PSYCHOPHYSIOLOGY

Chistyakova N.V ., Sergienko E.A.

Genotype-environment interaction: a molecular genetic approach to the study of volitional control during pregnancy*

The adaptive ability of organism to be changed environmentally throughout the lifespan requires the plasticity of link between a genotype and a phenotype. The genotype/environment dyad determines an adaptive profile of a phenotype and functional potential of its plasticity. By the regulation of gene expression, the environment influences the genotype and determines phenotypic variability, which is adaptive by nature. Therefore, the need for the integrative study of genotype-environment interaction and its prospects becomes clear in order to obtain objective and comprehensive data about the true nature of individual differences in psychological features. Using this approach, heterogeneous etiology of volitional control differences among women in the third trimester of gestation was assessed. Identification of pregnancy-specific molecular and genetic predictors of the volitional control allows defining its role in the psychological readiness of women for childbirth.

Keywords: *genotype, phenotype, genotype-environment interaction, volitional control.*

There is a tight relation between the genotype and the environment in the mechanism of phenotype regulation, in which the genotype and the environment are co-dependent to each other. At the same time, they act as determinants of individual differences in psychological features.

In psychogenetics (behavioral genetics) the additive model of development is widely used, in which the phenotype is a cumulative product of the genotype-environment interaction. Taking into account recent achievements in modern science, the need in the interdisciplinary study of phenotype regulation mechanisms at the interface of molecular genetics, psychophysiology, and developmental psychology is obviously required to holistically understand genotype-environment relation, which explain individual differences in psychological features.

In recent years, the integrity of basic and social science becomes even more essential to achieve a complete knowledge about a human being [1, 6]. The level of

* The work is supported by a research grant no. 11–06-00015-a from the Russian Foundation for Basic Research.

modern science is high enough to study specific genetic mechanisms of mentality in dissecting genotype-environmental relationships in human development and to involve genetic data and approaches for solution of psychological tasks. The entire picture of functional relations between the genotype and environment (that determine the phenotype) cannot be disclosed only by applying additive models for analysis of individual differences in psychological traits as complex phenotypic systems independently on the consideration of their mechanisms influencing all levels of the mental organization.

In behavioral genetics, two basic approaches are commonly used to describe the relation between the genotype and phenotype. The first strategy involves searching associations and correlations between nucleotide sequences and a phenotype of interest. Certainly, it is a rational approach in evaluating a potential role for a specific genetic variant [15]. However, the search for genotype-phenotype associations does not define the underlying cause-effect mechanisms. In addition, a specific genotype may be associated with a certain phenotype, but not underline this phenotype. This is in agreement with an established scientific point of view that there are no genes, which regulate this or that kind of behavior, but there are genes that involved in the control of behavioral regulators such as mediator systems in the body [4].

The genotype influences the development and function of neurotransmitter systems that regulate pro- or antisocial behaviors through specific metabolic pathways. The genotype could also indirectly influence behavioral regulators. In this regard, it is necessary to determine a functional significance of a specific genotype taking into consideration the environment under which the ratio between a specific genotype and a relevant phenotype becomes apparent [15]. Indeed, the main obstacle that limits a suitability of this approach for analysis of genotype-phenotype relationships is the misinterpretation of observed correlations and cause-effect mechanisms.

A second approach, which also implies statistical analysis, has evoked greater debates. Behavioral geneticists (psychogeneticists) do not consider the ratio between the genotype and phenotype at the level of specific genotypic variants (so-called genetic polymorphisms*), but just characterize the link between a phenotype variable outlined by the set of specific traits and genetic or environmental effects [14]. These studies evaluate the genotype effects on the formation of a specific phenotype considering neither the genotype itself nor the variations at the genotype level. Behavioral geneticists are focused on studying how these or those traits could be inherited assuming the genotype effect on the basis of obtained data.

The twin study is a traditional approach in psychogenetics (behavioral genetics). Twin studies involve determination of the similarity level between specific traits

* Polymorphism in biology (from Ancient Greek, Πολύμορφος – variable) is the capacity of some organisms to exist in states with different internal structure or different external forms. The external (and internal such as biochemical) polymorphism may be due to intraspecies genetic differences. On the other hand, it may be a polymorphism, in which organisms with almost identical genome, depending on the environmental conditions, acquire different forms of phenotype.

in mono- and dizygotic twins in order to estimate heritability (h^2) of those traits. The results showing a high heritability for a specific phenotype lead to the question of whether genotype variation at the level of DNA sequence might serve as the mechanism for transmission of individual phenotypic differences from parents to offspring.

