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Review

Genetic factors of nitric oxide's system in psychoneurologic disorders

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Abstract. According to the recent data, nitric oxide (NO) is a chemical messenger that mediates functions such as vasodilation and neurotransmission, it also possesses antimicrobial and antitumoral activities. Nitric oxide has been implicated in neurotoxicity associated with stroke and neurodegenerative diseases, neural regulation of smooth muscle, including peristalsis, and penile erection. We searched for full-text English publications in Pubmed and SNPedia databases using keywords and combined word searches (nitric oxide, single nucleotide variants, single nucleotide polymorphisms, genes) over the past 15 years. In addition, earlier publications of historical interest were included in the review. In our review, we have sum up all *NOS1*, *NOS2*, *NOS3*, and *NOS1AP* single nucleotide variants (SNVs) involved in the development of mental disorders and neurological diseases/conditions. The results of studies we have discussed in this review are contradictory, that might be due to different designs of the studies, small sample sizes in some of them, as well as different social and geographical characteristics. However, the contribution of genetic and environmental factors has been understudied, that makes this issue increasing for researchers as the understanding of these mechanisms can support a search for new approaches to pathogenetic and disease-modifying treatment.

Keywords: NO; NOS; genetics; nitric oxide; nitric oxide synthase; oxidative stress; pathogenesis; mental disorders, neurological diseases

1. Introduction

According to the recent data, nitric oxide (NO) is a chemical messenger that mediates functions such as vasodilation and neurotransmission, it also possesses antimicrobial and antitumoral activities. Nitric oxide has been implicated in neurotoxicity associated with stroke and neurodegenerative diseases, neural regulation of smooth muscle, including peristalsis, and penile erection [1]. NO is synthesized from L-arginine by macrophages, endothelial cells, neurons, smooth muscle cells and cardiac myocytes. Three main NO synthase (NOS) isoforms catalyzing the formation of NO are well characterized. This family includes NOS1, NOS2, NOS3, encoded by *NOS1, NOS2, NOS3* genes, respectively [2]. Owing to inducible NOS (iNOS), produced by the gene *NOS2* high levels of NO are generated to combat environmental insults in a wide range of cells upon induction, while neuronal NOS (nNOS), produced by the gene *NOS1* and endothelial NOS (eNOS), produced by the gene *NOS3* control a fluctuating low level of NO to perform normal physiological functions in neurons and vascular endothelial cells [3].

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Single nucleotide variants (SNVs) of the NOS gene family are associated with diseases and conditions such as hypertension, QT interval prolongation, a syndrome of sudden cardiac death in children, diabetes mellitus, the risk of miscarriages as well as neuropsychiatric disorders. In our review, we have decided to sum up all *NOS1*, *NOS2*, *NOS3*, and *NOS1AP* SNVs involved in the development of mental disorders and neurological diseases/conditions. We searched for full-text English publications in Pubmed and SNPedia databases using keywords and combined word searches (nitric oxide, single nucleotide variants, single nucleotide polymorphisms, genes) over the past 15 years. In addition, earlier publications of historical interest were included in the review. Despite our comprehensive search in these frequently used databases and by search terms, some publications might have been overlooked.

2. Results

2.1. *NOS1* Gene

NOS1 is nitric oxide synthase 1 also known as neuronal nitric oxide synthase. However, despite its name it is expressed not only in the brain, but also in muscle and other tissues of the body (Figure 1).

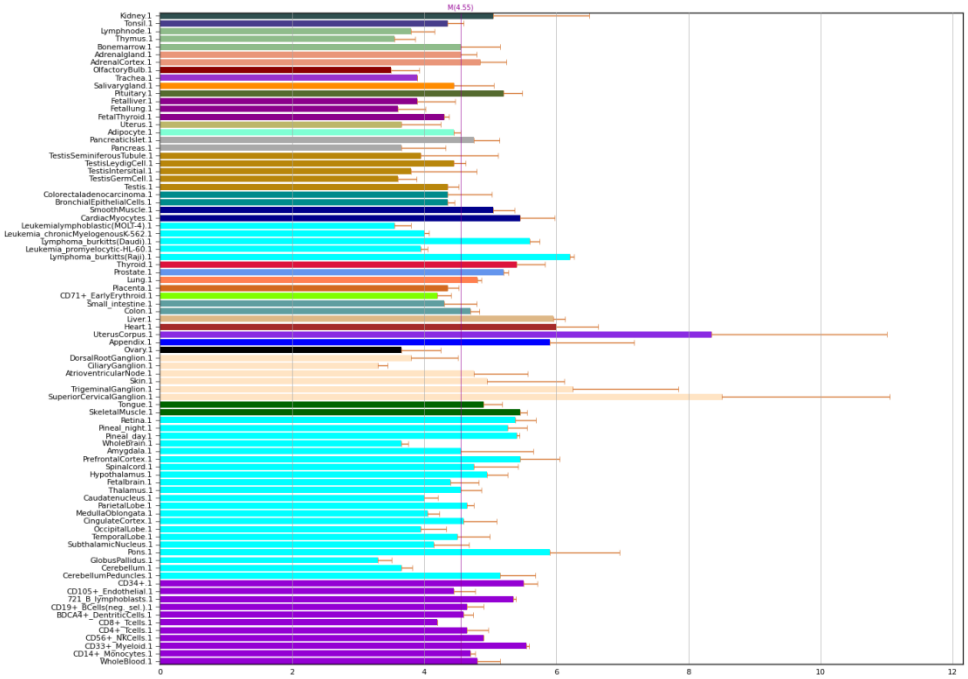

Figure 1. Expression of nitric oxide synthase 1 in the human body [4, 5].

This enzyme is encoded by the *NOS1* gene located on the long arm of chromosome 12, position 12q24.22 (Figure 2).

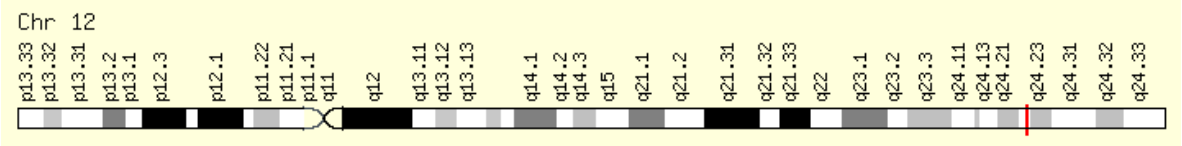

Figure 2. Localization of the *NOS1* gene [6, 7]

2.1.1. Schizophrenia

Shinkai T. et al. studied the association of the *NOS1* SNVrs2682826 with a risk of schizophrenia. The study involved 215 Japanese patients with schizophrenia and 182 healthy volunteers as a control group. There was a significant difference in the genotype distribution between the patients and the controls (p = 0.00122). Moreover, the allele frequency differed significantly between patients with schizophrenia and the controls (p = 0.000007; relative risk = 1.92; 95% confidence interval = 1.44-2.55).

Thus, the *NOS1* gene was suggested as a candidate gene which increases the susceptibility to schizophrenia [8].

Based on this study, *NOS1* aroused scientific interest of Fallin M.D. et al. They screened 440 SNVs of 64 genes for their associations with a risk of schizophrenia and bipolar affective disorder (BAD) (see section "Depression and bipolar affective disorder" *NOS1*) in 597 (including 323 schizophrenia and 274 BAD) patients and their family members. Only Ashkenazi Jewish families were recruited into the study in order to reduce genetic heterogeneity. Two out of eight *NOS1* SNVs such as rs3782219 and rs3782221 (p = 0.0003 and p = 0.0014, respectively) appeared to be associated with schizophrenia. The rest six SNVs including rs2682826, showed no associations [9].

