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Reviews

Genetic outline of autism spectrum disorders (ASD) – part I. Genetic diversity and syndromic ASD

Genetyczny zarys zaburzeń ze spektrum autyzmu (ADS) – część I. Zróżnicowanie genetyczne oraz objawy ADS

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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

Autism Spectrum disorder (ASD) comprises a group of the following neurodevelopmental disorders: autism disorder, not specified pervasive developmental disorder and Asperger's disorder. It is diagnosed when impaired social and communication skills and unusual repetitives occur. The aetiology of ASD has partially the genetic background, especially in syndromic ASD cases. Many genes were found to be associated with ASD, including those involved in central nervous system functioning and immune response. Additionally, multiple genetic variants were identified in genome of autistic patients. However, mutations discovered to date are either rare variants participating in ASD aetiology in handful of autistics or common variants of a small risk toward ASD. These all state that specific locus/loci for the disorder may not exist. In the following review we analyzed data from PubMed, Google Scholar using the following key words: autism spectrum disorder, genetic, immunogenetic, polymorphism. The Simons Foundation Autism Research Initiative (SFARI) gene database was evaluated as well. The review is divided into two parts. In the first part we present diversity of genetic variations in individuals with ASD and analyse genetic background of syndromic ASD. The objective of the second part is to review key genes involved in the idiopathic form of the disorder, including neuro- and immunogenetic aspects of ASD. Overall, the study present the diversity of genomic architecture of ASD.

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

STRESZCZENIE

Zaburzenia ze spektrum autyzmu (ang. Autism Spectrum disorder, ASD) obejmują następujące schorzenia neurorozwojowe: zaburzenia autystyczne, zespół Aspergera oraz całościowe zaburzenia rozwoju inaczej nieokreślone. Diagnoza ASD stawiana jest w przypadku stwierdzenia deficytów w relacjach społecznych, zachowań nacechowanych stereotypią i powtarzalnością oraz upośledzeniach zdolności komunikowania się i rozwoju mowy. W etiologii ASD odgrywają czynniki genetyczne, zwłaszcza w syndromicznej formie zaburzenia. Zidentyfikowano wiele genów potencjalnie związanych z patogenezą ASD, wśród nich geny kodujące białka zaangażowane w funkcjonowanie układu nerwowego oraz odpowiedź immunologiczną. Jednocześnie w genomie osób z ASD dowiedziono istnienia różnego rodzaju zmian genetycznych. Należy zaznaczyć, że dotychczas odkryte mutacje są identyfikowane u małego odsetka pacjentów, zaś opisane polimorfizmy stanowią niewielkie ryzyko rozwoju ASD. Według aktualnego stanu wiedzy specyficzne locus/loci dla ASD nie istnieją. W niniejszej pracy dokonano analizy prac opublikowanych w bazach PubMed i Google Scholar. Przy wyszukiwaniu stosowano następujące deskryptory: zaburzenia ze spektrum autyzmu, genetyka, immunogenetyka, polimorfizm. Przeanalizowano również bazę The Simons Foundation Autism Research Initiative (SFARI). Pracę podzielono na dwie części. W pierwszej zaprezentowano dane na temat rodzaju zmian genetycznych oraz podano dowody na podłoże genetyczne ASD będącego składową zespołu wad. Obiektem zainteresowania drugiej części pracy uczyniono geny zaangażowane w rozwój idiopatycznych postaci ASD. Scharakteryzowano neuro- oraz immunogenetyczne podłoże ASD. W obu częściach pracy ukazano różnorodność podłoża genetycznego ASD.

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

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BACKGROUND

Autism Spectrum Disorder is a behavioural syndrome with multifactorial background, first described in 1943 by Leo Kanner [1-4]. There is an extensive body of evidence including research on twins, indicating that the disorder is heritable, although additional environmental factors for its manifestation/exacerbation are needed [5]. Additionally, the increased prevalence of mental disorders in family members of child with ASD is consistent with the genetic risk of the disorder [6-9]. The disorder usually manifests before the age of 3 years, predominantly in males [10], lasts lifelong [11], and clinically comprises impaired social interaction, restricted communication skills and unusual repetitive skills [5].

During last decade, the increase in prevalence of ASD has been observed. In Europe, North America and Asia at about 1% of the entire population has been diagnosed with ASD [12]. By the latest report of Center for Disease Control and Prevention Morbidity and Mortality Weekly Report in United States of America, 78% increase in ASD prevalence over 5 years was observed [13].

Genetic studies in ASD patients have found many of candidate genes probably linked with the disease [14]. Majority of those genes are involved in the chromatin remodelling and development of neurons, thus responsible for the functioning of synaptic signalling within neurons. Genes associated with abnormal immune response in central nervous system, peripheral blood and gastrointestinal tract are of particular interest as well [15].