However, the estimate of heritability cannot be the direct equivalent of the genotype influence. Otherwise, such an estimate ignores the functional significance of the genotype-environment interaction and, in addition, the mechanisms of inheritance act not only on the genetic level, but also on the neurophysiological (biochemical) level. There are so-called epigenetic imprintings* [11], protein heredity (e.g., prion proteins)** [18] and other examples, which can and do influence the phenotype. Thus, it is incorrect to solely equate the heritability to genotype effects.

To determine the development trend and severity of phenotype traits, twin studies do not reveal the cause-effect mechanisms of genotype-environment interactions, by focusing on the assessment of a relative contribution of a genotype and environmental conditions to the variability of these features [14]. Thus, until recently, the genotype and the environment in these studies were considered as independent variables.

The problem of individual development should be considered in the context of the permanent interaction between the genotype and environment [12]. Unraveling principles of how the genotype works and gene sequence analysis can help in objective understanding of the nature of individual differences in psychological features. Multiple processes acting at the cellular level lie between the genotype and the phenotype. The genotype effect on the phenotype can be assessed only taking into account the individual environmental (internal and external) conditions. The genotype and environment are the sources of variations in the phenotype [2].

The relation between the genotype and phenotype is not straightforward. The genotype effects (e.g., consequences of changes in a genetic sequence) on the phenotype depend on the environment. The genotype correlates with the phenotype only in the degree to which the gene operates and functions at the cellular level. The degree, to which the genotype influences the phenotype, depends on the environmental conditions. In this case, the inherited genome variation determines the functional capacity of genes only in the degree within which the environment effect

* Epigenetic imprinting assumes various DNA epigenetic modifications. An offspring receives one set of chromosomes containing father's imprinted genes, and other – from mother's imprinting. When offspring's germ cells are generated, the former "imprinting" is erased, and the genes are marked according to the individual sex. Epigenetic modifications of DNA that determine genomic imprinting are located on specific chromosomal regions called imprinting control regions. The essence of genomic imprinting is that genes passed from both parents to offspring have specific "imprints" of the parent sex. Thus, father's and mother's genes are differently imprinted.

** Prion proteins might translate the information on their 3-D structure from one protein to another.

on the phenotype is mediated by changes in the genetic sequence. Thus, it is possible to speculate about so-called environmental modeling of the relation between the genotype and phenotype.

The environmental effect on the individual development must be considered in regards to its genotype. It is truthful to talk about the nature of the bilateral relation between the genotype and environment, which is based on the mechanisms regulating gene expression at the cellular level*. The mechanisms provide a link between the biological and psychological levels of the genotype-environment interaction analysis.

The genotype-environment dyad determines the adaptive phenotype profile, its potential plasticity [8, 13]. The main estimate of the adaptive phenotype feature is its functional role in a particular environment to achieve the adaptation. Functional capacity of any phenotypic profile depends on the individual environmental conditions. Thus, it is possible to conclude that the universal, single, "ideal" phenotype does not exist. Ideal environmental conditions do not exist too. From this point of view, the development can be considered as an active adaptive process to the environment, which is under the permanent influence of the genotype-environment interaction.

We suggest studying molecular genetic predictors of the volitional control in pregnancy as an example of the genotype-environment interaction in the phenotype regulation.

In pregnancy, the volitional control, which is mediated by the genotype-environment interaction, supports the regulation of the adequate development of readiness to childbirth as a behavioral phenotype, whose core is represented by psychological component of the gestational dominant.

In this study, volitional control is considered accordingly to the Sergienko's concept of the behavior control. The arbitrariness in the organization of own behavior, freedom of choice and action (free will) are the integral part of our own behavior control. The system of volitional regulation of behavior displayed as an action control is based on the individual resources of a subject updated in the difficult situation such as pregnancy [5].

As a natural physiological process, pregnancy presents a practical interest to study the relationships between genetic and psychological mechanisms of behavioral regulation, within which the genotype-environment interaction plays a role of a distinctive buffer between the regulatory and compensatory-adaptive mechanisms of the subject adaptation to both pregnancy and childbirth.

By assuming that the volitional control in pregnancy is heterogeneous in its nature and may be caused by the complex interaction between genetic and environmental factors, the allocation of psychophysiological features (biomarkers) of the volitional control is crucial for determining genetic predisposition to a risk of the low volitional control.

