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Systematic review of the literature on single-nucleotide polymorphisms within the neuroligin (NLGN) gene in the development of autism spectrum disorder

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ABSTRACT

Introduction: *Recently, multiple studies have attempted to explain the pathophysiology of autism spectrum disorder. Many researchers have suggested the potential role of mutations in genes encoding proteins called neuroligins as one of the triggers of autism. Potentially more than one factor is causing the development of ASD.*

Material and methods: *We reviewed publications obtained from PubMed, the Cochrane Library, APA PsychNET and Google Scholar. Articles were selected based on keywords such as "autism", "ASD", and "neuroligins". For the final analysis, 8 qualified articles were published from January 2008 to August 2022.*

Results: *Studies conducted recently have drawn our attention to the significant relationship between autism and NLGN mutations in some autistic populations. One of the studies showed a significant association between blockades of SNPs in the NLGN4X. The second confirmed that the three-marker haplotype blockade was related to an increased risk of ASD in males. On the other hand, one publication stated that SNPs found in the studied population did not significantly differ in allele frequency between ASD patients and controls.*

Conclusions: *Mutations in the NLGN gene should be investigated further as ASD factors. The results of these studies are not consistent. Some of these findings confirm the association between ASD and mutations in neuroligins. At the same time, others negate any links in that matter. It is possible that the ethnicity of the patients influenced the research outcomes. More studies with larger study groups are needed to clarify discrepancies between the authors.*

Keywords: autism spectrum disorder; SNP; neuroligin; autism; mutations

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that affects 23.2/10 000 people in Southeast Asia and 205/10 000 people in the African population [1]. According to the available studies, approximately 32/10 000 children aged 0–16 in Poland are affected by ASD depending on the region of the country taken into consideration [2]. The actual prevalence of autism is not known due to differences in classifications and diagnostic criteria; however, it is estimated that approximately 1–2% of the human population has autism [3–5]. In addition, multiple studies have shown an increase in the prevalence of autism

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in recent years [6, 7]. This could improve diagnostic procedures as well as acceptance and awareness of the disease among society.

Symptomatology of ASD

Based on the still applicable ICD-10 diagnostic classification and the DSM-IV diagnostic criteria that are no longer in use (but still used in the articles), the core symptoms of ASD include deficits in social interactions, communication and limited, repetitive and stereotypical patterns of behavior (according to DSM-IV, also interests and activities) [8, 9]. However, the clinical presentation of ASD is usually very heterogeneous and may include a variety of different symptoms. Symptoms of ASD usually develop in early childhood; nevertheless, they might remain undetected for several years, especially in the female population, until social expectations exceed the limited skills of the person. Furthermore, ASD in the female population is a particular issue because females may demonstrate more subtle symptoms or be more susceptible than males to masking their behavior [10]. Therefore, the incidence of ASD in girls is lower than that in boys, with a ratio of approximately 4.2:1 [1].

ASD pathophysiology

Autism spectrum disorder is a polygenic disorder with a significant environmental influence, modifying its course and clinical picture. However, the wide range of genes with a suggested role in the development of ASD, as well as the significant heterogeneity of the symptomatology of the disorder itself, means that the exact mechanism of its development remains unknown. Furthermore, an increasing amount of evidence suggests that symptoms from the autism spectrum might be common in the general population, and their severity is linked to the number of pro-ASD variants present in the genotype of each person. With an increasing number of pro-ASD alleles, the intensity of clinical presentation escalates, eventually leading to the cutoff point for clinical diagnosis. On the other hand, genetic susceptibility in individuals with ASD is not equal to phenotypic autism [11]. According to previous studies, both genetic and environmental factors are responsible for ASD development [11]. Genetics could be adjusted in a positive or negative way by alterations in epigenetic mechanisms, prenatal factors and the postnatal environment. The degree to which various factors increase or decrease the severity of autism symptoms is determined by genotype [11]. The complexity of the origins of autism has led researchers to seek potential etiologic mechanisms. One of those considered in previous years was malfunction of the neuroligin family of postsynaptic cell adhesion molecules [12].