Tang W. et al. conducted their study in a Chinese population involving 844 patients with schizophrenia (including 425 paranoid schizophrenia) and 861 individuals as comparative control. 11 SNVs and 1 microsatellite (within the exon 1f promoter region) were screened. The study was designed as two-staged. At the first stage 480 patients and 480 controls were examined; alleles of rs499776 and rs3782206 were found to have associations with a risk of schizophrenia (p = 0.014 and p = 0.015, respectively), while rs561712 tended to be associated (p = 0.054). The second stage involved the examination of these three SNVs as well as rs3837437, located nearby them in the 5'-flank region of *NOS1*. Here, only rs3782206 demonstrated a statistically significant association, which remained after the correction for multiple comparisons both in a total sample (p = 0.004), and when compared to paranoid schizophrenia (p = 0.012). However, all four SNVs were used in haplotype mapping and analysis. Based on these results a 2-SNV (rs3837437 T – rs3782206 C) haplotype (p = 0.0002) was identified as being significantly associated with schizophrenia. There were also statistically significant results for 3- and 4-SNV haplotypes [10].

Reif et al. demonstrated in a German population consisting of 267 patients with chronic schizophrenia and 284 healthy volunteers that SNV rs41279104 in the *NOS1* exon 1 promoter region was associated with schizophrenia and prefrontal cortex dysfunctions [11].

Moskvina V. et al. reported the association of rs6490121 in the *NOS1* intron 2 with schizophrenia based on the genome-wide association study (GWAS) results in 479 patients from Great Britain [12].

A group of investigators from Japan tried to reproduce positive results of previous studies conducted in Japanese populations (542 schizophrenic patients and 519 healthy controls at the first stage and 1,154 patients and 1,260 controls at the second stage of the study). Therefore, 7 SNVs were selected. Two SNVs such as rs3782219 (p = 0.0291) and rs3782206 (p = 0.0124) had statistically significant allele associations. Interestingly, when a sample size was increased at the 2-nd stage, values were approximately the same: rs3782219 (p = 0.0197) and rs3782206 (p = 0.0480). However, the results were finally considered erroneous, as they were not significant after the correction for multiple testing [13].

A year later another group of Japanese investigators repeated the study of their colleagues for the same seven SNVs. A sample size in their study involved 720 subjects (343 schizophrenic patients and 377 healthy controls). According to genotyping results only 1 SNV, rs41279104, which was considered insignificant by the previous authors, demonstrated a statistically significant association with schizophrenia (p = 0.006 after the correction for multiple testing). They also studied immunoreactivity in the postmortem brain of patients with schizophrenia. 12 brain samples collected from patients and 15 ones taken from people without lifetime schizophrenia were examined. Patients with the rs41279104 A-allele had significantly lower NOS1 immunoreactivity levels than GG homozygotes did (p = 0.002), that, in the authors' judgement, underlies a significantly decreased NOS1 expression in the prefrontal cortex [14].

Wang J. et al. evaluated the association between 28 SNVs of the *NOS1* gene in the Chinese Han population (382 patients with schizophrenia and 448 healthy subjects). One SNV rs1520811 showed the association with this disorder; however, it became insignificant after the correction for multiple testing. Thus, their results also do not support the previously identified association between *NOS1* gene polymorphisms and schizophrenia [15].

Weber H. et al. conducted a meta-analysis of previous studies for genes of the NO system, including *NOS1* and *NOS1AP* (see section "Schizophrenia" *NOS1AP*) and selected 8 *NOS1* SNVs for

analysis. However, 1 SNV (rs3837437) was excluded from the analysis as the minor allele frequency was extremely low. This study continues the project by Reif A. et al. described above. The sample size was extended to 270 German patients with schizophrenia and 720 normal volunteers. Three SNVs such as rs1879417, rs41279104, and rs499776 showed statistically significant associations. In the meta-analysis rs41279104 had the best odds ratio (OR = 1.29) [16].

Riley B. et al. investigated rs6490121 of the *NOS1* gene as well as SNVs of other gene and their effects on the development of schizophrenia in an Irish population. 1,021 schizophrenic patients and 626 controls were included into the study. There were no associations of the *NOS1* rs6490121 with schizophrenia ($p = 0.21$) [17].

2.1.2. Depression and bipolar affective disorder

Depression and stress are closely related to each other. Stress was shown in animal models to increase the NOS1 expression in many cerebral regions including the hippocampus [18, 19]. Taking this a group of scientists from Great Britain took an interest in mutual effect of the most common *NOS1*SNVs, stress factors and depressive disorders. They examined 1,222 subjects. The subjects were genotyped and questionnaired. Financial hardship was taken as a stress factor. There were significant associations between eight out of 20 *NOS1* SNVs (rs693534, rs10507279, rs1004356, rs3782218, rs9658281, rs561712, rs522910 and rs2293050) and human liability to depression under exposure to financial and psycosocial stress factors. The results were statistically significant after the correction for multiple testing [20].

Montesanto A. et al. studied the effect of the most common SNVs in genes of the *NOS* family on a human life span and a quality of life in an old age. *NOS1*SNVs such as rs1879417 and rs2682826 were screened. 763 individuals (see Section "Cognitive disorders" *NOS1*; *NOS2*; *NOS3*) were examined. The Geriatric Depression Scale (GDS) was used to evaluate a depression level. The authors demonstrated that subjects with even one minor allele T in SNV rs2682826 had a higher probability of depression symptoms in an old age ($p = 0.033$ after the correction for multiple testing). The second study SNV (rs1879417) had no statistically significant effect on depressive disorders; however, it was associated with maintaining cognitive abilities with age [21].

Winger P. et al. studied an association between polymorphisms of the genes related to oxidative and nitrosative stresses including *NOS1* and *NOS2* (see Section *NOS2*) and a risk of depression in a Polish population (281 depressed patients and 229 controls). The frequency of the study *NOS1* SNV (rs1879417) did not achieve significant differences between samples [22].

Also, a group of Japanese scientists (Okumura T. et al.) investigated an association of the *NOS1* SNV rs41279104 and mood disorders. In addition to depression they studied BAD. This SNV was chosen as plasma NO levels were previously reported to change in patients with mood disorders (a decrease in depressed patients [23] and an increase in I type BAD patients as compared to the control [24]). The study included 325 patients with depression, 154 ones with BAD and 807 healthy volunteers. However, there were no statistically significant associations with depressive or BAD [25].

Fallin M.D. et al. found no significant associations between BAD and the *NOS1*SNV in their study (see Section "Schizophrenia" *NOS1*) [9]. Buttenschon H. et al, the authors of the study preceding that conducted by Fallin M.D. and prompting the inclusion of this gene in the project, conducted their study in 2 populations - the British and Danish. No significant differences in the frequency of SNV rs2682826 were observed among all the subjects. However, there was a difference in genotypes between the Danish and the control group ($p = 0.045$). Yet, the investigators considered it incidental, as the Danish population was smaller (83 patients), than the British one (286 patients), and as there was no allelic association [26].

2.1.3. Autism spectrum disorders

Unlike *NOS2*the association study of *NOS1* and *NOS2* genes (see Section "Autism spectrum disorders" *NOS2*) with autism spectrum disorders (ASD) in an Asian population demonstrated no

statistically significant results in respect of *NOS1*. 9 *NOS1* SNVs such as rs2682286, rs2293044, rs3741475, rs3741476, rs1047735, rs2293054, rs3741480, rs9658255, and rs9658247 were analyzed [27].

2.1.4. Parkinson's disease

As mentioned above, high concentrations of NO produce a neurotoxic effect in the body. The balance between useful and toxic properties of NO in nerve cells (in particular, neurons of the substantia nigra) varies both under exposure to environmental factors and depending on expression levels of the genes responsible for nitrogen synthesis. Therefore, these genes are candidates increasing a risk of Parkinson's disease (PD).

Hancock D.B. et al. screened 1,065 patients with PD for *NOS1*, *NOS2A* and *NOS3*SNVs, increasing a risk of the disease (see Section "Parkinson's disease" *NOS2* and *NOS3*), as well as gene interaction with the environment (cigarette smoking, use of caffeine, nonsteroidal anti-inflammatory drugs and pesticides). 27 SNVs of the *NOS1* gene were included into analysis. There were significant associations between PD and SNVs rs12829185, rs1047735, rs2682826, rs3782218, rs11068447, rs7295972, rs2293052 and rs3741475 (a range of p = 0.00083-0.046). What is more, the first three of these SNVs demonstrated interaction with pesticides (a range of p = 0.012-0.034) [3].