---

* Gene expression is the mechanism by which the inherited information is translated from the gene (DNA sequence) into the functional product (e.g., RNA or protein).

In pregnant women, hormonal, immune, and homeostatic changes should be considered as a critical endogenously induced stress challenge. These intra-organismic transformations are regulated by the changes in the hypothalamic-pituitary-adrenal (HPA) axis, a key system of neuro-humoral regulation and the fundamental unit of adaptive systems of organism responsible for the individual mechanisms of self-regulation [7]. Stress hormones of the HPA axis are important for normal pregnancy and childbirth [9; 10]. There is a relationship between the neuroendocrine functions of organism and characteristics of the volitional regulation of the subject behavior in stressful conditions [16].

Hence, it is legitimate to consider the HPA axis as a psychophysiological basis of behavior control in pregnancy. Thus, the psychophysiological level plays a mediatory role of bilateral relations between the genotype and individual psychological features in pregnant women.

Assuming association between genetic polymorphism and a number of features that are expressed at the different mental levels including behavioral regulatory processes, polymorphic genetic variants encoding HPA axis hormone receptors, might be responsible for molecular genetic mechanisms of volitional control in pregnancy.

Corticoid receptors play the major role in the HPA axis regulation. Glucocorticoid receptor (GR) encoded by the NR3C1 gene mediates biological effects of glucocorticoid hormones, cortisol and dihydrocortisol, while the mineralocorticoid receptor (MR, a product of the NR3C2 gene) mediates effects of mineralocorticoids, aldosterone and deoxycorticosterone [17]. Marker rs6195, which causes the substitution of asparagine to serine (Asn363Ser) in the molecule of the mineralocorticoid receptor, is functionally active [19].

Thus, on the basis of the above mentioned data about the functional significance of these polymorphic markers and their effect on the HPA axis activity, these markers have been selected for genetic analysis of respondents' DNA.

The aim of this study is to identify molecular-genetic predictors of volitional control of women in the last trimester of gestation, using the genetic association analysis.

Materials and methods

The research was performed in the Moscow Centre of Protection of the Mother and Child Health of the Russian Academy of Medical Sciences, among women in the last trimester of gestation who underwent medical genetic counseling during 2011–2012 years. The respondents were selected by analysis of clinical and anamnestic data and through the interviewing procedure.

The study population involved 59 pregnant women 37 of whom were normally pregnant (the control group), while the remaining 22 subjects have adverse anamnesis (the experimental or "case" group). In the case group, the average age of respondents was 26 ± 4 years, whereas the age in the control group was 24 ± 3 years. Gestational duration ranged from 25 to 34 (29 ± 3) weeks.

The analysis of clinical and anamnestic data was performed to assess the individual psychosomatic women state in terms of predicting the complications during

childbirth and to define the type of psychological component of gestational dominant (PCGD) with help of the questionnaire entitled "Evaluation of prenatal risk factors", by O.G. Frolova and E.I . Nikolaeva, and I .V . Dobryakov's questionnaire entitled "Test of relation to pregnancy".

The Russian version of the J. Kuhl's questionnaire "Action Control Scale" (HAKEMP-90; adapted by S.A. Shapkin) was used to define the indicators of volitional control.

For genetic analysis of respondents, total DNA was isolated from whole-blood samples. Genotyping of individual DNA samples for loci of candidate-genes predisposing to a risk of reduced volitional control was conducted at the Department of Molecular Diagnostics in the State Research Institute for Genetics and Selection of Industrial Microorganisms using a Taqman SNP genotyping.

Statistical analysis was performed using the Fisher's exact test and chi-square test with Yates' correction to evaluate whether differences between the two samples are statistically significant. To reveal whether genotypes and alleles of the studied genetic markers are protective or predisposing, Odds Ratio (OR) was calculated with help of 2x2 contingency tables.

As the observed distribution of these values was different from the normal distribution, the Spearman's rank correlation coefficient, a non-parametric analogue of the classical Pearson's correlation coefficient, was applied to assess the correlation.

Results

The control group included apparently healthy pregnant women who filled themselves psychologically comfortable and had a dominant or predominantly optimal type of PCGD (9 points and 7–8 points in the column "O", respectively). Among the women studied, 37 subjects had an optimal type of PCGD (63.46% of a total sample) and a physiologically normal pregnancy.