The NLGN family

The *NLGN* family consists of five members in human species: *NLGN1*, *NLGN2*, *NLGN3*, *NLGN4X* and *NLGN4Y*. The genes encoding those proteins are located at chromosomes 3q26 (*NLGN1*), 17p13 (*NLGN2*), Xq13 (*NLGN3*), Xp22.3 (*NLGN4X*) and Yq11.2 (*NLGN4Y*) [13]. Neuroligins are large transmembrane proteins that form a transsynaptic complex with other proteins, such as presynaptic neurexin. On the other side of the cellular membrane, the cytoplasmic domain interacts with family of shank proteins [14]. The proper function of these proteins determines optimal synaptic transmission by regulating neurotransmitter release and controlling neuronal development [13]. Due to the highly dynamic and complex structure determined by posttranslational modifications and other protein-to-protein interactions, single amino acid differences can result in a deficit of protein function [15]. Moreover, all neuroligins have their own pattern of localization on synapses. Neuroligin-1 is mostly found at excitatory synapses and regulates synaptic transmission and plasticity. Neuroligin-2 is predominantly localized at inhibitory synapses and controls synaptic transmission. These two types of synapses are represented by one type of synapse that participates in one kind of transmission; in contrast, neuroligin-3 can be isolated from both types of synapses [16].

According to recent studies, neuroligins are expressed in most CNS cells, not only in neurons but also in astrocytes and oligodendrocytes. Glial cells and neurons can connect *via* the neuroligin-neurexin complex. In addition, neuroligins can be transcribed throughout life, especially in astrocytes, which indicates the importance of long-term support in astrocyte–neuron communication [17]. In other studies, interfering with neuroligin-neurexin signaling in oligodendrocytes was shown to interrupt the myelination process in a rat model [18]. Furthermore, neuroligins, mainly neuroligin-3, play a significant role in the regulation of mRNA translation in rodent brains [19]. It also modulates dendritic structure, which underlines the importance of neuroligins in synaptic development in animal brains [16]. Several studies in animal models have shown that *NLGN3*-mutant mice have a decreased size of the hippocampus, striatum, corpus callosum, somatosensory cortex and cerebral peduncles. Additionally, the *NLGN3* knockout mice had less white matter than the WT mice (wild type) [17, 18]. However, how ASD affects human development is unclear; however, ASD patients were found to have altered brain size and myelination [18, 20]. The individuals with ASD in other studies had relatively smaller volumes of corpus callosum, which suggests underconnectivity in cortical interhemisphe-

ric structures [21]. Although evidence from studies on animal models seems to be quite promising, at present, there are no sources analyzing the relationship between polymorphisms in *NLGN* genes and changes in brain structure in humans. However, there are studies in the literature indicating relationships between genotype and nosological entities in the field of neurodevelopmental disorders, e.g., intellectual disability [22].

Several mutations in genes encoding proteins from the neuroligin family have been detected in the DNA of people with autism but not in that of healthy people. Considering the important role that neuroligins play in a properly functioning brain, these mutations could participate in the development of clinical symptoms of ASD.

Neuroligins plasma levels

A 2020 human study in Saudi Arabia revealed that plasma levels of neuroligin-4 X-linked were higher ($p = = 0.001$) in children with autism than in controls [23]. This study assessed cognitive dysfunction and social impairment in autistic patients using the Childhood Autism Rating Scale (CARS) and the Social Responsibility Scale (SRS). Despite changes in of neuroligin-4 X-linked levels in the subgroups of autistic children, no correlation between plasma of neuroligin-4 X-linked concentration and cognitive impairment or social impairment ($p > 0.05$) was observed [23].

Considering the scientific reports presented above, we decided to further examine the role of polymorphisms in neuroligin genes in the pathogenesis of ASD. For this purpose, we collected and systematized all the research on this subject known thus far.