Genetic diversity of ASD

Genetic changes involved in ASD include: chromosomal aberrations, copy number variations (CNVs) and single nucleotide polymorphisms (SNPs). These changes are inherited or may occur de novo. Karyotype alterations occur from 3 to 6% subjects with ASD and include: translocations, inversions, duplications and chromosomal markers, in particular maternal isodicentric chromosome 15. with 15q11-q13 region usually being typically copied [16-17]. Mirror-image segments of genetic material, results in severe neurodevelopmental delay, motor impairment and seizures [18]. The CNVs (known as a large deletions or duplications) in a chromosome structure may also be linked with ASD. In a small percentage of individuals with ASD chromosomal rearrangements, including aneuploidy of chromosomes 21, X and Y were diagnosed [19]. These segmental aberrations may be recognized as allelic sequences in the cell cycle and cause non allelic homologous recombination, leading to recurrent genomic imbalance [20]. In ASD families, CNVs account for up to 19%, while in healthy population only 1% . In families with multiple individuals affected by ASD (multiplex family), and in families with only a single ASD individual (simplex family) Sebat et al. [21] identified de novo CNVs in 3% and 10%, respectively. Marshall et al. [22] reported that this ratio was 2% and 7%, respectively. Continuing, according to Levy et al. [23] de novo CNVs in simplex ASD families are around 8%. The highest CNVs prevalence, about 38%, was found in autistic individuals with dysmorphic features [24]. The important CNVs in ASD involve chromosomes: 1q, 2q, 7q, 15q, 16p, 17p, 18q and 22q, which include ASD candidate genes, coding among others, protein kinases (MARK1, MET, CRKL), transcription factors (FOXP2, HNF1B, TCF4, TBX1) and chromatin remodelling proteins (RAI1) [16].

Malhotra and Sebat [25] reported that CNVs in 16p11.2. locus, is the most common change linked with risk of ASD which occurs in 1% of cases. This rearrangement comprises about 27 genes and was linked with neurodevelopmental and psychiatric impairments, including brain differences. The deletion of the 16p11.2 region was associated with increased grey and white matter volume, opposite results were achieved in duplication carriers [26]. Microdeletion in 22q11.2 locus (known as Digeorge syndrome) in 20% of cases is characterized by developmental disabilities of autism [22]. The deletion causes brain ventricles enlargement, volumetric reduction of parietal lobes, hippocampus, cerebellum and corticol thickeness reduction being consistent with neuronal growth deficits in ASD

There are plenty of SNPs potentially involved in the development of ASD. The genome-wide association studies (GWAS) are relatively new genetic approach which does not require the formulation of hypotheses about the core cause of a disease and allow to examine many common genetic variants in association with a trait. There were many GWAS conducted for ASD. Although many single markers for ASD were identified and results were replicated in independent studies for most experiments the effect sizes were found to be relatively small [27-33].

On the other hand, Klei et al. [34] proved that common genetic polymorphisms may develop additive genetic effects in ASD, e.g. regarding the number of probants in a family. It has been found that effects of even a group of small SNPs, may highly affect the development of ASD. Simons Foundation Autism Research Initiative (SFARI) offers a comprehensive online database on genetics of ASD. The gene variants are scheduled by role in the pathogenesis of the disorder. The next paragraph prepared on the basis of SFARI database provides substantial information about common variants linked with ASD.

THE GENES INVOLVED IN THE AETIOLOGY OF ASD

Syndromic ASD

Autism Spectrum Disorder is often a comorbidity of monogenic diseases. It was reported that rare, well

known genetic variants (mutations) occur in up to 10% of ASD patients [16]. Among others [35], single-gene disorders including Fragile X Syndrome, tuberous sclerosis complex, Rett syndrome and Cowden syndrome are of particular interest. All of these disorders manifest clinically with dysmorphia. As stated in the Regulation of the Minister of Health in Poland [36] concerning guaranteed benefits in the field of outpatient specialist care, in all children with developmental disabilities of autism and altered physical features genetic counselling should be undertaken.

The most common inherited monogenic ASD is Fragile X syndrome (FXS), and in about 2% of ASD cases FXS is a primary disease 37, 38]. Wherein, almost 40-60% male and 20% of female FXS patients meet ASD diagnostic criteria [39-41]. The disorder phenotype includes: intellectual disability, cognitive and developmental impairments, macrocephaly, elongated face and enlarged ears [42].

The most common genetic cause of FXS is expansion of CGG trinucleotide repeats in 5'UTR region of the Fragile X Mental Retardation gene (FMR1, locus Xq27.3) coding Fragile X Mental Retardation Protein (FMRP). Typically the extension comprises more than 200 repeats, however in case of premutation (56-200 repeats) maternally transmission makes the alleles fully mutated [43]. This mutation makes the locus hypermethylated and transcriptionally silenced [44]. Also, there is a body of evidence indicating that not only epigenetic silencing of FMR1 may contribute to FXS thus ASD. According to SFARI, there are about 30 other point mutations within FMR1 gene contributing to autistic traits in FXS [45].