The case group consisted of 22 pregnant women (36.54% of a total sample) with burdened anamnesis and destructive types of PCGD including the mixed type (mean scores on the scales, 6 subjects), ignoring type (7–9 points in the column "I", 0 subjects), euphoric type (7–9 points in the column "E", 2 subjects), anxiety type (7–9 points in the column "A", 13 subjects), and depressive type of PCGD (7–9 points in the column "D", 1 subject).

Among respondents, women in officially registered marriage were prevailed, 22 and 15 subjects (37% and 25% of a total sample, respectively) had registered marriage or de facto marriage, respectively. Among pregnant women with destructive types of PCGD, 11 subjects had registered marriage (19% of a total sample), 8 had de facto marriage (14%), and 3 were divorced (5%).

The distribution of pregnant women in both groups was significantly different at the educational level (Shi-square Pearson=6, df =2, p=0.05), and by the factor of pregnancy planning (Shi-square Pearson = 4.51, df =1, p=0.03). Thus, the respondents with the optimal type of PCGD and planned pregnancy were shared by 60%, and the share among subjects with other types PCGD and planned pregnancy was 45%. Among patients with unplanned pregnancy, the percentage of those who had the optimal type

and other types of PCGD was 40% and 55%, respectively. Indeed, planning pregnancy with the normal development of the gestational dominant is involved not only in setting goals that are adequate to own capacities, but also in achieving those goals. In our case, planning pregnancy could mean the psychological readiness to childbirth.

In the controls with the optimal type of PCGD, the percentage of first-time mothers was 54%. In the cases with other types of PCGD, the percentage of first-time mothers was 68%, whereas the percentage women with two and more pregnancies was 46% in the control group and 32% in the case group (Shi-square Pearson=4.12, df=1, p=0.04).

The friction angle φ was used to assess differences in the frequency of pregnancy-related complications in the case and control groups. The results are shown in Table 1.

Table 1

Frequency of pregnancy-related complications in two groups of respondents

Indicators	Case group		Control group		Fisher's test φ*emp. p<0.01
	n	%	n	%	
Toxicosis at the first half of pregnancy	3	14	5	14	0
Gestosis	9	41	0	0	–
Threat of interruption (the uteral hypertonus)	6	27	6	16	1.909
Abortion	7	32	5	14	**3.083***
Spontaneous abortion	2	9	4	11	0.474
Anemia	3	14	3	8	1.365
Oligoamnios	2	9	0	0	–
Hydramnion	3	14	1	3	**2.963***

* Significant differences in friction angle φ are shown in bold.

The presence of gestosis (late toxicosis), a serious prenatal risk factor, was documented in 9 cases (41%) with destructive types of PCGD, while gestosis was not found in pregnant women with the optimal type of PCGD.

Compared to hydramnion, oligoamnios is less frequent in the case group. Oligoamnios indicates the presence of abnormalities in the female organism, which may be harmful for fetal health. Another significant risk factor is the abortion history in the anamnesis of studied women.

Among cases with destructive types of PCGD, various forms of somatic diseases were detected, and their pathogenesis was complicated by current physiological changes in the female body at the third trimester of gestation.

Statistical indicators of the volitional control on the subscale level greatly varied. This suggests for the presence of different levels of the volitional regulation system of behavior in the compared groups. The analysis shows (see Table 2) that the action control for failure (CF) is emphasized on the state (e.g., on the state-oriented disposition, SO) in 55% of cases. Indeed, these individuals are primarily focused on their own emotional reactions and states, they pay too much attention to their own failures and unable to concentrate on any action. When faced with the failure, the volitional control in these subjects is directed to their emotional state regulation, not for search for effective ways to overcome this setback.

Only in 13% of cases, the action CF has the action-oriented type (e.g., AO-disposition). They do not tend to carefully analyze their failures, have a tendency to forget those, and, consequently, can repeat them. In failure, those people prefer to act and not lost themselves.

Table 2

The diagnostic results of the dominant type of volitional regulation on action control (AC) subscales in two groups

Indicators	Low level of AC SO-disposition n (%)		Fisher's test φ*emp. p<0.01	Mean level of AC n (%)		Fisher's test φ*emp. p<0.01	High level of AC AO-disposition n (%)		Fisher's test φ*emp. p<0.01
	Case group	Control group		Case group	Control group		Case group	Control group	
Action control for failure (CF)	12 (55)	13 (35)	**2.864***	7 (32)	21 (57)	**3.592***	3 (13)	3 (8)	1.16
Action control for planning (CP)	7 (32)	8 (22)	1,605	11 (50)	23 (62)	1.711	4 (18)	6 (16)	0.375
Action control for realization (CR)	3 (13)	16 (43)	**4.89***	14 (64)	15 (41)	**3.288***	5 (23)	6 (16)	1.252

* Significant differences in friction angle φ are shown in bold.