Materials and methods

The search engines PubMed, the Cochrane Library, APA PsychNET and the Google Scholar browser were searched by each author separately. The following keyword combinations were used: "autism", "ASD", "autism spectrum disorder", "neuroligin", "neuroligins", "*NLGN*", "neuroligin mutation", "SNP", "single nucleotide polymorphism". The authors also checked the bibliography of the analyzed articles in terms of related research. When duplicate reports were observed during the search, only the most complete one was included in the aggregate meta-analysis. Eligible studies met the following inclusion criteria: 1) were published between January 2008 and August 2022; 2) were published in English or Polish; 3) were published in periodical publication; 4) focused on the role of single nucleotide polymorphisms within neuroligin genes in ASD populations; 5) provided a clear presentation of the applied methodology; and 6) applied proper methodology. The Newcastle–Ottawa (NOS) scale was used to assess the quality of the nonrandomized studies included in the meta-analyses. Parameters such as the selection of research groups, group comparability, and determination of the exposure or outcome of interest in case–control studies or cohort studies, as appropriate, were assessed.

Results

An initial review revealed 10,310 publications. After eliminating the articles unrelated to the topic of interest and eliminating duplicates, 120 articles remained. In the next stage, the abstracts of the remaining studies were analyzed. At this stage, 60 articles were selected, the entire texts of which were then analyzed. Additionally, during the selection process, 1 study from the analysis of the bibliography was included. The inclusion criteria, as well as the Newcastle–Ottawa Scale (NOS), made it possible to qualify 8 studies for the final analysis. The exact process of selecting articles is presented in Figure 1. The characteristics of all the studies included in the analysis are shown in Table 1. Table 2 summarizes the results of the analyzed publications.

Tables 3 and 4 present an overview of the NLGN4X and NLGN3 gene polymorphisms, respectively, that have been studied in randomized clinical trials in large populations and can be found in the study population.

The review of gene polymorphisms for *NLGN4X* and *NLGN3*, which have been studied in large populations in randomized clinical trials and did not show significant differences in allele frequencies between ASD patients and controls can be found in Table 5.

The SNPs rs5916269, rs1882260 and rs3810688 in *NLGN4X* were mentioned in four of the analyzed publications. All of these SNPs were found to be significantly associated with ASD when they were included in a blockade of SNPs in the Landini et al. study [26]. Moreover, these SNPs were detected in the ASD population in a study published by Hedge et al. in September 2021 [29]. Lu Y et al. [30] also identified those SNPs in *NLGN4X*; however, association analysis with ASD showed no significant difference in SNP frequencies between autistic patients and healthy controls.