2.1.5. Brain tumors

A group of American scientists led by Bhatti P. studied lead exposure (as an environmental factor), its involvement in mechanisms of neurotoxicity and genetic aspects of these interactions. Oxidative stress is a component of neurotoxicity (particularly with lead intoxication). For example, lead was shown to deplete antioxidant proteins and to stimulate the production of reactive oxygen species [28, 29]. 496 patients (362 gliomas including 176 glioblastomas and 134 meningiomas) were included into the study (see Section "Brain tumors" *NOS1, NOS2*). 11 *NOS1* SNVs demonstrated at first a statistically significant association ($p \leq 0.05$) with one or more types of cerebral tumors or a significant modification of lead cumulative effects on brain tumors. However, none of the associations was significant after the correction for multiple testing [30].

2.1.6. Cognitive disorders

The above study (see Section "Depression" *NOS1*) also included the measurement of subject cognitive functions with the use of the MMSE (Mini mental state examination) scale. The C minor allele of SNV rs1879417 was at first an associated with low cognitive characteristics, i.e, the lowest MMSE scores (p = 0.045). However, after the correction for multiple testing this association was deemed statistically insignificant (p = 0.093) [21].

At the same time, we have found a number of studies which confirm the role of *NOS1*SNV in a risk of cognitive impairment in neuropsychiatric diseases, particularly in schizophrenia, based on previously shown associations of some SNVs and schizophrenia. To date it is not clear which of these factors are primary and which ones are secondary. Cognitive impairments in tasks involving the prefrontal cortex (for example, working memory or verbal fluency) are key in schizophrenia. This led to the hypofrontality hypothesis of schizophrenia. The impairment of glutamatergic neurotransmission is certainly to play a role. The promoter region of *NOS1*, affecting the prefrontal transmission of glutamate, has been repeatedly associated with schizophrenia.

A group of Irish scientists studied rs6490121. In 2009, they conducted a large study involving 349 Irish patients with schizophrenia, 232 German patients and a control group. The Irish were first examined, then the results were confirmed in the second population. G allele carriers among patients showed poorer verbal intelligence quotient (IQ) and working memory test results [31]. Studies of this SNV were further continued. O'Donoghue T. et al. demonstrated its participation in early sensory processing in 54 healthy subjects. G allele carriers had lower electroencephalogram (EEG) responses to visually evoked potentials P1 [32]. Rose E.J. et al. reported structural and functional changes in the prefrontal cortex in G allele carriers [33].

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Studies suggesting impaired prefrontal functioning in schizophrenia continued to extend and there was more and more evidence of the genetic variation of *NOS1* in cognitive dysfunction, probably by decreasing glutamatergic transmission. Reif A. et al. sought for associations between another SNV rs41279104, which leads to a decreased transcript expression, schizophrenia (see Section "Schizophrenia" *NOS1*) and the prefrontal cortex functioning. The study involved 87 subjects (43 patients with schizophrenia and 44 controls). In addition to genotyping, functional spectroscopy was performed with simultaneous working memory testing. Task-related changes in oxygenation were significantly reduced in patients with schizophrenia. Schizophrenic patients (A allele carriers) showed the worst results [34].

Zhang Z. et al. summarized previous studies and repeated them in respect of another SNV rs3782206. They showed that the schizophrenia risk allele (T) of rs3782206 was associated with the poorest results in five measures of cognitive performance deficiency in patients (580 patients with schizophrenia) and only in three ones among the controls (720 healthy volunteers). Functional spectroscopy revealed reduced activation in the right inferior frontal gyrus of the risk allele carriers during cognitive testing [35].

These results strongly suggested an association between *NOS1* gene variants and cognitive functions as well as their neural underpinnings; they have important implications for our understanding of the neural mechanism underlying the association between *NOS1* SNVs and schizophrenia.

Research in neurooncology has also been conducted in parallel to a more comprehensive study of associations with schizophrenia. Liu Y. et al. conducted a large exploratory study of 10,967 SNVs in 580 genes including *NOS1* in 233 newly diagnosed glioma patients before surgery. The strongest associations in respect of NOS1 were in executive function testing and rs11611788 (p = 0.000000018) [36].

2.1.7. Ischemic stroke

NO, produced by endothelial cells causes vasodilatation and hypotension; it has a number of anti-thrombotic and anti-atherosclerotic properties as well [37]. Therefore, NOS, neuronal in particular, plays a pivotal role in the development of atherosclerosis and the regulation of blood flow, and it is likely that its effect on ischemic stroke (IS) might be mediated by these two main clinical risk factors.

For example, Manso H. et al. investigated effects of *NOS1* and *NOS3*SNVs on IS susceptibility and outcome after an IS (see Section "Ischemic stroke" *NOS3*). The study population consisted of 551 IS patients and 530 controls. 37 *NOS1* SNVs were included into analysis. 4 SNVs (rs2293050, rs2139733, rs7308402 and rs1483757) were significantly associated with IS susceptibility (a range of p = 0.036-0.048 corrected for multiple testing); NOS1 variants were not associated with IS outcome [38].

Dai Y. et al. conducted a study with the similar design (a case-control study) in a Chinese population. 413 patients with IS and 477 healthy individuals were examined. It was shown that only rs7308402 was associated with an increased risk of IS (the A allele is a protective factor: genotype AG, p = 0. 037; allele A, p = 0.041 as compared to the control). Unlike in the study conducted by Manso H.rs1483757, rs2139733 and rs2293050 did not achieve statistically significant differences [39].

2.1.8. Restless legs syndrome

Winkelmann J. et al. performed a three-stage study. The first stage involved screening for 1,536 SNVs in 366 genes. At the second stage the most significant SNVs of Stage 1 were genotyped. Significant associations were observed with *NOS1* rs7977109 and rs693534 in both explorative and replication study stages. However, the same alleles were protective in the former, while being a risk factor in the latter. The investigators suggested this might be due general difference between certain samples, rather than the *NOS1* association with restless legs syndrome (RLS). They tested this hypothesis using the method of genomic control. The discrepancy in the results between two samples may be alternatively accounted for by the interaction of *NOS* with environmental factors.

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This seems possible, given that NOS is involved in the metabolism of arginine, and its levels may differ due to eating habits. Finally, differences can also be accidental. The revision was performed only in one replication sample. In conclusion, the investigators do not consider that opposite associations should be excluded from further analysis and research, since they may well indicate a true relationship. However, further research in independent populations is required [40].

2.1.9. Multiple sclerosis

The association study of NO-encoding genes with multiple sclerosis (MS) demonstrated no statistically significant results in relation to the *NOS1* gene unlike other enzymes of this family (see Section "Multiple sclerosis" *NOS2* and *NOS3*). SNVs rs2682826 and rs41279104 were included into analysis [41].

2.2. *NOS1AP* Gene

When discussing neuronal nitric oxide synthase, it is necessary to note its adaptor protein. NOS1 (neuronal) adaptor protein (NOS1AP) is a cytosolic protein that binds to the signaling molecule, nNOS. The protein has a C-terminal PDZ-binding domain that mediates interactions with nNOS, and a N-terminal PTB-domain, that binds to the small monomeric G-protein, DEXRAS1.

The expression of NOS1A P is given in Figure 3.

