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Reviews

Genetic outline of autism spectrum disorders (ASD) – part II. Neuro- and immunogenetics

Genetyczny zarys zaburzeń ze spektrum autyzmu (ADS) – część II. Neuro- i immunogenetyka

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A – koncepcja i przygotowanie projektu badań, B – wykonanie analiz diagnostycznych, zbieranie danych, C – analiza statystyczna, D – interpretacja danych, E – przygotowanie manuskryptu, F – opracowanie piśmiennictwa, G – pozyskanie funduszy.

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SUMMARY

The early opinion stated that autism spectrum disorders (ASD) is caused by bringing up a child in a family with emotionally withdrawn mother. From the 50s of the last century until present the research in developmental biology provided essential evidence that the disorder is caused by multiple genetic variants and environmental factors, acting possibly via epigenetic processes.

In multiple population studies, genetic aetiology of ASD was discussed. Data on ASD concordance in twins, risk ratio in siblings and heritability of relative risk factors confirmed the thesis that the disorder has a clear genetic basis but the inheritance pattern is complex. The autistic brain structure and function were shown to be altered as a reflection of skewed physiological processes during neurodevelopment. Other line of inquiry suggests that core symptoms of autism may develop as a result of disruptions within immune circuitry.

To date, number of genes were found to be candidates to ASD, although the majority of individuals with idiopathic form of the disorder will not have an identifiable genetic background. In the first part of the review we discussed diversity of genetic variations in individuals with ASD and analysed genetic background of syndromic ASD. This part of the review provides information on the crucial „candidates" genes, that may play a role in the pathogenesis of ASD. Here we present neurogenetical and immunogenetical aspects of the disorder.

Key words: **autism, aetiology, immunogenetic, genetic**

STRESZCZENIE

Jedną z pierwszych dyskutowanych przyczyn rozwoju zaburzeń ze spektrum autyzmu (ang. autism spectrum disorders, ASD) była hipoteza emocjonalnego odrzucenia dziecka przez matkę. Począwszy od lat 50. ubiegłego wieku do czasów współczesnych, badania z dziedziny biologii pozwalają stwierdzić, że w patogenezę ASD zaangażowanych jest wiele czynników środowiskowych oraz liczne czynniki genetyczne i epigenetyczne.

Przeprowadzono liczne badania populacyjne dotyczące genetycznych uwarunkowań ASD. Współwystępowanie zaburzenia u bliźniąt monozygotycznych, zwiększona częstość rozwoju ASD u rodzeństwa oraz odziedziczalność czynników ryzyka potwierdziły, że ASD jest wynikiem zmian genetycznych, jednak mechanizm dziedziczenia zaburzenia jest złożony. Wykazano, że struktura oraz funkcje mózgowia autystów są zmienione i odzwierciedlają nieprawidłowości procesów fizjologicznych podczas rozwoju układu nerwowego. Inna teoria głosi, że objawy osiowe ASD mogą być konsekwencją zaburzeń funkcjonowania układu odpornościowego.

Do dnia dzisiejszego zidentyfikowano liczne geny potencjalnie zaangażowane w rozwój ASD. Należy jednak wspomnieć, że u większości osób z idiopatycznymi postaciami zaburzenia, nie jest możliwe zidentyfikowanie specyficznego podłoża genetycznego. W pierwszej części pracy podano informacje na temat różnorodności zmian genetycznych w ASD oraz zademonstrowano podłoże genetyczne syndromicznych postaci ASD. W niniejszej, drugiej części, dostarczono informacji na temat kluczowych genów-kandydatów mogących odgrywać rolę w patogenezie ASD. Zaprezentowano neuro- oraz immunogenetyczne podłoże ASD.

Słowa kluczowe: **autyzm, etiologia, immunogenetyka, genetyka**

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IDIOPATHIC ASD

Neurogenetics – synaptic genes

Variants of genes involved in synaptogenesis and synaptic connectivity were shown to be associated with cases of typical autism, Asperger syndrome and mental retardation [1]. Number of genes including, among others, neurexins (NRXN), neuroligins (NLGN), SH3 and multiple ankyrin repeat domains (SHANK) and contactin associated protein-like 2 (CNTNAP2), attract the most attention. Nevertheless, one should note that variations within synaptic genes are not limited to ASD, but also occur in numerous neuropsychiatric disorders (e.g. schizophrenia, epilepsy, Alzheimer's disease) [2-3].