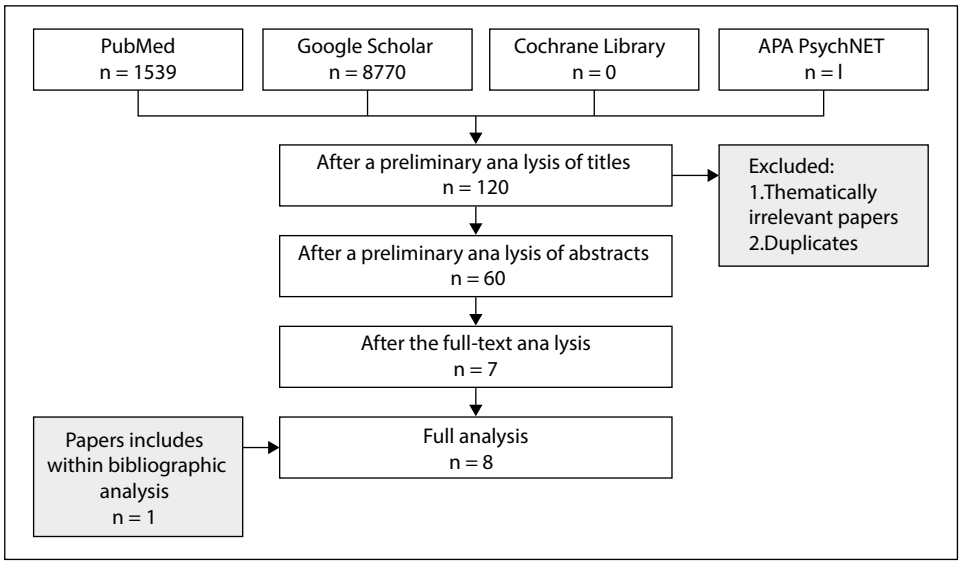

Figure 1. Flow diagram of the analysis

Table 1. Characteristics of all studies included in the analysis

Author (year)	Ethnicity	Study design	Genotyping type	Diagnostic criteria
Xu X. et al. (2014) [24]	Chinese	Case–control	PCR-DS	DSM-IV, CARS
Yu J. et al. (2011) [25]	Chinese	Case–control	MALDI-TOF mass spectrometry	DSM-IV, ICD-10
Landini M. et al. (2016) [26]	Italian	Case–control	PCR-HRM	DSM-IV, ADOS
Yanagi K. et al. (2012) [27]	Japanese	Case–control	PCR-HRM	DSM-IV, CARS, ADI-R
Hegde R. et al. (Dec. 2021) [28]	Indian	Case–control	RT–PCR	DSM-5, ICD-10
Hegde R et al. (Sept. 2021) [29]	Indian	Cross-sectional	RT–PCR	DSM-5, ICD-10
Liu Y. et al. (2013) [30]	Chinese	Case–control	Multiplex PCR	DSM-IV
Khaleda L. et al. (2022) [31]	Bangladeshi	Case–control	PCR-DS	DSM-IV

ADI-R — Autism Diagnostic Interview-Revised; ADOS — Autism Diagnostic Observation Scale; CARS — Childhood Autism Rating Scale; DHPLC — Denaturing high-performance liquid chromatography; DSM-IV — Diagnostic and Statistical Manual of Mental Disorders, 4th ed.; DSM-5 — Diagnostic and Statistical Manual of Mental Disorders, 5th ed.; ICD-10 — Tenth Revision of the International Classification of Diseases; MALDI-TOF — Matrix-assisted laser desorption ionization time-of-flight; Multiplex PCR — Multiplex fluorescence competitive polymerase chain reaction; PCR-DS — Polymerase chain reaction-direct sequencing; PCR-HRM — Polymerase chain reaction-High Resolution Melting.

Table 2. Summary of the analyzed publications

No.	Publication	Type/data	Results
		Studies regarding genes for *NLGN4X* and *NLGN3*	
1.	Xu X. et al. (2014) [24]	318 unrelated Chinese autistic patients (270 men and 48 women) mean age 6 years ranging from 3–18 years	A common SNPs (rs3747333 and rs3747334) were identified in the *NLGN4X* gene significantly associated with the risk of autism. Four rare missense variants were also identified in the *NLGN3* and *NLGN4X* genes (p.G426S in *NLGN3* and p.G84R, p.Q162 K, p.A283T in *NLGN4X*) in the autism cohort, which were not detected in a group of 453 controls.
2.	Yu J. et al. (2011) [25].	229 unrelated patients with ASDs (mean age: 5.5 years, 83.4% males, 16.6% females)	In males, a significant association between ASD and mutations in the *NLGN3* genes was observed for the three-marker haplotype blockade (rs11795613-rs4844285-rs4844286). The rs4844285--X^G allele had an increased risk for male with ASDs. In females, one two-marker haplotype blockade in the *NLGN4X* genes (rs11795613-rs4844285) and SNP rs5916397 was significantly more frequent in the ASD population than in controls. The rs5916397-X^A allele was overrepresented in female individuals with ASDs.

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Table 2 cont. Summary of the analyzed publications