The low values on the subscale of the action control for realization (CR) observed in cases may suggest for a more severe dysfunction of the volitional regulation compared to the low values of other scales. At the same time, 23% of pregnant women with burdened anamnesis have a high level of CR. Performing an action, they are focused on the action itself and prefer to not respond to irritant stimuli and to interrupt the action.

In general, most destructive types of PCGD, which are more frequent among pregnant women with severe somatic diseases, are associated with the SO-disposition of the volitional behavior control. In the case group, pregnant women with burdened anamnesis have a tendency to self-immersion, leaving in their own, fear of failure, and strong tendency to be self-controlled.

In this study, the following putative molecular genetic predictors of the volitional behavioral regulation were analyzed in 59 respondents:

1) the mineralocorticoid receptor NR3C2 (polymorphism c.-2 G>C; rs2070951), in which a guanine (G) and cytosine (C) nucleotides are linked to DNA and RNA;
2) the glucocorticoid receptor NR3C1 (polymorphism Asn136Ser; rs6195), in which an asparagine (Asn) and serine (Ser) amino acid residues are involved in the protein synthesis and reflect the flexibility of genetic relations (see Table 3).

Table 3

Frequencies of markers alleles rs2070951 and rs6195 gene NR3C2 gene NR3C1 in two groups

Gene (marker)	Genotype/ Allele	Frequency n (%)		OR (95% CI)*	P (two-tailed Fisher's test)
		Case group (n=22)	Control group (n=37)		
Mineralocorticoid receptor NR3C2 (c.-2 G>C; rs2070951)	GG	8 (36)	19 (52)	0.52 (0.29–0.91)	0.032
	GC	5 (23)	9 (24)	0.95 (0.49–1.82)	1
	CC	9 (41)	9 (24)	2,2 (1.2–4.04)	0,02
	Allele G	10 (45)	23 (62)	0,5 (0.29–0.88)	0.023
	Allele C	12 (55)	14 (38)	2 (1.13–3.51)	0.023
Glucocorticoid receptor NR3C1 (Asn136Ser; rs6195)	Asn/Asp	17 (77)	30 (81)	0,79 (0.4–1.55)	0.6
	Asn/Ser	5 (23)	7 (19)	1,27 (0,64–2,52)	0.6
	Ser/Ser	0	0	–	–
	Allele Asn	19 (86)	33 (89)	0,76 (0.33–1.76)	0.67
	Allele Ser	3 (14)	4 (11)	1,32 (0.57–3.06)	0.67

*OR – odds ratio; 95%CI -95% confidence interval

Statistically significant differences are observed in cases homozygous for the genotype CC. This may be associated with increased stress-induced activation of the HPA axis in the third trimester of gestation due to the severe somatic diseases and provoke alterations in the PCGD development. The assessment of the polymorphic marker Asp363Ser (rs6195) revealed no statistically significant differences in the compared groups.

When subscales of the volitional control were compared with genetic data, a significant inverse correlation between CR and frequency of the mineralocorticoid recep-

tor gene NR3C2 variants in the control group (r=-0.58; p<0.01). The lower the action control for realization of pregnant women with the optimal PCGD type the higher the frequency of the homozygous genotype CC.

In the case group, we also observed significant inverse correlations between the volitional control subscales such as CF and CR and genetic variants of the mineralocorticoid receptor NR3C2 (respectively, r=-0.571, r=-0.66, p<0.01). This finding suggests that cases homozygous for CC tend to have the SO-disposition of volitional control and the destructive type of PCGD whereas homozygotes GG are trended to have the AO-disposition of volitional control.

Conclusions

The destructive types of PCGD are more frequently observed in pregnant women with severe somatic diseases and are associated with the SO-disposition of the volitional control of behavior mediated by the functional links of the HPA axis. The corticoid receptors play a key role in the HPA axis regulation. Functional effects of these genes are complex and reflect the multi-level character of the individual self-control. Pregnant women with burdened anamnesis have the tendency to self-immersion, leaving their own, fear of failure and excessive self-control in the presence of the homozygous genotype CC of the mineralocorticoid receptor NR3C2 (c.-2 G>C; rs2070951).