The neurexin gene family (NRXN) encodes presynaptic, transmembrane receptors acting as adhesion molecules of postsynaptic proteins (neuroligins) to form Ca(2+)-dependent complexes mediating neurotransmission and synaptic formation. The NRXN gene family comprises three genes, namely: NRXN1, NRXN2, NRXN3, generating over 3000 splice variants [4]. Mutations of CNVs and rare variant types in the NRXN1 gene mapped on chromosome 2p16.3 affect both exons and introns of the gene. As NRXN1 was reported to express numerous mRNA transcripts, it was postulated that deletions within introns disrupt proper splicing thus participate in ASD phenotype. A number of recent studies confirmed that deletions/microdeletions in neurexin 1 locus strongly correlate with ASD and other psychopatologies, such as schizophrenia, developmental and speech delay. Breakpoint analysis of these deletions suggested that coexistence of small-size inverted repeats may produce local genomic instability. Duong et al. [5] identified a compound heterozygous mutation involving a deletion and a point mutation in a patient suffering from autism, mental retardation, and epilepsy. The same deletion was found in probant's mother with subdiagnostic autism. The point mutation was also present in probant's brother with a psychotic disorder, probably inherited from father, who suffered from schizophrenia. This clinical differences and presence of NRXN1 deletions in unaffected carriers draws attention to not full penetrance and expressivity of NRXN1 variants [5-8]. To date, only in two individuals, ASD was probably originated in NRXN2 gene mutations. One case was a patient with a truncating mutation within exon 12 inherited from his father suffering from severe speech disability and family history of schizophrenia [9]. The other one, a 21-year-old patient, was carrying a 0.57 Mb de novo deletion of 24 genes in 11q13.1 locus, comprising NRXN2 and MEN1 (multiple endocrine neoplasia type 1) genes. Clinically he presented core autistic traits, speech impairments, dysmorphic facial features, broad thumbs with short distal phalanges and a pancreatic gastrinoma [10].

Vaags et al. [11] reported four ASD cases with exonic microdeletions in NRXN3 gene. In one case the deletion was inherited from the father diagnosed with subclinical autism. In others, the variations were found in healthy parents of the probant. Similarly to neurexin1 gene, NRXN3 deletions are of reduced penetrance and/or variable expressivity nature [11].

Contactin associated protein-like 2, encoded by CNTNAP2 gene, belongs to neurexin family. The protein mediates neural interactions, localization of K(+)-channels and synapses maturation. This gene has been involved in numerous neurodevelopmental disorders, including ASD, ADHD, schizophrenia and Tourette syndrome. [12]. Several studies support CNTNAP2 relevance in autism spectrum disorder pathogenesis [13-14]. Common CNTNAP2 SNP (rs7794745) frequency was evaluated in research on 72 multiplex families providing positive association toward ASD [15]. In a male-only study, by Alarcón et al. [16], authors found significant association for CNTNAP2 SNP rs2710102. Li et al. [17] confirmed significant correlation between CNTNAP2 rs10500171, haplotype T-A (rs7794745; rs10500171) and haplotype A-T-A (rs10244837; rs7794745; rs10500171ASD in Chinese Han population.

Neuroligins (NLGNs) are postsynaptic cell-adhesion proteins acting as ligands for neurexins. NLGNs are involved in signal transmission, as well as formation and remodelling of synapses. They may also play role in the development of peripheral nervous system. Neuroligins aggregate with neurexins in order to localize the specified synaptic receptors. Neurexins induce both glutaminergic and GABA-ergic differentiation in postsynaptic dendrites. Similarly NLGNs stimulate presynaptic differentiation in axons. Whereas NLGN1, NLGN3, and NLGN4 proteins are specific to glutaminergic receptors, NLGN2 connect with both kinds of synapses, but its primary affinity is to GABA-ergic axons [18]. Furthermore Yasuda et al. [19], by examining lymphoblastoid cell lines, concluded that these protein expression is lower in individuals with ASD than in healthy controls, which confirmed possible involvement in the pathophysiology of this condition.

This family consist of 5 genes, namely NLGN1, NLGN2, NLGN3, NLGN4X, NLGN4Y. Mutations in these genes are known to be associated with neurodevelopmental abnormalities and other cognitive disorders, including ASD. Multiple alternative transcript variants have been identified [20]. Copy number variations in the NLGN1 were proved to be associated with ASD via genome-wide CNV study in cohorts of European ancestry [21]. In a study of 100 Finnish families one SNP in NLGN1 (rs1488545) was proved to be associated with ASD [22]. Rare genetic variations in NLGN3 and NLGN4X have been identified in several cases of ASD. Some of these NLGNs mutations was reported to alterate excitatory (EPSP) or inhibitory (IPSP) neurotransmission. One of them - a missense mutation NLGN3 (451R>C) - enhanced IPSP without

changing EPSP impairing excitatory–inhibitory balance in central nervous system. Another missense mutation within NLGN3 (704R>C) reduced AMPA-ergic neurotransmission (EPSP) in the hippocampus, but did not alterate NMDA- or GABA-ergic transmission (EPSP and IPSP respectively) [23]. Ylisaukko-oja et al. [22] reported that NLGN3 variant (DXS7132) and NLGN4Y variant (DXS996) correlated with ASD in a cohort of Finnish autism families. Other studies confirmed that rare, deleterious variants in NLGN3 and NLGN4X genes are associated with ASD [24-26].