No.	Publication	Type/data	Results
		Studies regarding genes for *NLGN4X* and *NLGN3*	
3.	Landini M. et al. (2016) [26].	202 autistic children from Italy (165 (81.7%) males; 37 (18.3%) females) aged 2 to 12	No statistically significant haplotypes have been found in the *NLGN3*. A 6-SNPs haplotype blockade in *NLGN4X* shows a significant association with ASD (rs6638575(G)-rs3810688(T)- rs3810687(G), −rs3810686(C), −rs5916269(G), −rs1882260(T)) Also shorter haplotypes with 5-,4-,3-,2- loci blockades in the region spanning from SNPs rs6638575 to rs3810686 were found to be associated with ASD.
4.	Yanagi K. et al. (2012) [27].	62 Japanese patients with ASD (51 males, 11 females)	Identification of one SNP (rs6639602) in the *NLGN4X* in a female ASD patient. Also, there were found: one synonymous substitution, c.297C > T (p.G99G) observed in a female patient, and two substitutions, c.516C > T (p.I172I) and c.1590C > T (p.F530F) in two male patients. Identification of a synonymous substitution in *NLGN3* c.1698G > A in a male ASD patient.
5.	Hegde R. et al. (Sept. 2021) [29].	108 children with ASD diagnosis (85 males, 23 females); age range 5–18 years and mean age 11.7 ± 3.5 years	Identification of 25 different variants in the *NLGN4X* gene (eight 5'UTR variants, four missense variants, four synonymous variants, one frameshift variant and eight 3' UTR variants). Nine (36%) variants were novel and sixteen (64%) variants were previously recorded in the databases. All 5' UTR variants were found to be heterozygous. Two missense and two synonymous variants were also heterozygous. The rs149114901 was found 3 times, rs755890454 once, rs971248204 five times. The not reported mutations were: g. 5082C > Y, g. 5159 T > Y, g.5160 A > M, g.5266 T > K, g.5295C > Y.
6.	Hegde R. et al. (Dec. 2021) [28].	108 children with ASD diagnosis (85 males, 23 females); age range 5–18 years and mean age 11.7 ± 3.5 years	Identification of one coding sequence variant and four noncoding sequence variants in *NLGN3* genes not reported previously SNP databases. The coding sequence variant c.551 T > C (p.V184A) was a missense variant observed in 27 autistic children (25%). The 5'-UTR variant g.5040 C > W was found in one (0.92%) and –g.5041 T > A was found in five (4.6%) studied children, while the 3'-UTR variant g.30370 C > Y was observed in 75 autistic children (69.4%) and –g.30349–30350 Ins AC was observed in 21 (19.4%) patients. The g.5040 C > W and g.30370 C > Y variants were heterozygous.
7.	Khaleda L. et al. (2022) [31].	A total of 60 members of 15 families (including ASD subjects) and another 60 ASD subjects and 60 healthy people ASD children mean age 4–30 years	One SNP of *NLGN3* (rs4844285) was significantly associated with ASD at a 5% level of significance. The A allele of *NLGN3* rs4844285 was found as the risk allele of ASD in the study. For *NLGN4X* rs6638575 G allele and GG genotype and for rs3810686 T allele and TT genotype were observed to be preferentially transmitted to the affected individuals which presumably points to the inheritance postulation.
8.	Liu Y. et al. (2013) [30].	285 Chinese patients with ASD diagnosis (246 males and 39 females) with a mean age of 7.05	Only one synonymous mutation in *NLGN4X* listed as rs7049300 was found in one ASD individual. No nonsynonymous mutation in *NLGN4* was detected in the cohort. In *NLGN4* six common SNPs were identified in the coding region and regulatory region (minor allele frequency > 5%). They were rs5916355 in the promoter region, rs3810688, rs3810686, rs5916269, rs1882260, and rs140700235 in 3'UTR. Association analysis of these six SNPs with ASD did not show significant difference of allele frequencies between ASD patients and controls.