As FRMP protein is predominantly localized in the soma and dendrites and negatively mediates mRNA trafficking from nucleus to cytosol, the downstream regulation of FMR1 gene is an example of neuronal overgrowth phenotype [44]. In the post mortem brain bioptates of FXS patients with autism and in mice models of FXS, synaptic overabundance, neural hyperconnectivity/hyperexcitability and elevated neuronal proteins synthesis was reported [46-49].

Loss of function of FMR1 gene alters proper developmental timing. Harlow et al. [50] found that the FRMP is essential for barrel cortex plasticity, while He et al. [51] reported that the protein mediates the hyperpolarization of GABA (Glutamate gamma AminoButric Acid) signals. The body of research in FXS patients discovered overregulation within ERK1/2 (Extracellular-signal-Regulated Kinases) and mTOR (mechanistic Target Of Rapamycin) pathways and BDNF (Brain-Derived Neurotrophic Factor) signalling. The elevated phosphorylation status in abovementioned cascades and excessive BDNF signalling were found to be associated with upregulated neuronal proliferation in the brain thus confirming the pro-growth phenotype in this syndromic cause of ASD [52]. Although the loss of FRMP protein alter these cascades per se, precise mechanism of these actions needs to be elucidated.

Tuberous sclerosis (TS) is accompanied by ASD in almost half cases and characterized by a combination of symptoms including intellectual disability, developmental impairments and seizures. The physical features are usually facial angiofibromas [53-55].

The disorder is caused by mutations in Tuberous Sclerosis genes (TSC1 and TSC2) mapped on chromosomes 9q34 and 16p13.3, respectively. The mutations are inherited in autosomal dominant pattern. The coding proteins are tumor suppressors negatively mediating in mTOR signalling pathway thus contributing to mRNA translation [56]. The genes plays therefore important role in the nervous system, controlling brain growth, structure and connectivity [52]. In SFARI database multiple mutations within both genes are listed, with TSC2 mutations predominance. Majority of the mutations are nonsynomic thus leading to loss of function of corresponding genes. Particular rare variants make mTOR signalling hyperactivated which enhance neural protein synthesis, mimicking the overgrowth phenotype of ASD in FXS. In multiple in vivo studies it was shown that heterozygous mutations within TSC1/TSC2 genes impair synaptic functions, cognitive and social interactions [57-59]. Homozygous TSC1 mutations were found to be associated with severe neuronal hypertrophy and macrocephaly and/or lethality [58]. Complete loss of function TSC1/TSC2 mutations in post-mitotic neurons induced neuronal dysplasia, neural network overexcitability and reduced dendritic pruning [56, 60-61].

The Cowden Syndrome in 80% of cases is of known genetic background comprising mutations within phosphate and tensin homolog (PTEN) gene mapped on chromosome 10q23.3 [52]. The encoding protein PTEN being a phosphatase is involved in downregulating P13K-AKT (Phosphatidylinositol-4,5-bisphosphate 3-kinase - Protein kinase B) pathway. This intracellular cascade regulates the cell cycle [62] and its alterations are reflected in the phenotype of Cowden syndrome including cancers [63] and nervous systems impairments such as intellectual disability and other autistic traits with comorbid macrocephaly [64-67]. To date, over 20 autism reports concerning PTEN mutations were published mostly based on chromosomal microarray analysis (CMA) and whole-exome sequencing (WES) techniques [68]. The majority of rare genetic variants associated with autism, similarly to previously described genes, cause loss of function of PTEN protein thus predispose to overgrowth phenotype in central nervous system [69].

Rett syndrome (RTT), almost exclusively affecting females, in almost 100% cases is caused by genetic mutation within Methyl-CpG-binding protein 2 gene (MeCP2) located in X chromosome (Xq28). The MeCP2 protein is able to both inhibit and activate transcription in methylated

promoter [70]. In central nervous system its biological role comprises as well maturation as pruning of synapses [71]. Physically these mutations manifests as core autistic features comprising social impairments and repetitive behaviours accompanied by stereotypic hand movements. In contrast to previously described syndromic genes, loss of function mutations within MeCP2 gene, observed in aproximately 95% cases of RTT patients, result in undergrowth synaptic/neuronal phenotype. Reiss et al. [72] and Jellinger [73] in post mortem RTT brain specimens found a decrease in branching and density of dendritic network and reduced white matter volume, however noticed no signs of neurodegeneration. The latest research stated that MeCP2 deficiency lower the level of ribosomal RNAs [74]. Additionally, it was proved that MeCP2 deficiency suppress the activity of a few neuronal-plasticity genes, including BDNF [75]. In SFARI database multiple mutations within MeCP2 are listed, with a relatively high percentage of autistic related ones [76].

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