Another group of genes involved in neurotransmission is SH3 and multiple ankyrin repeat domains family, including SHANK1, SHANK2 and SHANK3 genes. Encoded proteins interact with neuroligins in excitatory synapses forming molecular scaffolds in postsynaptic density (PSD). SHANK proteins comprises various domains for protein-protein interaction. Abundant molecular structure as well as numerous splice variants contribute to wide spectrum of Shank-interacting proteins in PSD. SHANK proteins support signal transmission by interconnecting NMDA-ergic and metabotropic glutamate receptors with cytoskeleton in adult and developing brain [27].

Several studies indicated CNVs and SNPs in SHANK genes involvement in aetiology of ASD. In recent meta-analysis of over 5,500 patients with ASD, mutations in SHANK genes presented approximately 1% prevalence (of which 0,04%- SHANK1; 0,17%- SHANK2 and 0,69%- SHANK3). Interestingly, no truncating mutations in SHANK3 were detected in over 1,000 controls. Authors concluded, that clinical relevance of SHANK1 and SHANK2 deletions remains to be of ascertain significance, while SHANK3 mutations should be considered for screening in clinical practice [28].

Sato et al. [29] revealed two deletions in SHANK1 locus; one was segregated in a four-generation family with only male carriers affected. The other was de novo mutation found in unrelated male. In both cases patients suffered from high functioning ASD. A polymorphism, rs3810280 in SHANK1 promoter was reported to cause impaired auditory working memory in patients with schizophrenia [30]. SHANK1 loss of function was reported to result in behavioural features, i.e. reduced levels of ultrasonic vocalizations, scent marking, motor activity and others [31-32].

Genetic alterations (mostly CNVs and microdeletions) in SHANK2 revealed to be associated with ASD in numerous studies. These mutations were reported to be functional affecting protein localization, dendritic spine morphology and synaptic transmission. In patients with SHANK2 mutation one can observe decrease in synaptic density at dendrites compared to the variants only detected in controls. [33-36]. Apart from relatively common variations, two de novo loss-of-function mutations have been reported to by strongly correlated with ASD by Sanders et al. [37] SHANK3 locus belongs to a polygenic region, deletion of which is correlated with Phelan-McDermid syndrome, that is accompanied by ASD. Number of studies revealed associations between ASD and SHANK3 genetic variation. To date, eight de novo mutations in this gene have been identified in simplex families. Detected mutations included CNVs, deleterious variants, missense mutations, insertions and chromosome abnormalities. [28, 38-40]. Durand et al. [40] described a couple of patients with ASD and SHANK3 mutations. Boy with deletion located in intron 8 presented autism, mental retardation and non-language skills. Insertion in exon 21 in two brothers with ASD lead to severely impaired speech and mental retardation in both of them. Girl with terminal 22q deletion had autism and severe language delay while her brother with a 22q partial trisomy despite of suffering from Asperger syndrome, demonstrated fluent speech and precocious language development. Their cytogenetic abnormalities were inherited because of paternal translocation.

Immunogenetics

It was demonstrated that in individuals with ASD immune response is altered. The observations were made in central nervous system [41-44], peripheral blood [45-48] and the gastrointestinal tract [49-52]. Moreover, maternal autoimmunity correlation with autism occurrence was found [53-54]. Dysregulated production of inflammatory cytokines, chemokines, immunoglobulins and altered cellular response attract an attention in immunogenetical aspects of autism pathophysiology [55]. However, a relatively small number of research was published concerning immunogenetical factors in ASD. The most important in our opinion are discussed below.

Major histocompatibility complex (MHC) proteins loci has been linked to ADS recently. GWAS studies comprising neuroatypical patients revealed genetic variations in MHC region proving the impact of these molecules on brain development, synaptic function, T cell family formation and shaping the specific properties of antigens that are presented to T cells [56-58]. In few studies it was reported that human leukocyte antigen (HLA) loci present the most abundant common variant risk for autism [59-60].

HLA locus was mapped on chromosome 6p21.31 and consists of more than 160 coding genes [61]. HLA class II region gene, DRB1, encodes a subunit of HLADR protein acting as a mediator in antibodies production [62]. It was proved that ASD individuals and their mothers often carry the major susceptibility allele for rheumatoid arthritis, HLA-DRB1*04 [63-66]. However, Torres et al. [67] proved that autism risk allele HLA-DRB1*04 was inherited more frequently from fathers while a protective allele HLA-

DRB1*13 less frequently from mothers. An American study conducted in a population of Tennessee reported that HLA-DRB1*0401 and DRB1*0404 alleles were more frequently observed in autistics and their mothers [68]. According to Johnson et al. [69] transmission disequilibrium of HLA-DRB1*04 was significantly only from grandmothers to mothers of autistic children, indicating the risk allele is acting predominantly in prenatal period [69].