Table 3. Review of *NLGN4X* gene polymorphisms

	SNP/nucleotide position (*in the case of unreported SNP)	Description
Xu X. et al. (2014) [24]	rs3747333 *	Missense
	rs3747334 *	Synonymous
	p.Q162K	Missense
	p.G84R	Missense
	p.A283T	Missense
Yu J. et al. (2011) [25]	rs11795613-rs4844285-rs4844286	(In male)*
	rs11795613-rs4844285	(In female)*
Landini M. et al. (2016) [26]	rs6638575(G)-rs3810688(T)-rs3810687(G)-rs3810686(C)--rs5916269(G)-rs188260(T)	
Yanagi K. et al. (2012) [27]	rs6639602 c.-305-86T > G 5′UTR	
	c.297C > T	Synonymous
	c.516C > T	Synonymous
	c.1590C > T	Synonymous
Hegde R. et al. (Sept. 2021) [29]	g.324659_324060 insG	Frameshift
	rs1460330547	Synonymous
	rs770601703	Missense
	g. 82,723 A > R	Missense
	rs201534650	Missense
	g. 82,774C > Y	Synonymous
	rs7049300	Synonymous
	rs3747333	Missense
	rs3747334	Synonymous
	rs149114901 5′UTR	
	g. 5082C > Y 5′UTR	
	rs755890454 5′UTR	
	g. 5159 T > Y 5′UTR	
	g.5160 A > M 5′UTR	
	rs971248204 5′UTR	
	g.5266 T > K 5′UTR	
	g.5295C > Y 5′UTR	
	rs3810688 3′UTR	
	rs3810687 3′UTR	
	rs3810686 3′UTR	
	rs3810685 3′UTR	
	rs5916269 3′UTR	
	rs16983882 3′UTR	
	rs1882260 3′UTR	
	g.342537A > G 3′UTR	

*Polymorphisms significantly more frequent in the study group than in the control group

The SNP rs3810686, like the three mentioned above, was also found in the studies described above. In addition, in the study by Khaleda et al., the T allele and TT genotype of this SNP were observed to be preferentially transmitted to the affected individuals [31].

Khaleda et al. also showed that the rs6638575 G allele and GG genotype were preferentially transmitted to ASD patients [31]. The same SNP was found within the blockade of SNPs in the research of Landini et al. [26]. This blockade, as mentioned above, was significantly associated with autism.

Xu X et al. identified two SNPs in the *NLGN4X* gene, rs3747333 and rs3747334, in the autistic population [24]. Both of these terms were also mentioned in the publication by Hedge et al. [29].

The SNP rs4844285 in the *NLGN3* gene is one of the most promising mutations found in the present study. Yu J et al. [25] showed that rs4844285, found in

Table 4. Review of *NLGN3* gene polymorphisms

	SNP/nucleotide change	Description
Xu X. et al. 2014 [24]	p.G426S	Missense
Hegde R. et al. (Dec. 2021) [28]	g.15417 T > C	Missense
	g.30370 C > Y 3'UTR	
	g.30349-30350 Ins AC 3'UTR	
	g.5041 T > A 5'UTR	
	g.5040 C > W 5'UTR	
Yanagi K. et al. (2012) [27]	c.567+22C > T	Intronic
	c.567+52C > T	Intronic
	c.727+47G > C	Intronic
	c.1698G > A	Synonymous
Yu J. et al. (2011) [25]	rs4844285	
Khaleda L. et al. (2022) [31]	rs4844285 AA alleles	

Table 5. Review of gene polymorphisms for *NLGN4X* and *NLGN3*

	SNP/nucleotide change					
Liu Y. et al. (2013) [30]	rs5916355	rs3810688	rs3810686	rs5916269	rs1882260	rs140700235

the three-marker haplotype blockade, was related to an increased risk of ASD in males. Khaleda et al. [31] confirms that rs4844285 is significantly associated with ASD.

Discussion

Dysfunction of neuroligins caused by mutations in *NLGN* genes was primarily described in 2003 in a Swedish family with two ASD-affected brothers. All the patients carried the same frameshift mutation, which led to premature termination of the neuroligin-4 protein. Both of these patients inherited it from their unaffected mother. Jamain et al. suggested that a defect in *NLGN*s may increase susceptibility to developing autism [12]. Since then, dozens of scientists have performed different types of studies on *NLGN* mutations to determine its role in the pathophysiology of ASD. Our analysis of these reports indicates that malfunctioning neuroligins may indeed influence autism development.