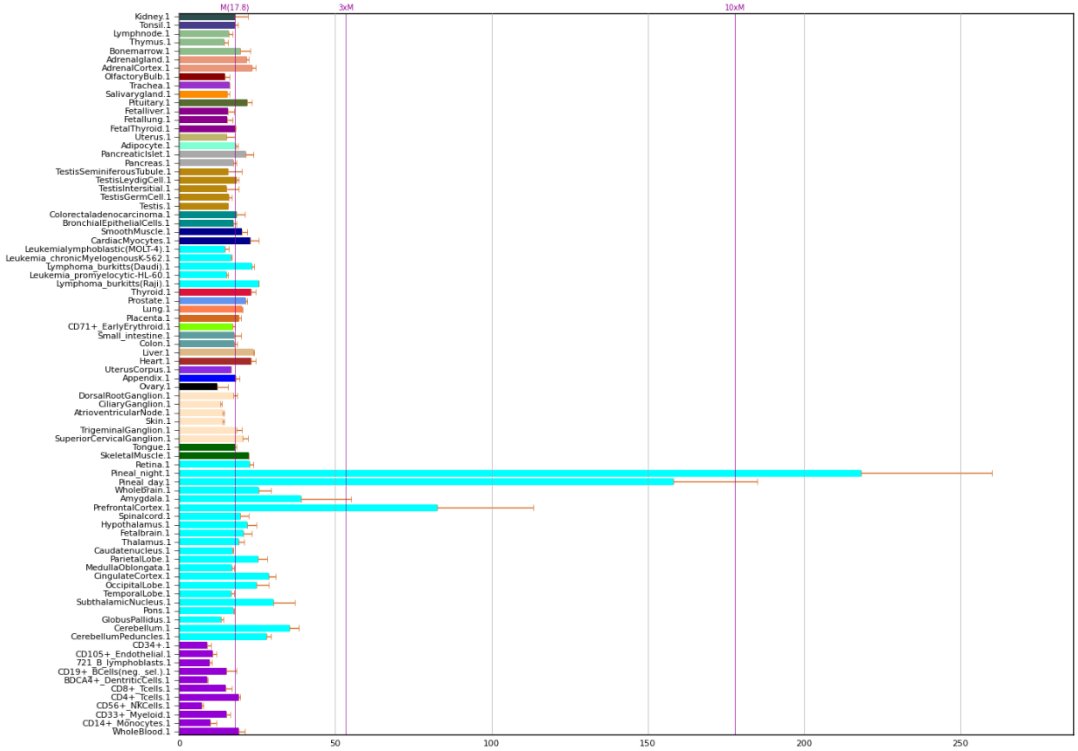

Figure 3. Expression of nitric oxide synthase 1 adaptor protein in the human body [5]

This enzyme is encoded by the *NOS1AP* gene located on the long arm of chromosome 1, position 1q23.3 (Figure 4). Its original name – *CAPON* is also encountered in the literature.

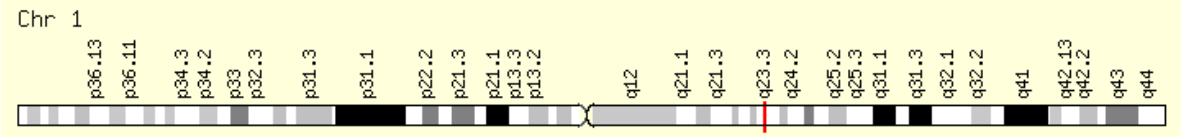

Figure 4. Localization of the *NOS1AP* gene [7]

2.2.1. Schizophrenia

As NOS1AP is involved in signal transmission in the system of N-methyl-d-aspartate-receptors (NMDAR), it is a potential important component in the etiology of schizophrenia.

A group of American scientists studied associations between SNVs of this gene and a risk of schizophrenia. 24 Canadian families participated in the study. Brzustowicz L.M. et al. screened for 15 SNVs (rs1572495, rs1538018, rs945713, rs1415263, rs4306106, rs3934467, rs3924139, rs4145621, ss16342089, rs2661818, rs1508263, rs3751284, rs7521206, rs348624). Out of them 6 SNVs had statistically significant associations (rs1572495 – $p = 0.021$; rs1538018 – $p = 0.047$; rs945713 – $p = 0.016$; rs1415263 – $p = 0.0016$; rs4145621 – $p = 0.0016$; rs2661818 – $p = 0.0032$) [42]. Wratten N.S. et al. continued this project and extended the number of SNVs up to 38. They showed alleles C of rs1415263, T of rs4145621 and A of rs12742393 to be associated with schizophrenia that acts by enhancing transcription factor binding and increasing gene expression. Thus, one more SNV–rs12742393 demonstrated significant differences in allele expression. Allelic variation in this SNV changed the affinity of a core protein that binds to this deoxyribonucleic acid (DNA) region. Therefore, the authors suggested the A allele of rs12742393 to be possibly a risk allele associated with schizophrenia [43].

A study was performed in an Asian population. Zheng Y. et al. studied 9 *NOS1AP* SNVs (rs1572495, rs945713, rs1415263, rs4145621, rs2661818, rs3751284, rs2275643, rs905721, rs348624, rs11422090, and rs1964052). However, rs2275643 and rs11422090 were excluded during the study. A study sample consisted of 664 patients with schizophrenia and 941 controls of the Chinese Han population. One SNV demonstrated statistically significant differences in analysis of both allelic ($p = 0.000017$) and genotype ($p = 0.000030$) frequencies, and haplotypes with this SNV (rs905721, rs348624, rs1964052 – $p = 0.000025$). This study is one of those that support for the potential importance of NMDAR-mediated glutamatergic transmission in the etiology of schizophrenia [44].

13 *NOS1AP*SNVs (rs1572495, rs1538018, rs945713, rs1415263, rs4306106, rs3924139, rs1508263, rs3751284, rs7521206, rs905721, rs348624, rs1964052, rs4145621) were analyzed in the above study performed by Weber H. et al. (see Section "Schizophrenia" *NOS1*). SNV rs4145621 was excluded during the analysis. 6 SNVs of *NOS1AP* were significantly associated with schizophrenia in at least one population (German, Swedish, Spanish): rs945713 ($p = 0.002$ – German), rs1415263 ($p = 0.006$ – Swedish), rs4306106 ($p = 0.018$ – Swedish), rs3924139 ($p = 0.003$ – Swedish), rs1508263 ($p = 0.006$ – Spanish), rs3751284 (genotype $p = 0.022$ – Swedish). Notably, rs945713 was statistically significant after the Bonferroni correction in the German sample ($p = 0.048$) and demonstrated a tendency to association in the Swedish one ($p = 0.064$) [16].

2.2.2. Depression

As discussed above, depression and stress are two causal factors that are inseparably related to each other. The nitric oxide synthase 1 adaptor protein modulates stress-evoked N-methyl-d-aspartate (NMDA) activity. Post-traumatic stress disorder (PTSD) is an anxiety-depressive disorder that debuts after exposure to a traumatic event. PTSD is most common among combat veterans. Lawford B.R. et al. screened for associations between this disorder and *NOS1AP* SNVs in 121 Vietnam combat veterans and 237 healthy Caucasian volunteers. PTSD patients were assessed for symptom severity and depression levels using the Mississippi Scale for Combat-Related PTSD and the Beck Depression Inventory-II (BDI). 13 SNVs (rs945706, rs1415259, rs4656355, rs6704393, rs1415263, rs4531275, rs6683968, rs4657178, rs2341744, rs347300, rs1858232, rs347313 and rs386231) were investigated in the study. The G allele of rs386231 appeared to be significantly associated with PTSD ($p = 0.002$). There were reliable data that the GG genotype increased the severity of depression ($p = 0.002$ $F = 6.839$) and had higher Mississippi Scale for Combat-Related PTSD scores ($p = 0.033$). The haplotype analysis revealed that the C/G haplotype (rs451275/rs386231) was associated with PTSD ($p = 0.001$). However, the authors note that their study is one of the first in this direction and that their sample sizes were not sufficient to detect SNV associations with very small effects. Nevertheless, they suggest that the *NOS1AP* SNV rs386231 may increase susceptibility to severe depression in patients with PTSD and thereby increase a risk for suicide [45].

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2.3. *NOS2* Gene

The *NOS2* gene encodes nitric oxide synthase 2, which is expressed in the liver and induced by a combination of lipopolysaccharide and certain cytokines. This radical is encoded by the same-name gene *NOS2* (OMIM:163730) on the long arm of chromosome 17 (position 17q11.2) (Figure 5). The gene is also known as *NOS; INOS; NOS2A; HEP-NOS* [7].

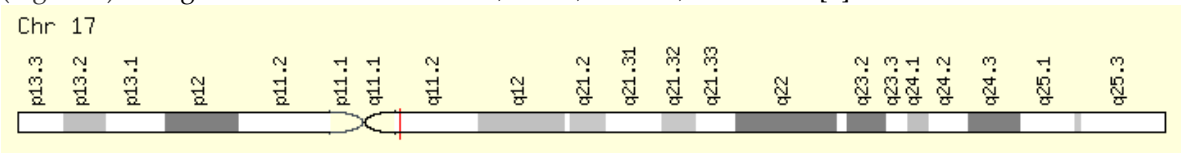

Figure 5. Localization of the *NOS2* gene [7]

NOS2 is mainly expressed in the small and large intestine, kidneys, liver and lungs (Figure 6) [5].

