (GRM1)	C/C	(+)	(+)	(+)
	T/C	(-)	(-)	(-)
	T/T	(+)	(+)	(+)

Note: (+) – positive connection; (-) – negative connection; (0) – no connection.

CONCLUSIONS

As a result of the undertaken research, systemic connections between risk indicators of aggressive, suicidal and addictive behavior with polymorphisms and corresponding human genotypes were determined. An information table has been developed that specifically reflects the relationship between the genotypes of the identified polymorphisms and the presence and direction of their influence on the studied vectors of deviant behavior.

The work was carried out as part of the project "Forecasting the risks of developing aggressive, suicidal and addictive behavior among the population of territories with different physical-geographical and biogeochemical status" under the academic strategic leadership program "Priority–2030".

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Мулик А. Б. Конкретизация генетических оснований системного проявления склонности человека к агрессивному, суицидальному и аддиктивному поведению / Мулик А. Б., Шатыр Ю. А., Назаров Н. О., Трандина А. Е., Бунтовская А. С., Улесикова И. В., Глушаков Р. И. // Ученые записки Крымского федерального университета им. В. И. Вернадского. Биология, химия. – 2024. – Т. 10 (76), №2. – С. 128–143.

Проведено исследование генетической обусловленности системного проявления склонности человека к агрессивному, суицидальному и аддиктивному поведению. В результате эксперимента с участием 150 мужчин и 150 женщин определены системные связи показателей риска агрессивного, суицидального и аддиктивного поведения со следующими SNP: rs1800497 (DRD2), rs6280 (DRD3), rs1851048 (CACNA2D3-1), rs6777055 (CACNA2D3-2), rs4680 (COMT), rs2562456 (ZNF-LD), rs6923492 (GRM1). Разработана информационная таблица, предметно отражающая связи генотипов выделенных полиморфизмов с наличием и направленностью их влияния на исследуемые векторы девиантного поведения.

Ключевые слова: SNP, генотип, генетика агрессивного поведения, генетика суицидального поведения, генетика аддиктивного поведения