One of the SNPs found in the studied populations was rs4844285 in the *NLGN3* gene, which was mentioned in two publications as a potential risk factor for ASD. Yu J et al. demonstrated that the rs4844285-X^G allele increased the risk of autism in males, with an odds ratio (OR) = 1.872 [95% confidence interval (CI) = = 1.175–2.981] [25]. Moreover, in this study, three--marker haplotype blockades (rs11795613-rs4844285--rs4844286), which include the rs4844285 polymorphism, were found to be significantly more frequent in the autistic population. This finding suggested that combinations of SNPs play a role as susceptibility factors for ASD (in this case, with an OR = 1.834) [25]. Additionally, Khaleda et al. concluded that the rs4844285 polymorphism has a significant genetic association with autism [31]. Here, the A allele was considered to be a risk factor for ASD (p = 0.028, c2 = 5.414, OR = 1.833, 95% CI = 1.098–3.061) [31]. Notably, only the affected members of the family possessed this genotype, while most of the parents and siblings, who were healthy, had the GG genotype. This finding led us to conclude that the disease was not inherited from parents. Both studies have shown that this polymorphism has a statistically significant influence on the risk of developing ASD.

The available literature shows support for the association between ASD and *NLGN* dysfunction as one of the potential factors for developing autism. On the other hand, some of the papers are in opposition to this point of view. One, in detail shown in a section above, conducted by Liu et al. [30] seems to reject the connection of *NLGN* mutations and autism. However, the sample size (285 patients) was relatively large, other factors might have had an influence on the negative outcome of the study [30]. The absence

of these mutations may be the effect of differences in ethnicity and background between the studied groups, for example, Caucasian versus Chinese. Other contradictory studies included a smaller sample of patients, e.g., Volaki et al. (only 40 patients) and Wermter et al. (107 individuals) [32, 33]. All of those studies sequenced only the coding exons and associated splice junctions of *NLGN3* and *NLGN4X*; we can assume that other mutations in regulatory regions, such as promoters, also influence the function of neuroligins, thus affecting ASD development.

The negative outcomes of these studies may be the result of the complex pathophysiology of ASD. The presence of *NLGN* mutations might be one of the many yet unknown factors predisposing patients to developing this disease. Moreover, the appearance of polymorphisms in *NLGN* genes can also be a cause of different forms of disability in addition to autism. In 2009, Hongbin et al. reported an association between two haplotype combinations, rs3810686-rs1882260 and rs6638575-rs3810686-rs1882260, in the *NLGN4X* gene and nonspecific forms of mental retardation in Chinese children [22]. In this study, autistic children were excluded. Similar SNPs and SNP combinations were found in the Italian cohort and linked to ASD diagnosis in the research carried out by Landini M et al. [26] in 2016 as described in detail in the text above. This only emphasizes the complexity of the influence that genetics can have on phenotype outcomes.

We should consider ASD development a multicausal process conditioned by multiple variables, such as genetics, epigenetics and the environment. Each factor or mutation intensifies the severity of ASD to the point where we can diagnose autism with specific diagnostic criteria and psychiatric tools.

Further research in this field, which is definitely necessary, should involve large sample sizes from different backgrounds and ethnicities to better understand the role of *NLGN* mutations in ASD pathophysiology. Nonetheless, studies investigating the mutations in regulatory sequences of *NLGN* genes should be conducted to explain in detail the influence of neuroligins malfunction in autism.

Conclusions

Even though the pathophysiology of autism spectrum disorder is still unknown, the potential role of described mutations in the *NLGN* genes should be taken into consideration in case of ASD development. Since some of the related studies confirm the association between autism and SNPs in those genes this case should be researched further. It seems that blockades of SNPs are more common in the autistic population. Interestingly, some studies disagree and deny the association between *NLGN* mutations and ASD. However, the outcomes of these studies may differ because of the different ethnic backgrounds of the studied populations. More studies should be carried out on larger populations to verify the role of *NLGN* mutations in ASD pathology.

Article information and declarations

Author contributions

Methodology: K. S. and N.F.
Investigation: D.S. and A.S.
Conceptualization: J.Sz.
Writing — review and editing: K.Ś and W.W.
Writing — rough preparation: M.B. and M.M.
Supervision: J.S and N.L.
All authors read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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