Review Article

Non-coding RNA in relation to autism spectrum disorder

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Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder that represents a serious public health concern due to its increasing prevalence rates, severity of symptoms, and absence of a causal treatment. Increasing number of experimental studies as well as review articles indicate that dysregulation of non-coding RNAs (ncRNAs) contribute to ASD development. Some ncRNA have been already suggested as biomarkers for ASD screening. This review highlights the importance of all types of ncRNA already investigated in relation to ASD. Additionally, the most frequent study limitations are discussed at the end of this paper.

Keywords: Autism spectrum disorder (ASD); non-coding RNA (ncRNAs); biomarkers

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by its core symptoms that include impairments of social interaction, verbal and non-verbal communication, and restricted and stereotyped patterns of behavior and interests. The term "spectrum" refers to the wide range of symptoms and levels of impairment that may be present in individuals with ASD (1). According to recent data about 1 in 68 or 1.5% of children were identified with ASD in the United States, males being affected 4 to 5 times more frequently than females. ASD is a lifelong disability that represents a serious public health concern due to its increasing prevalence rates (2), severity of symptoms, and absence of a causal treatment (3).

A broad variety of changes in the brain anatomy have been described (4), also various mechanisms have been suggested to be involved in abnormal development and function of the central nervous system (CNS) in ASD, but neurobiology of the disorder remains poorly understood (5). Current understanding of the pathogenesis of ASD takes into account genetic factors along with the environmental factors. Hundreds of genes linked to ASD were confirmed, and it seems that ASD is a result of an interaction of multiple genes and gene combinations (6). Similarly, a number of environmental factors associated with ASD risk have been identified including air pollutants, heavy metals, pesticides, polychlorinated biphenyls and other chemicals, or perinatal factors. Still, scientific data have not proven any causal effects between the environmental factors and ASD, yet (7). There are a variety of other symptoms not considered as "core", which affect a sizeable proportion of individuals with ASD such as psychiatric or neurological conditions, gastrointestinal disturbances, or immune disorders. The reported co-occurrence rate of one or more diagnoses is reported to be as high as over 90% (8). The cognitive and behavioural features of ASD are thought to arise from dysfunction of the CNS. Given the diversity of etiological factors and clinical presentations of ASD, it has been proposed that ASD may involve also systemic abnormalities rather than being an exclusively a CNS disorder, at least in a major subset of individuals (9).

Non-coding RNAs (ncRNA) are defined as all RNA transcripts not translated into proteins. Given their association with various diseases, ncRNAs are thought to be important targets for their diagnosis and/or treatment. There is increasing number of research as well as review articles regarding the ncRNA and ASD in available databases documenting high interest of scientists in this field. This review highlights the importance of all types of ncRNA already investigated in relation to ASD. Additionally, the most frequent study limitations are discussed at the end of this paper.

NcRNA are generally divided into following types: small and long ncRNA. First type—the small ncRNA comprises a heterogeneous group of ncRNA that are transfer and ribosomal RNA, small nuclear RNAs (snRNA), small nucleolar RNAs (snoRNA), microRNAs (miRNAs), piwi-interacting RNAs (piRNAs), small interfering RNAs (siRNAs) and small Cajal body-specific RNAs (scaRNAs). Long ncRNAs (lncRNAs) are longer than 200 nucleotides in length. It was suggested that they appeared later in evolution. LncRNAs are found within protein coding genes, overlapping with promoters, exons or introns in either sense or antisense orientations. Additionally, lncRNAs that are transcribed from non-coding DNA sequences between protein-coding genes are called long intergenic ncRNAs. Both small and long ncRNAs have been demonstrated to be essential for brain development and higher cognitive abilities. Thus, they are also associated with a variety of neurodevelopmental, psychiatric and neurodegenerative diseases, including ASD (10). To the best of our knowledge, the most important and the most investigated ncRNA linked with ASD are miRNA and lncRNA.