Considering genes involved in innate and adaptive immunity, variations in for example protein kinase C (PRKCB1) or MET proto-oncogene can be inherited by ASD children [60, 70]. The PRKCB1 gene was mapped on chromosome 16p11.2 and alternative splicing of the gene results in expressing two isoforms of the protein . Theses protein kinase isosymes were found to regulate B-cell mediated immune response, T-cell migration, inflammatory cytokines production and monocyte/macrophage function. In gastrointestinal tract they regulate gut permeability and endothelium proliferation [60]. Philippi et al. [71] found that CGT haplotype consisted of rs3785387, rs196002 and rs1873423 was more frequently observed in autistic individuals. The replication of the finding was performed by Lintas et al., [60], nevertheless the aforementioned haplotype in intron 2 differed at SNP rs1873423 (haplotype CGC). The researchers also proved that PRKCB1 gene variants, namely rs3785392 and rs3785387, results in oligopeptiduria phenotype. Additionally they reported the PRKCB1 gene expression in temporal neocortex was decreased by approximately 30% in ASD patients in comparison to healthy controls and the expression of PKCb-related genes (TGFβ2, MCP1, Endothelin-2, Collagen IV, VI, Fibronectin) was lost. These all state that the PRKCB1 in ASD may be involved in deregulated immune response consisted with symptoms seen in autistics.

The MET proto-oncogene was discovered on chromosome 7q31. The coding protein, namely MET receptor tyrosine kinase, plays essential role in neuronal growth and maturation but also in immunity, including gastrointestinal tract repair [72-73]. Multiple studies confirmed that disruption within MET pathway contributes to altered interneuron migration and maturation in cortex and decreased proliferation of granule cells in cerebellum, both of which are often seen in ASD individuals [74-76]. Importantly, MET cascade induces tolerogenic phenotype via activating IL-10, which makes T cells respond to antigen thus limiting the risk of autoimmunity [77]. A functionary element of transcription, common variant rs1858830 (G>C polymorphism) in MET promoter was reported to be more frequently carried by autistic individuals and associated with 2 fold reduction in gene expression [72]. Later it was presented that in cerebral cortex specimens collected post mortem from autistic individuals, significantly decreased MET protein concentration was observed, in recessive model of inheritance [78]. Moreover, rs1858830 variant was found to play role in co-occurence of gastrointestinal dysfunctions in children with ASD [79], confirming the hypothesis that maternal immune related factors in gestation may be involved in ASD aethiopathogenesis. [55]. Interestingly, Heuer et al. [80] demonstrated that mothers carrying MET rs1858830 C allele more frequently produce ASD autoantibodies to fetal brain. Additionally, in peripheral blood mononuclear cells obtained from these women, MET protein expression was significantly reduced. At last, it was demonstrated that in mothers homozygous for MET rs1858830 C allele, expression of IL-10 was decreased and associated with reduced MET protein levels [80].

Migration inhibitory factor (MIF) gene was located on chromosome 22q11 and the encoded protein (MET) is an innate immunity mediator, particularly regulating cytokines production, thereby associated with the incidence and a clinical course of autoimmune disorders [81]. On the other hand, it was proposed that inadequate concentration of MIF protein during the neurodevelopment may disturbed innate immunity thus predispose to ASD [41]. Grigorenko et al., [42] conducted research involving more than 1000 participants and concluded that functional polymorphisms in promoter region of MIF gene, particularly CATT repeat (−794 CATT5–8) and single nucleotide polymorphism −173 G>C, may be important in developing ASD phenotype. The researchers found that −794 CATT6 allele was strongly associated with stereotypical components of ASD. The plasma level of MIF was elevated in autistic individuals and positively correlated with social dysfunction and imaginative abilities evaluated with the Autism Diagnostic Observation Schedule (ADOS).

CONCLUSIONS:

In aetiology of Autism Spectrum Disorders participates many genes with complex patterns of inheritance. However, the results of studies confirmed that additional environmental factors are needed to manifest/exacerbate the disorder. The ASD comprises few neurodevelopmental disorders with a variable phenotype, and genetic research are still growing but the results are often inconsistent or contradictory. It should be emphasized that genetic abnormalities are discovered only in about 10% of ASD patients, which taken together state that specific ASD locus may even not exist. Nevertheless, the impact of genetic variations in biology underlying behaviour is being still explored making these studies attractive toward understanding the pathogenesis of ASD.

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