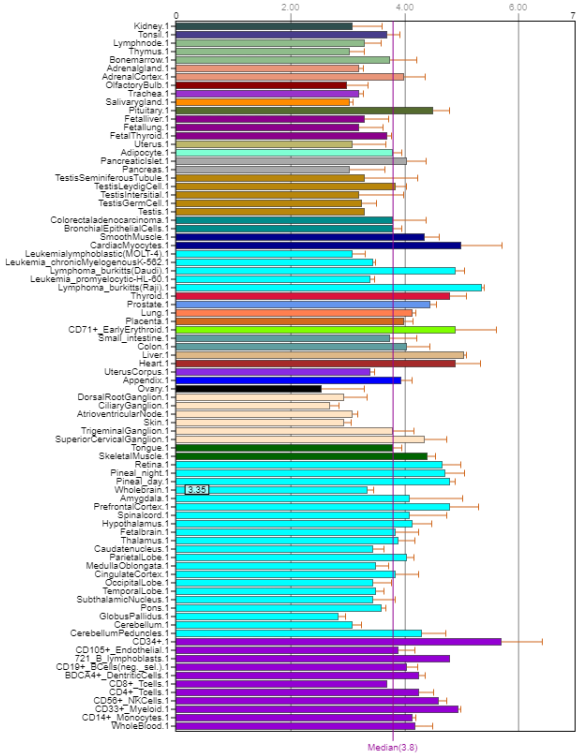

Figure 6. Expression of nitric oxide synthase 2 in the human body [5]

2.3.1. Depression

There is certain evidence of the imbalance in generation and elimination of reactive oxygen (ROS) and nitrogen (RNS) species in depression [46]. This imbalance results in increased levels of intensified oxidative and nitrosative stress biomarkers, such as 8-hydroxyguanine (8-oxoG), 8-iso prostaglandin F2a (8-iso-PGF2a), malondialdehyde (MDA) and NO [47, 48]. Moreover, patients with depression have an increased expression of cellular NOS in neurons of the suprachiasmatic nucleus as compared to the control group. The excessive activity of a prooxidant enzyme NOS resulted in increased ROS and RNS levels that can lead to neurodegenerative changes [49, 50].Wigner P. et al. (2018) investigated SNVs of *SOD2, CAT, GPx4*, and *NOS1* genes (see Section "Depression" *NOS1*) and *NOS2* SNVs c.-227G>C (rs10459953), c.1823C>T (p.Ser608Leu) (rs2297518) in 281 depressed patients in comparison with 299 controls of the Polish population. The analysis revealed no association of a risk of depression with SNVs c.-227G>C (rs10459953) and c.1823C>T (p.Ser608Leu) (rs2297518) in *NOS2*. No correlation between haplotypes of these SNVs was found. However, the gene-gene analyses revealed that a risk of depression increased five-fold with genotypes such as T/T-T/T of *SOD2* c.47T>C (p.Val16Ala) (rs4880) and *NOS2* c.1823C>T (p.Ser608Leu) (rs2297518)

polymorphisms ($p = 0.013$). A risk of depression increased twice with combined T/T–T/T genotypes of *NOS2* c1823C>T (rs2297518) and *GPx4* c. 660T>C (rs713041) polymorphisms ($p<0.001$). There was also a correlation between genotypes such as G/C-T/T ($p = 0,001$) and G/G-T/T (p=0,015) of *NOS2* SNV c.- 227G>C (rs10459953) and *GPx4 SNV*c.660T>C (rs713041) with depression. T/TC/T genotypes of SNVs c.-89A>T (rs7943316) in *CAT* and c.1823C>T (rs2297518) in *NOS2* increased a risk of depression ($p = 0.002$), while the T/T-T/T genotype reduced the risk ($p = 0.036$). The A/T-G/G genotype of c.-89A>T (rs7943316) in *CAT* and c.-227G>C (rs10459953) in *NOS2* was associated with a risk of depression ($p = 0.001$) [22].

2.3.2. Autism spectrum disorders

NO is an important signaling molecule that is involved in the development of the central nervous system (CNS) and certain physiological functions, such as the release of noradrenaline and dopamine, memory and learning. It is also involved in the development of BAD, schizophrenia and depression [51, 52]. In the brain the *NOS2* gene is found in activated immune cells such as the microglia and astroglia. It is involved in demyelination of the central nervous system and neuronal death. Patients with ASD have immune and inflammation diseases, including T-, B- and NK-cells dysfunction and increased levels of pro-inflammatory cytokines [53]. Since NO plays an important role in neuroinflammation, it has been proposed to consider it in the pathogenesis of ASD [27]. Kim H.W. et al. (2009) conducted a genetic study in 151 women with ASD, where 9 *NOS1* SNVs (see Section "Autism spectrum disorders" *NOS1*) and 9 *NOS2*SNVs (rs7406657, rs3201742, rs2255929, rs8068149, rs1060826, rs2297518, rs1137933, rs10459953 and rs2779248) were analyzed. The analysis results demonstrated that the allele A of SNV rs8068149 ($p = 0.039$) and allele G of SNV rs1060826 ($p = 0.035$) in *NOS2* were associated with a risk of ASD. Moreover, a risk of ASD was higher for GG or AG genotypes, than for that of AA of *NOS2* SNV rs1060826 [27].

2.3.3. Parkinson's disease

Hancock D.B. et al. (2008) studied associations of 27 *NOS1* SNVs (see Section "Parkinson's disease" *NOS1*), 18 *NOS2* SNVs (rs3730014, rs3794766, rs2072324, rs8072199, rs16966563, rs3794764, rs17722851, rs944725, rs4795067, rs1137933, rs12944039, rs2314810, rs2248814, rs2297518, rs2297516, rs2297515, rs1060826, rs2255929) and 5 *NOS3*SNVs (see Section "Parkinson's disease" *NOS3*) with a risk for PD in 337 families with sporadic PD from the USA and 358 families with familial PD. The analysis results showed the A allele of rs2072324, A allele of rs3794764, G allele of rs12944039 ($p < 0.0001$), A allele of rs2297516 ($p < 0.0001$) and T allele of rs2255929 ($p < 0.0001$) of the *NOS2* gene were associated with a risk for PD in 337 families with sporadic PD at the age of 40 to 80. However, no association of *NOS2* with familial PD was found. A carrier status of the *NOS2* SNV rs2255929 was associated with PD in patients younger than 40 years old ($p = 0.046$) [3].

2.3.4. Migraine

The etiology of migraine is based on a neurogenic inflammatory component, that affects blood vessels by enhancing the formation of NO with subsequent pain. Excessive NO amounts are possibly derived from increased *NOS2* expression and activity [54].

De OS Mansur T. et al. (2012) tested two potentially functional clinically relevant SNVs G2087A (rs2297518) and C(-1026)A (rs2779249) of *NOS2* in 148 women with migraine with aura and 52 women with migraine without aura in comparison with the control group consisting of 152 healthy women from Brazil. It was found that a carrier status of the *NOS2* SNV G2087A (rs2297518) was associated with a risk of migraine. Notably, the A allele of G2087A SNV was more common in the group of patients with migraine with aura than in those without aura ($p = 0.0243$). The AA genotype for *NOS2* SNV G2087A (rs2297518) and C(-1026)A (rs2779249) was associated with migraine with aura ($p = 0.0349$) [54].

Gonçalves F.M. et al. (2012) studied SNVs of *NOS2* C-1026A (rs2779249) and G2087A (rs2297518), *NOS1* (see Section "Migraine" *NOS3*) and *VEGF* in 150 women with migraine in

comparison with the control group consisting of 99 healthy women from Brazil. The analysis results showed that *NOS2* SNV G2087A (rs2297518) was associated with a risk of migraine ($p = 0.0120$). At the same time a similar association of *NOS2* SNV C(-1026)A (rs2779249) was not found [55].