Small ncRNAs in ASD

MiRNAs represent evolutionarily conserved type of ncRNA that can negatively regulate gene expression. About half of identified miRNA in humans is expressed in the brain and shows regulatory functions for a variety of biological processes related to prenatal and adult neurogenesis, brain maturation and synaptic plasticity (11,12). It has been shown that dendritic spines (protrusions from neuron's dendrites forming postsynaptic membranes) are more numerous in cortical pyramidal cells of ASD subjects (13). The function of a number of miRNAs was identified in regulation of dendritic spine density, structure and morphology, e.g., miRNA-132, miRNA-125b, miRNA-138 and miRNA-137 (14).

The ASD-related miRNA as well as snoRNA are unequally expressed in different regions across the brain. Stamova with colleagues (15) examined two regions in the human superior temporal gyrus: the superior temporal sulcus (STS) and the primary auditory cortex (PAC). Although both are neighboring, they have different functions. The STS as association cortex is involved in social interactions that are abnormal in ASD individuals. In contrary, PAC is a primary sensory cortex that modulates auditory processing, a function not usually associated with ASD impairments. Specific expression patterns of miRNA and snoRNA differ significantly between STS and PAC within normal human superior temporal gyrus and change significantly with age. In contrast, there were fewer differences of miRNA and snoRNA between STS and PAC in ASD brain post-mortem tissue, and there was loss of the typical age-related changes (15).

As ASD is a neurodevelopmental disorder that displays sexual dimorphism, the recent study of the same team of authors studied sexual dimorphism in ASD-related small ncRNAs expressions. There have been found 20 small ncRNAs differentially expressed in STS of ASD females compared to control females, but only 8 dysregulated in STS of ASD males compared to control males. Additionally, 8 small ncRNAs were differentially identified in PAC of ASD females compared to control females, and the 3 small ncRNAs dysregulated in PAC of ASD male compared to control males. Taken together, there are generally more dysregulated small ncRNA in ASD females compared to ASD males. This is consistent with a greater genetic load in females, a female protective effect, and possibly greater plasticity of female ASD brain. The authors speculated that there are specific miRNAs dysregulated in STS of female ASD brain associated with oligodendrocyte differentiation (miR-219 and miR-338) that could relate to sexual dimorphism of white matter tracts, miR-488 that could relate to more anxiety in females, and miR-125 and miR-181 implicated in neuronal development that may be sexually dimorphic (16).

Cerebellum was recognized as a structure responsible for some cognitive and affective symptoms in ASD (17). Comparing the post-mortem cerebellar brain tissue derived from ASD individuals with healthy age- and gender-matched individuals, 28 miRNAs were recognized as significantly differentially expressed (18). However, there is a concern regarding the used statistical method that may lead to misinterpretation of the results (19).

Using cultured lymphoblastoid cell lines, the study of Talebizadeh *et al.* (20) pointed to differential (either

higher or lower) expression for nine of the 470 miRNAs in ASD samples compared with controls. Three of them were replicated in the study of Sarachana *et al.* (21) using lymphoblasts derived from individuals with ASD, their discordant monozygotic co-twins, and/or their unaffected siblings. They have found differential expression of 43 miRNA and similar upregulation of miRNA-23a and miRNA-23b, but downregulation of miRNA-132. The above mentioned upregulation of miRNA-23a together with downregulation of miRNA-106b in this study reflected changes in miRNA expression previously reported in post-mortem cerebellar brain tissue (18). These findings support the hypothesis that miRNA dysregulation in peripheral blood cells can reflect at least some miRNA alterations occurring in the brain, thus lending support to the use of lymphoblastoid cell lines as a surrogate tissue to study miRNA expression in individuals with ASD. It should be added that target genes of the differentially expressed miRNAs identified in this study could be associated with both neurological as well as co-morbid features of ASD. Reported genes are involved in development of gastrointestinal diseases, circadian rhythm signaling, steroid hormone metabolism and receptor signaling (21).