The results obtained in this study may be of great prognostic value for women preparing themselves to childbirth since they help to detect women with destructive types of PCGD who carry the homozygous genotype CC of the mineralocorticoid receptor NR3C2 (c.-2 G>C; rs2070951) predisposing to the low level of volitional control. Dysfunction of the volitional behavioral regulation during pregnancy contributes to the childbirth dysadaptation [3].

The use of genetic information in combination with psychological data sheds light on the genetic and psychological mechanisms of behavioral regulation and contributes to the accuracy of diagnosis, prognosis, and monitoring of women's adaptation problems to pregnancy in order to provide them a timely individual psychological care during the antenatal period.

References

1. Batuev, A. S., Sokolova, L. V . (1994). About relation between biological and social aspects of the human nature. Voprosy psihologii, (1), pp. 81–92. [Article in Russian].
2. Maryutina, T. M. (1998). Individualization of the development: a psychogenetic approach. Mir psihologii, (1), pp. 11–20. [Article in Russian].
3. Kovaleva, Yu. V ., Sergienko E. A. (2007). Control of behavior in different pregnancy courses. Psihologicheskij zhurnal, 22 (1), pp. 70–82. [Article in Russian].
4. Popova, N. K. From gene to aggressive behavior: the role of brain serotonin. (2007). Rossijskij fiziologicheskij zhurnal, Institut citologii i genetiki SO RAN, (6), pp. 569–575. [Article in Russian].

5. Sergienko, E. A., Vilenskaya, G. A., Kovaleva, Yu. V . (2010). Control of behavior as subject control. Institut psihologii RAN, M. [Book in Russian].
6. Khomskaya, E. D. (2005). Neuropsychology. Piter, SPb. [Book in Russian].
7. Chistiakova, N. V ., Savost'ianov, K. V . (2011). The hypothalamic-pituitary-adrenal axis and genetic variants affecting its reactivity. Genetika, 47 (8), pp. 1013–1025. [Article in Russian].
8. Agrawal, A. A. (2001). Phenotypic plasticity in the interactions and evolution of species. Science, 294, pp. 321–326.
9. Berkowitz, G. S., Lapinski, R. H., Lockwood, C. J., Florio, P., Blackmore-Prince, C., Petraglia, F. (1996). Corticotropin-releasing factor and its binding protein: maternal serum levels in term and preterm deliveries. American Journal of Obstetrics and Gynecology, 174, pp. 1477–1483.
10. Challis, J. R. (1995). CRH, a placental clock and preterm labour. Nature Medicine, (1), pp. 401–416.
11. Chong, S., Whitelaw, E. (2004). Epigenetic germline inheritance. Current Opinion in Genetics and Development, 14, pp. 692–696.
12. Gottlieb, G. (1997). Synthesizing nature–nurture. Mahwah, N.J.
13. Mousseau, T. A., Fox, C. W. (1998). The adaptive significance of maternal effects. Trends in Ecology and Evolution, 13, pp. 403–407.
14. Plomin, R., DeFries, J. C., McClearn, G. E. (1990). Behavioral genetics. A primer (2nd ed.). New York: W. H. Freeman and Company.
15. Plomin, R., Rutter, M. (1998). Child development, molecular genetics, and what to do with genes once they are found. Child Development, 69, pp. 1223–1242.
16. Quirin, M., Koole, S. L., Baumann, N., Kazén, M., Kuhl, J. (2009). You can't always remember what you want: the role of cortisol in self-ascription of assigned goals. Journal of Research in Personality, 43, pp. 1026–1032.
17. Reul, J. M., de Kloet, E. R. (1985). Two receptor systems for corticosterone in the rat brain: microdistribution and differential occupation. Endocrinology, 117, pp. 2505–2511.
18. Shorter, J., Lindquist, S. (2005). Prions as adaptive conduits of memory and inheritance. Nature Reviews Genetics, (6), pp. 435–450.
19. Van Winsen, L. L., Hooper-van, V . T., van Rossum, E. F. et al. (2005). The impact of glucocorticoid receptor gene polymorphisms on glucocorticoid sensitivity is outweighted in patients with multiple sclerosis. Journal of Neuroimmunology, 167, pp. 150–156.