2.3.5. Brain tumors

Bhatti P. et al. (2009) studied associations of 9 *NOS1* SNVs (see Section "Brain tumors" *NOS1*), *NOS2* SNVs rs944725, rs4795067, rs2297516, rs2779252, rs8072199 and 3 *NOS3* SNVs (see Section "Brain tumors" *NOS3)* with a risk of brain tumors in 362 patients with glioma (176 of whom had glioblastoma multiforme), 134 patients with meningioma and 494 healthy controls. There is statistically significant evidence that a carrier status of *NOS2* SNVs rs944725, rs2779252, rs8072199 was associated with a risk of meningioma ($p = 0.03$), SNV rs4795067 associated with a risk of glioblastoma ($p = 0.05$) and meningioma ($p = 0.02$), while SNV rs2297516 ($p = 0.05$) associated with a risk of glioma [30].

2.3.6. Ischemic stroke

Yan J.T. et al. (2011) studied 588 patients with IS and 557 healthy controls for associations of SNVs of *NOS2* Leu608Ser (rs2297518), *NOS3* (see Section "Ischemic stroke" *NOS3*), as well as *GCH1* and *CYBA* with a risk of IS. The analysis results showed no statistically significant associations of *NOS2* SNV G>A Leu608Ser (rs2297518) with a risk of IS in the study Chinese Han population [56].

Wang X. et al. (2009) investigated SNVs of *NOS2* 231C>T (rs1137933) and *NOS3* (see Section "Ischemic stroke" *NOS3*). The meta-analysis of 6 studies performed in the USA, Europe and China did not obtain statistically significant results in 3,550 patients and 6,560 controls [57].

2.3.7. Multiple sclerosis

Al Fadhli S. et al. (2013) screened 122 patients with MS and 188 healthy individuals for SNVs of *NOS1* (see Section "Multiple sclerosis" *NOS1*), *NOS2* (CCTTT)n/(TAAA)n and *NOS3* (see Section "Multiple sclerosis" *NOS3*). The analysis results showed the association of the *NOS2* (CCTTT)n/(TAAA)n genotype with a risk of MS in the population of Kuwait [41].

2.4. *NOS3* Gene

The *NOS3* gene encodes nitric oxide synthase 3. *NOS3*, also known as *eNOS*, *ECNOS*, is localized on the long arm of chromosome 7, position 7q36.1, (Figure 7). It's expression is shown in figure 8.

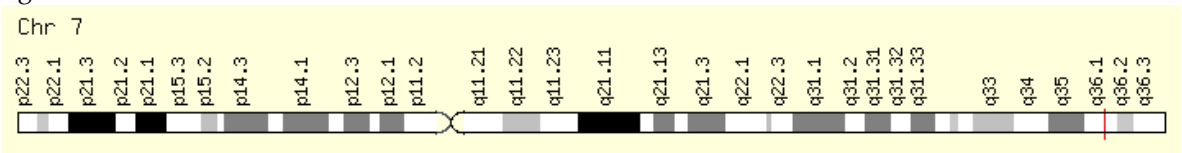

Figure 7. Localization of *NOS3* [7].

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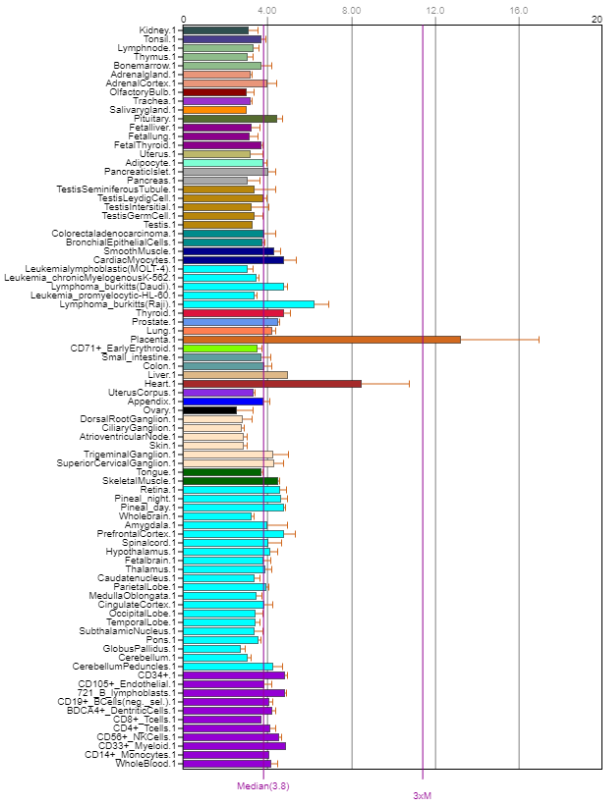

Figure 8. Expression of nitric oxide synthase 2 in the human body [5].

2.4.1. Methamphetamine-induced psychosis

Methamphetamine (METH) is an illegal addictive drug that causes mental disorders. According to recent findings METH selectively increases the NO concentration in the (corpus) striatum that leads to dopaminergic neurotoxicity in the human brain. Okochi T. et al. (2011) studied functional SNVs (rs1800779, rs2070744, rs1799983, rs3918188, rs743507, rs7830) of *NOS3* in 183 patients with METH-induced psychosis (METH-i.ps.) in comparison with 267 controls. No significant association was found between the study *NOS3* SNVs and the risk of METH-i.ps in the Japanese population [58].

2.4.2. Depression

There is evidence that depression is related to an increased risk of mortality and morbidity with to coronary artery disease (CAD). Three *NOS3* SNVs such as rs2070744, rs1799983, VNTR are reported to be associated with CAD. Ikenouchi-Sugita A. et al. (2011) studied these SNVs in 51 depressed patients in the Japanese population. The study results suggest no association between the study SNVs and a risk of depression [59].

2.4.3. Suicide

The *NOS3* gene is involved in proliferation of neuronal precursors, that might be associated with the pathology of depressive disorders. *NOS3* SNVs T-786C (rs2070744) and 27bpVNTR are supposed to be associated with a risk of BAD and suicidal behavior. Sáiz P.A. et al. (2007) had no statistically significant findings in 186 suicide attempters as compared to a group of 420 healthy controls from the Spanish population [60].

2.4.4. Parkinson's disease

Hancock D.B. et al. (2008) studied associations of 27 *NOS1* SNVs (see Section "Parkinson's disease" *NOS1)*, 18 *NOS2* SNVs (see Section "Parkinson's disease" *NOS2*) and 5 *NOS3* SNVs rs1800783, rs1549758, rs1799983, rs3918227, rs1808593 with a risk of PD in 337 families with sporadic

PD from the USA and 358 families with familial PD. The study found no association of *NOS2* with PD in patients at the age of 40 to 80. However, a carrier status of *NOS3*SNV rs1808593 was associated with PD in patients younger than 40 years old ($p = 0.046$) [3].

2.4.5. Ischemic stroke

Yan J.T. et al. (2011) investigated the association of *NOS2* SNV (see Section "Ischemic stroke" *NOS2*), and *NOS3* SNVs G>T (D298E) (rs1799983), T>C (rs2070744) with a risk of IS in 558 patients with IS and 557 healthy controls. No associations with the study SNVs were found [56].

In the meta-analysis of 6 studies performed in the USA, Europe and China Wang X. et al. (2009) analyzed the association of *NOS2*SNVs (see Section "Ischemic stroke"*NOS2*)and *NOS3*SNVs (-922) A>G (rs1800779), (-690)C>T (rs3918226), 298Glu>Asp (rs1799983) with a risk of IS in 3,550 patients ischemic stroke and 6,560 controls no associations were detected [57].

Du D. et al. (2008) found that the A allele of *NOS3*SNV rs3918181 ($p = 0.684$) was associated with a risk of IS in men in the sample of 560 patients with IS and 153 healthy controls in the Chinese population. At the same time, this association was not observed among women [61].

Manso H. et al. (2011) investigated the effect of *NOS1*SNVs (see Section "Ischemic stroke" *NOS1*) and *NOS3* SNVs rs1800783, rs2373929 on IS susceptibility and outcome after IS. The study population consisted of 551 stroke patients and 530 controls. The study results revealed no statistically significant evidence that supported the association of the study SNVs and a risk of IS [38].