Genome-wide miRNA expression profiling in post-mortem brains from individuals with ASD and controls identified numerous differentially expressed miRNAs that have not be seen previously reported together with those that overlapped with already published findings, i.e., miRNA-107, miRNA-106a-5p, miRNA-10a-5p, miRNA-136-5p and miRNA-155-5p (22). This study also pointed to the role of miRNA-21-3p as its transcripts showed enrichment for ASD candidate genes and genes downregulated in ASD cortex. Except the mentioned facts, this study provided multiple lines of evidence for a functional role of miRNA dysregulation in ASD, either as contributory or compensatory factors (22). The study of Mundalil Vasu *et al.* (23) pointed to promising potential of 13 serum miRNAs as possible biomarkers of ASD. Five miRNAs (miRNA-181b-5p, miRNA-320a, miRNA-572, miRNA-130a-3p and miRNA-19b-3p) showed a good discriminative power in receiver operating characteristic analysis. This analysis was used to evaluate the predictive power of differentially expressed miRNAs to distinguish ASD and control individuals. Most of the affected genes and pathways by these miRNA have already been implicated in the pathogenesis of ASD.

MiRNA profiling was also performed in olfactory mucosal stem cells that were biopsied from living ASD patients and controls. These cells represent a neurologically relevant tissue used for transcriptomic studies with great potential to identify genes and pathways relevant for neurodevelopmental disorders. Nguyen *et al.* (24) identified four miRNAs significantly dysregulated in the ASD patients—miRNA-146a (upregulated), miRNA-221, miRNA-654-5p, and miRNA-656 (all three downregulated). This abnormal miRNA expression was not mediated by DNA variations but likely due to transcriptional deregulation or altered posttranscriptional processing of pri-miRNA transcripts (24).

MiRNAs can be found in various body fluids. Plasma has the highest number of unique miRNA species and is followed by saliva. Commonly detected miRNA species between the different fluid types showed that plasma shares a large number of miRNAs with saliva, perhaps as the result of exchange between the two fluids (25). Measurements of salivary miRNAs in subjects with mild ASD and no history of neurologic disorder, pre-term birth, or known chromosomal abnormality demonstrated differential expression of 14 miRNAs; ten miRNAs were upregulated in ASD subjects and four were downregulated compared with controls. These miRNAs are widely and highly expressed in the developing human brain. Most of these miRNAs also showed significant correlations with Vineland neurodevelopmental scores (26).

Kichukova with colleagues (27) have found that miRNA-365a-3p, miRNA-619-5p, miRNA-664a-3p are the most upregulated species and miRNA-3135a, miRNA-328-3p, miRNA-197-5p, miRNA-424-5p, miRNA-500a-5p are down-regulated in the serum of patients with ASD (27).

In comparison to miRNA, relatively less is known about the possible role of snoRNA in ASD. SnoRNAs are important in modifications and processing of another small ncRNA (28). Several snoRNAs are brain-specific (28,29), and their contribution to neurological development was already defined (30,31). Interestingly, brain-specific snoRNA are not involved in modification of typical snoRNA targets. Expression studies of snoRNAs in mice have shown potential involvement of two brain-specific snoRNAs, MBII-48 and MBII-52, in learning and memory. The human homolog of MBII-52 appears to be involved in regulation of 5-HT2C receptor subunit mRNA (28) and elevated blood serotonin (5-HT) levels were recognized as a biomarker in ASD (32).

Moreover, piRNAs were identified in neurons as well, where they control memory-related synaptic plasticity (33). Thus, in addition to miRNA both snoRNA and piRNA may

be also involved in development of neurodevelopmental, psychiatric and neurodegenerative diseases, including ASD.

Long non-coding RNA (lncRNAs) in ASD

LncRNAs are a highly diverse group of ncRNA that includes transcripts of various structure, function and mechanism of action. Overexpression and knockdown studies have shown that lncRNAs have important roles in regulating a variety of processes, including splicing, transcription, localization and the organization of subcellular compartments (34). As the long ncRNAs are to a high degree expressed in the brain, they can function as translational and posttranslational regulators of brain development and differentiation, and are associated with various human brain disorders. They provide tissue- and activity-specific epigenetic and transcriptional regulation that is at least partly ensured via functional control of evolutionary conserved effector small RNA activity, e.g., miRNA (10). LncRNAs were recognized as essential to the development, maintenance and function of the brain. Specifically, they take part in neurogenesis, synaptogenesis, and GABAergic interneuron function (35). LncRNA are also involved in modulation of chromatin structure and conformation via their interaction with regulatory proteins (36).

The assessment of lncRNAs in postmortem brain tissue identified 222 lncRNAs that were differentially expressed between ASD and control individuals, of them 82 were unique to the prefrontal cortex, and 143 were unique to the cerebellum. These lncRNAs were enriched for genes associated with neuronal migration and gene targets for miR-103/miR-107. In addition, this study compared intra-individual differences in expression of the above mentioned lncRNA between the prefrontal cortex and cerebellum. In total, 1,375 lncRNAs were differentially expressed between the prefrontal cortex and cerebellum in controls, while only 236 lncRNA where differentially expressed in ASD prefrontal cortex versus ASD cerebellum. However, it should be cautioned that the sample size was small with only 2 ASD patient samples and 2 controls in this study (37). Nevertheless, these findings pointed to a relatively high tissue specificity of lncRNAs as well as to their regional transcription homogeneity in ASD when compared with controls.

Wang *et al.* (38) identified and replicated common genetic variants on 5p14.1 chromosome region that are associated with susceptibility to ASD. These variants may be involved in shaping the physical structure and functional connectivity of the brain and corresponding clinical manifestations of ASD (38). Kerin *et al.* (39) characterized lncRNA that is transcribed from this region and is encoded by the opposite (antisense) strand of moesin pseudogene 1 (MSNP1). Therefore, it was designated as MSNP1AS (moesin pseudogene 1, antisense). MSNP1AS was highly overexpressed (12.7-fold) in postmortem cerebral cortex of ASD individuals than in those from controls (39).

The impact of the MSNP1AS on neuronal architecture and gene expression was studied using human neural progenitor cells. The data presented in the study of DeWitt *et al.* (40) indicate that MSNP1AS over-expression does not significantly alter the expression of the MSN transcript, suggesting that MSNP1AS functions specifically at regulating the translation of the MSN transcript to moesin protein. Further, presented data revealed that over-expression of MSNP1AS alters the expression of genes that contribute to chromatin organization together with genes that are involved in translation more globally (40).

A genome-wide differential expression of lncRNAs was identified in blood specimens of ASD. A total of 3,929 lncRNAs were found to be differentially expressed in ASD peripheral lymphocytes, including 2,407 that were upregulated and 1,522 that were downregulated. The gene loci where these lncRNAs are localized were subjected to pathway and gene ontology analysis. Thirteen pathways derived from upregulated lncRNAs and fourteen from downregulated lncRNAs were identified as being significant in the ASD group. These pathways were predominantly involved in infection and inflammatory pathways, synaptic vesicle cycling and long-term potentiation pathways. Several differentially expressed lncRNA were transcribed from the HOX gene or HOX-related genes, suggesting an important role of this gene in ASD development. These lncRNA that are also referred as lncHOXs, may represent a new set of biomarkers for ASD. Moreover, the expressions of lncRNA SHANK2-AS and BDNF-AS transcribed from corresponding genes (SHANK—gene for SH3 and multiple ankyrin repeat domains protein, and BDNF—gene for brain-derived neurotrophic factor) were different in ASD subjects too. Interestingly, the range-axis was lower in the upregulated pathways than in the downregulated, suggesting more important pathogenic impact of lncRNAs in downregulated pathways than in upregulated pathways (34).

BDNF treatment on the neuronal cells resulted in differential expression of 155 lncRNA after 1 hour. A fold change above 1.5 was found in 41 lncRNAs, of them

24 were up- and 17 were down-regulated. Out of them, five lncRNAs were hypothesized to have a role in physiological and pathological processes in neuronal cells by regulating gene expression. However, the biological functions of a majority of lncRNAs identified in this study are not currently understood (41).

Another genome-wide analysis performed by Parikshak *et al.* (42) using post-mortem brain tissue of frontal and temporal cortex and cerebellum from 48 ASD and 49 control individuals showed 60 lncRNA differentially expressed between the experimental groups. The authors highlighted two lncRNA—LINC00693 and LINC00689 that interact with miRNA processing complexes and are typically downregulated during development, but upregulated in ASD context compared to controls. These data demonstrate that dysregulation of lncRNAs, many of which are brain-enriched, primate-specific, and predicted to affect protein expression through miRNA or FMRP (fragile X mental retardation protein) associations, is an important component of the transcriptomic signature of ASD (42).