2.4.6. Dementia

Dementia develops in 25% of patients who sustained IS. The *NOS3* gene is one of those associated with vascular regulation; however, it has not been considered as a potential risk factor for dementia. In the study performed by Morris C.M. et al. (2010) the TT genotype of *NOS3* SNV p.Asp298Glu (rs1799983) ($p = 0.001$) increased a risk of dementia as compared to the GG genotype in the study population of 253 post-stroke patients older than 75 years [62].

2.4.7. Migraine

Schürks M. et al. (2009) studied *NOS3* SNVs rs1800779, rs3918226, rs1799983 in 4,705 women with migraine and 21,008 healthy women. The analysis results supported the association of *NOS3*SNV rs3918226 with the risk of migraine without aura ($p = 0.04$) [63].

The study of Toriello M. et al. (2008) did not confirm the association of *NOS3* SNVs 786T>C (rs1800779) and Glu298Asp (rs1799983) with migraine in 337 patients, including 188 migraines with aura, and 341 healthy individuals from the Spanish population [64].

Gonçalves F.M. et al. investigated *NOS3* SNVs T(-786)C (rs2070744), Glu298Asp (rs1799983), 27 bp variable number of tandem repeats (VNTR), rs3918226 and rs743506 in 178 women with migraine including 44 patients with aura and 134 ones without aura. Neither of five SNVs was statistically significant. The GA genotype of *NOS3* SNVrs743506 was more common in the control group than in patients with migraine with aura. However, haplotypes CCaGluG and "CCbGluG" of the *NOS3* gene ($p < 0.0015$) were associated with migraine with aura [65].

2.4.8. Brain tumors

Bhatti P. et al. (2009) screened SNVs of *NOS1* (see Section "Brain tumors" *NOS1), NOS2* (see Section "Brain tumors" *NOS2),* and *NOS3* rs1799983, rs4496877, rs12703107 for a risk of brain tumors. Statistically significant findings indicate that a carrier status of SNV rs1799983 ($p = 0.04$) was associated with the risk of glioblastoma multiforme, rs12703107 associated with glioblastoma multiforme ($p = 0.007$) and glioma ($p = 0.04$), while rs4496877 associated with meningioma ($p = 0.02$) [30].

2.4.9. Infantile cerebral palsy

Asphyxia, neurological diseases, infections in the uterine cavity, amnionitis, maternal autoimmune diseases, metabolic disorders, as well as vascular lesions are risk factors for infantile cerebral palsy (ICP). Genetic theory has been recently considered and *NOS3* is one of the candidate genes. Wu D. et al. (2011) performed a meta-analysis of 11 studies and found no association of *NOS3* SNVs rs1800779, rs1799983 and rs3918226 with a risk of ICP in 2,533 patients with ICP in comparison with the control group consisting of 4,432 healthy children [66].

2.4.10. Multiple sclerosis

Al Fadhli S. et al. (2013) studied SNVs of *NOS1* (see Section "Multiple sclerosis" *NOS1)*, *NOS2* (see Section "Multiple sclerosis" *NOS2)* and *NOS3* (rs1800783, rs1800779, rs2070744, 27bpVNTR). The analysis results demonstrated that the G allele of *NOS3*SNV rs1800779 ($p = 0.04$) and the GG genotype ($p = 0.02$) were associated with a risk of MS. The A allele of *NOS3* SNV 27bpVNTR was associated with an early onset of MS (≤26 years old, $p = 0.043$). The A/b haplotype of *NOS3* SNV 27bpVNTR leads to a 23% decrease of NO production, while the *NOS3* expression decreased with the AA genotype of the gene SNV rs1800779 [41].

2.4.11. Gentamicin-induced vestibular dysfunction

The use of aminoglycoside antibiotics, such as gentamicin (GM), is known to lead to permanent ototoxicity. NOS inhibition has been shown to reduce the toxicity of GM. Roth S.M. et al. (2008) studied candidate genes which promote susceptibility to GM-induced vestibular dysfunction (GM-i.v.d.). A proposed oxidative stress's model of GM-induced ototoxicity underlay the selection of these candidate genes. The authors studied *NOS3* SNVs c.893G>T (p.Glu298Asp) (rs1799983), c.-813T>C (rs10952298), c.582+250N27 (4_5)** VNTR in 137 patients with unilateral or bilateral GM-i.v.d. and 126 healthy controls from the American population. It was found that a carrier status for SNV c.893G>T (p.Glu298Asp) (rs1799983) was associated with a risk of GM-i.v.d. ($p = 0.03$) [67].

2.4.12. Hypoxic-ischemic encephalopathy (HIE)

The blood-brain barrier permeability is impaired in hypoxic-ischemic encephalopathy (HIE). This process is multifactorial and results from oxidative stress, increased vascular endothelial growth factor levels, and increased inflammatory cytokines and NO concentrations. *NOS3* is predominantly expressed in vascular endothelial cells and can prevent neuronal injury by producing small amounts of NO to expand blood vessels, maintain cerebral blood flow, inhibit platelet aggregation or prevent oxidative damage. Wu Y. et al. (2016) studied *NOS3* SNVs rs1800783, rs1800779 и rs2070744 in 226 children with HIE and 212 healthy children with a birth weight of 1,001-1,449 g in a Chinese population. Apgar scores and magnetic resonance image scans were used to estimate the symptoms and brain damage. According to results the distribution of *NOS3* SNV rs2070744 significantly varied in children with different Apgar scores (≤5, TT/TC/CC = 6/7/5; 6~7, TT/TC/CC = 17/0/0; 8~9, TT/TC/CC = 6/2/0; 10, TT/TC/CC = 7/1/0; $p = 0.006$). Thus, the *NOS3* SNV rs2070744 ($p = 0.026$) was associated with high susceptibility to HIE [68].

Kuzmanić Samija R. et al. (2011) analyzed *NOS3* SNVs rs3918186, rs3918188, rs1800783, rs1808593, rs3918227, rs1799983, and rs1800779 in the Croatian population consisting of 110 preterm born children with HIE and 128 preterm born children without HIE at the age of 2 years and older. Genotyping results showed the association of SNV rs1808593 ($p = 0.0023$) only with a risk of HIE. At the same time, the TG haplotype of rs1800783-rs1800779 ($p < 0.00$) also showed an association with HIE [69].

2.4.13. Cerebral ischemia following subarachnoid hemorrhage

Endothelial dysfunction, pro-inflammatory processes in the vascular bed and an impaired fibrinolytic cascade following aneurysmal subarachnoid hemorrhage (aSAH) due to aneurysm

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rupture, contribute to cerebral microthromboembolism. Massive cerebral vasospasm reduces the cerebral blood flow and increases the risk of a cerebrovascular accident. NO is a key molecule to maintain the cerebral blood flow and regulate platelet aggregation, white blood cell adhesion and migration, and smooth muscle proliferation. Results of the study performed by Hendrix P. et al. (2017) for 4 years (2012-2015) demonstrated the C allele of *NOS3* SNV rs2070744 ($p = 0.040$) increased a risk for a delayed cerebral ischemia in a group of 149 patients with aSAH. At the same time this SNV was not associated with a functional outcome or a size of aneurysm at the time of rupture [70].

3. Conclusion

Results of critical analysis of the available literature (Tables 1-3) demonstrate an apparent scientific and clinical interest in studying a prognostic role of polymorphisms of the genes encoding enzymes involved in NO synthesis. However, the results of studies we have discussed in this review are contradictory, that might be due to different designs of the studies, small sample sizes in some of them, as well as different social and geographical characteristics. However, the contribution of genetic and environmental factors has been understudied, that makes this issue increasing for researchers as the understanding of these mechanisms can support a search for new approaches to pathogenetic and disease-modifying treatment.

Table 1. Association of *NOS1* SNVs with neuropsychiatric disorders

SNV	Psychiatric Disorders					Neurologic Disorders				
	Schizophrenia	Depression	BAD	ASD	PD	Brain tumors	Stroke	Cognitive disorders	MS	RLS
rs1004356		+ [20]								
rs1047735	- [9, 11]		- [9]	- [27]	+ [3]					
rs10507279		+ [20]								- [40]
rs10774907										- [40]
rs10774910					- [3]					
rs10850803						- [30]				
rs10850807										- [40]
rs1093329										- [40]
rs1093330							- [38]			
rs11068428							- [38]			
rs11068438							- [38]			
rs11068445							- [38]			
rs11068446										- [40]
rs11068447					+ [3]					
rs1123425					- [3]	- [30]	- [38]			- [40]
rs11611788					- [3]		- [38]	+ [36]		
rs12578547					- [3]					- [40]
rs12829185					+ [3]		- [38]			
rs1353939						- [30]				
rs1483757					- [3]		+ [38] - [39]			
rs1520810		- [20]					- [38]			
rs1520811	+ [15]				- [3]					
rs1552227					- [3]		- [38]			- [40]
rs1552228					- [3.]					
rs1607817							- [38]			
rs17509231							- [38]			
rs1875140		- [20]								
rs1879417	+ [16] - [10]	- [21] - [22]					- [38]	- [21]		- [40]

rs2133681	- [11]							
rs2139733						+ [38] - [39]		
rs2291908					- [30]			
rs2243044			- [27]					
rs2293048								- [40]
rs2293050		+ [20]				+ [38] - [39]		
rs2293051	- [9]		- [9]					
rs2293052				+ [3]				
rs2293054	- [11]		- [27]	- [3]				- [40]
rs2293055				- [3]				- [40]
rs2650163								- [40]
rs2682826	+ [8] - [9, 10, 13, 14]	+ [21]	- [9, 26]	- [27]	+ [3]		- [21]	- [41]	- [40]
rs3741473	- [10]							
rs3741475			- [27]	+ [3]		- [38]		
rs3741476			- [27]					
rs3741480			- [27]					
rs3782206	+ [10] - [9, 13, 14, 16]		- [9]				+ [35]	
rs3782218		+ [20]		+ [3]		- [38]		
rs3782219	+ [9] - [10, 13, 14, 16]		- [9]					
rs3782221	+ [9] - [10, 13, 14, 16]		- [9]	- [3]		- [38]		
rs3837437	+* [10]							
rs41279104	+ [11, 14, 16] - [10, 13]	- [20, 25]	- [25]				+ [34]	- [41]	
rs473640								- [40]
rs4766836								- [40]
rs4767523				- [3]				
rs4767533		- [20]						
rs4767535					- [30]			- [40]
rs4767540	- [10, 16]							
rs478597				- [3]				
rs483589					- [30]			
rs499776	+* [10] + [16]							
rs499813								- [40]
rs522910		+ [20]						
rs527590		- [20]				- [38]		- [40]
rs530393								- [40]
rs532967	- [9]		- [9]					
rs545654				- [3]	- [30]			- [40]
rs547954				- [3]		- [38]		
rs561712	+* [10] - [9, 13,	+ [20]	- [9]	- [3]				

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	14]						
rs576881					- [38]		
rs579604		**-** [20]					
rs6490121	**+** [12] **-** [13, 14, 17]			- [30]		**+** [31, 32, 33]	**-** [40]
rs693534		**+** [20]		**-** [3]			**+** [40]
rs7133438							**-** [40]
rs7139256				**-** [3]			
rs7298903					- [30]	- [38]	
rs7295972				**+** [3]			
rs7308402						**+** [38] **-** [39]	
rs7309163						- [38]	
rs7314935						- [38]	
rs7959232		**-** [20]					
rs7977109						- [38]	**+** [40]
rs816292							**-** [40]
rs816293					- [30]	- [38]	
rs816296		**-** [20]					
rs816346						- [38]	
rs816347							**-** [40]
rs816351					- [30]		
rs816353						- [38]	
rs816354				**-** [3]		- [38]	
rs816357		**-** [20]				- [38]	
rs816361						- [38]	
rs877995							**-** [40]
rs904658						- [38]	
rs9658247			**-** [27]				
rs9658255			**-** [27]				
rs9658266						- [38]	
rs9658267						- [38]	
rs9658281		**+** [20]				- [38]	
rs9658536						- [38]	
rs9658570							**-** [40]

* – gaplotype

Table 2. Association of *NOS2* SNVs with neuropsychiatric disorders

SNV	Psychiatric Disorders			Neurologic Disorders			
	Depression	**ASD**	**PD**	**Migraine**	**IS**	**Brain tumors**	**MS**
rs944725			-[3]			+ [30]	
rs10459953	-* [22]	- [27]					
rs1060826		+[27]	-[3]				
rs1137933		- [27]	-[3]		- [57]		
rs2072324			+ [3]				
rs2248814			- [3]				
rs2255929		- [27]	+ [3]				
rs2297515	+*[22]		- [3]				
rs2297516			+ [3]			+ [30]	
rs2297518	- [22], +* [22]	- [27]	- [3]	+ [54, 55]	- [56]		
rs2314810			- [3]				

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rs2779248		- [27]					
rs2779249				+ [54], - [55]			
rs2779252					+ [30]		
rs3201742		- [27]					
rs3730014			- [3]				
rs3794764			+ [3]				
rs3794766			- [3]				
rs4795067			- [3]		+ [30]		
rs7406657		- [27]					
rs8068149		+ [27]					
rs8072199			- [3]		+ [30]		
rs10459953	- [22], +* [22]	- [27]					
rs12944039			+ [3]				
rs16966563			- [3]				
rs17722851			- [3]				
(CCTTT)n/(TAAA)n						+ [41]	

* – gaplotype

Table 3. Association of *NOS3* SNVs with neuropsychiatric disorders

SNV	Psychiatric Disorders				Neurologic Disorders							
	METH-i.ps	**Suicide**	**Depression**	**PD**	**Migraine**	**Brain tumors**	**Dementia**	**IS**	**ICP**	**MS**	**HIE**	**GM-i.v.d.**	**aSAH**
rs7830	- [58]												
rs743506					- [65]								
rs743507	- [58]												
rs1549758				- [3]									
rs1799983	- [58]		- [59]	- [3]	- [63, 64, 65]	+ [30]	+ [62]	- [56, 57]	- [66]		+* [69]	+ [67]	
rs1808593											+ [69]		
rs1800779	- [58]				- [63, 64]			- [57]	- [66]	+ [41]	- [68]		
rs1800783				- [3]				- [38]		- [41]	- [68, 69] +* [69]		
rs1808593				- [3]							+ [69]		
rs2070744	- [58]	- [60]	- [59]		- [65]			- [56]		- [41]	+ [68]		- [70]
rs2373929								- [38]					
rs3918181								+ [61]					
rs3918186											- [69]		
rs3918188	- [58]										-		

							[69]	
rs3918226			+ [63] – [65]		- [57]	- [66]		
rs3918227		- [3]					- [69]	
rs4496877				+ [30]				
rs10952298								- [67]
rs12703107				+ [30]				
27bpVNTR	- [60]	- [59]	- [65]			+ [41]		- [67]

* – gaplotype

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Abbreviations

NO	Nitric oxide
NOS	Nitric oxide synthase
iNOS	Inducible nitric oxide synthase
nNOS	Neuronal nitric oxide synthase
eNOS	Endothelial nitric oxide synthase
SNV	Single nucleotide variant
BAD	Bipolar affective disorder
GWAS	Genome-wide association study
OR	Odds ratio
GDS	Geriatric Depression Scale
ASD	Autism spectrum disorders
PD	Parkinson's disease
MMSE	Mini mental state examination
IQ	Intelligence quotient
EEG	Electroencephalogram
IS	Ischemic stroke
RLS	Restless legs syndrome
MS	Multiple sclerosis
NMDAR	N-methyl-d-aspartate-receptors
DNA	Deoxyribonucleic acid
NMDA	N-methyl-d-aspartate
PTSD	Post-traumatic stress disorder
BDI	Beck Depression Inventory
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
8-oxoG	8-hydroxyguanine
8-iso-PGF2a	8-iso prostaglandin F2a
MDA	Malondialdehyde
CNS	Central nervous system
METH	Methamphetamine
METH-i.ps.	METH-induced psychosis
CAD	Coronary artery disease

VNTR	Variable number of tandem repeats
ICP	Infantile cerebral palsy
GM	Gentamicin
GM-i.v.d.	GM-induced vestibular dysfunction
HIE	Hypoxic-ischemic encephalopathy
aSAH	Aneurysmal subarachnoid hemorrhage

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