In more recent research article, Gudenas *et al.* (43) have identified 14 lncRNA that may serve as candidate ASD-associated lncRNA. These lncRNA are differentially expressed in the ASD cortex, highly expressed in brain tissues, and co-expressed with ASD risk genes in the developing cortex. They are important for the synaptic signaling and transmission of signals, immune responses and lipid transport pathways. However, their dysregulation was not uniform. Specifically, those related to synaptic transmission showed down-regulation, while lncRNAs involved in immune response and lipid transport were up-regulated (43).

Study focused on individuals affected with ASD, intellectual or learning disability reported mutations in the X-chromosome PTCHD1 gene in seven families with ASD and in three families with intellectual disability. PTCHD1 gene encodes a membrane protein with a patched domain. Deletions in this gene are associated with intellectual disability. The authors simultaneously identified overlapping spliced lncRNAs (PTCHD1AS1, PTCHD1AS2) that may serve as regulators for PTCHD1 through a number of mechanisms, including modification of chromatin, transcriptional regulation, and posttranscriptional modification (44).

Another gene—RAY1 localized on human chromosome 7 (7q31) was supposed as another candidate gene in ASD (45). Vincent *et al.* (46) showed its high degree of complexity at the transcriptional level. Four ncRNA were identified as possible regulatory RNAs that may be implicated in ASD research.

Velmeshev *et al.* (47) have found noncoding antisense RNA transcripts at approximately 40% of loci previously implicated in ASD and confirmed the expression of 10 antisense RNAs in different postmortem human brain tissues. The expression of five antisense transcripts was found to be region-specific, suggesting a role for these ncRNAs in the development and function of specific brain regions. Some antisense RNAs overlapping suspected ASD genes exhibited concordant expression relative to their sense protein-coding genes, while other sense-antisense pairs demonstrate a discordant relationship. SYNGAP1 encodes protein that is critical for the development of cognition and proper synapse function (48). Interestingly, the antisense lncRNA corresponding to the SYNGAP1 locus (SYNGAP1-AS) was found to be significantly upregulated in prefrontal cortex and superior temporal gyrus but not in cerebellum of patients with ASD compared to control individuals (47).

The most common study limitations

Firstly, ASD represent a quite heterogeneous group of clinical presentations, so the heterogeneity is expected also in corresponding ncRNA dysregulation. Therefore, there is no specific biomarker at present that can be applied in clinical practice. Moreover, abnormalities found in expression of numerous ncRNA are not typical only for ASD, but at the same time for other neurodevelopmental disorders, e.g., schizophrenia and bipolar disorder (12).

The postmortem brain tissue (that seems to be the most clinically relevant tissue) is prone to defects induced by cause of death and handling of the body after the death. Furthermore, any difference found by analysis of postmortem brain tissues from adults cannot elucidate the role of individual ncRNA during development of the brain. In addition, brain tissue cannot be used as a clinical material for early screening or for diagnostic purposes. In the absence of access to a sufficient number of ASD brain samples for analyses, evaluation of peripheral blood cells, serum or saliva might be informative in detection of changes for a subset of ncRNAs expressed in brain tissue. Nevertheless, it is not clear whether these ncRNAs are identical to those expressed in neuronal cells or whether they reflect ASD brain functions. The expression of selected ncRNA is potentially affected by many confounding factors that should be taken into the

consideration during interpretation of the study results including age, sex, medication, circadian rhythm and ethnicity (12,16,34,37,49).

Conclusions

NcRNAs represent potential epigenetic regulators of gene expression and can operate in this fashion. The understanding of their role in ASD is still not fully known, but constantly growing field, since the relation between the ncRNA and ASD conditions is extremely complex. Nevertheless, the dysregulation of numerous ncRNAs, predominantly miRNA and lncRNA, appears to correlate with the status involved in ASD. Some of them have been already suggested as biomarkers for ASD screening, but further studies involving ASD individuals as well as patients with other psychiatric disorders are necessary for confirmation of their specificity. Identification and understanding of ncRNA biological roles in ASD is prerequisite for their implication as suitable tools for the diagnosis, prognosis and therapy of this disease.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ncri.2017.11.07). JR serves as an unpaid editorial board member of *Non-coding RNA Investigation* from June 2017 to May 2019. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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