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Research Article

Gene HOX-Associated Long Noncoding RNAs in Autism, Attention Deficit Hyperactivity Disorder, and Non-Syndromic Intellectual Disability

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Abstract

Previously we identified genome-wide differential expression of long noncoding RNAs (lncRNAs) in bloods of autism children, and characterized synaptic vesicle associated transcripts that were differentially expressed in plasma exosomes of autism in addition to pathophysiologic pregnancies. In the current study, we aimed to examine the expression of gene HOX-associated lncRNAs in autism, attention deficit hyperactivity disorder (ADHD), and Intellectual disability (ID). We found gene expression of HOXA13-targeting lncRNA, along with mRNA of HOXA13 (as well as mRNA of HOXA6), was significantly down-regulated in autism. HOXB5 and HOXA6, in addition to BDNF and SHANK2 were down-regulated significantly in ADHD, but no difference for the expression of selected lncRNAs. A gender-dependent difference for lncRNAs and targeted mRNAs expression in ID was indicated. In male ID, there was a significantly down-expressed expression of mRNAs of HOXA13 and HOXB5 accompanied by the differentially decreased expression of lncRNAs targeted mRNAs of SYT15, PKNOX2, SHANK2, HOXB5, HOXA6 and HOXA13. In female ID, the mRNAs of HOXB5 and HOXA6 were significantly down-regulated with a significantly down-regulated expression for lncRNAs targeted mRNA of BDNF, PKNOX2, HOXB5 and HOXA6, and a differentially increased expression of lncRNAs targeted SYT15 and SHANK2. Our results indicated a differential expression pattern for lncRNA and targeted mRNA in peripheral lymphocytes of different neurological disorders, and the identified differentially expressed lncRNAs may be used as biomarkers for early detection and diagnosis of autism.

Keywords: LncRNA; Autism; ADHD; ID; Gene expression; qRT-PCR

Introduction

Autism is a representative paediatric neurodevelopmental disorder, characterized by reciprocal social interactions, verbal and non-verbal communication, and rigid and stereotyped behaviours. Many efforts have been invested into the elaboration of etiology of this disease. Differential expression of long non-coding RNAs (lncRNAs) has been observed in both postmortem brain tissue and lymphoblastoid cell lines from autism patients. LncRNAs, refer to RNAs exceeding 200 nucleotides in length (as compared to ~21–23 nucleotide length of miRNAs), which do not encode for protein [1]. It was initially assumed that lncRNAs merely act as primary or precursor transcripts to produce short ncRNAs such as microRNAs (miRNAs) or small nucleolar RNAs [2]. Further investigations gradually revealed the complex and special functionality of lncRNAs in various life processes by acting solely or together with proteins. LncRNAs have been shown to be involved in major mechanisms of gene expression regulation, such as targeting transcription factors, initiating chromatin remodelling, directing methylation complexes and blocking nearby transcription [3]. Multiple studies have emphasized an important role for lncRNAs in epigenetic regulation, development, and disease [4-9], despite the underlined specific mechanisms remain to be clarified. LncRNAs have been shown to be regulated in both a temporally and spatially manner during development [10], with the greatest abundance of transcripts displaying in central nervous system [11].

LncRNAs are essential to the development, maintenance, and function of the brain. They have been shown to take part in fundamental processes such as synaptogenesis, neurogenesis and GABAergic interneuron function. Studies analysing the differential expression of lncRNAs upon differentiating human ESCs or iPSCs to neurons have identified several lncRNAs as integral components

of neurogenesis [12,13]. Additionally, 659 evolutionary conserved murine lncRNAs have been identified. Of which, the brain-specific lncRNAs are preferentially (2 to 3-fold increase) located adjacent to brain-expressed protein-coding genes, involved in transcriptional regulation, or nervous system development [14]. Synaptogenesis is a pivotal process during neuronal development, metastasis-associated lung-adenocarcinoma transcript 1 (MALAT1) is a lncRNA that was shown to regulate synaptic density and the expression levels of neuroligin1 (NLGN1) and synaptic cell-adhesion molecule (SynCAM1), which are involved in controlling synapse formation [15]. GABA is one of the most abundant neurotransmitters in the brain and has key roles in development [16]. During fate-specification from neuronal oligodendrocyte bipotent progenitors into GABAergic interneurons, 56 lncRNAs were found to be upregulated [17].

The involvement of lncRNA in neurobehavioral and neurodevelopmental, neurodegenerative, neuro-immunological and neuro-oncological disorders highlighted the functional importance of this subclass of brain-enriched RNAs [18-21]. Deregulation of lncRNAs is becoming recognized as a major feature of many types of neurological disorders. More than 200 lncRNAs have been identified differentially expressed in a microarray of postmortem prefrontal cortex and cerebellum tissue of autism patients [22]. Earlier, we identified genome-wide differential expression of (lncRNAs in the bloods of autism children [23]. Recently, we characterized that synaptic vesicle associated transcripts were differentially expressed in plasma exosomes of autism in addition to pathophysiologic pregnancies [24]. Intellectual disability (ID) is another cluster of developmental disorder diseases which implied the involvement of disturbance of synaptogenesis and normal synaptic function through regulation of gene transcripts by small and large ncRNA [25]. Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent psychiatric disorders in childhood and adolescence and has many negative consequences for both the child and the family. The role of lncRNAs in ADHD development has not yet been published.

In the current study, we aimed to examine the expression of seven lncRNAs and lncRNA-targeted mRNAs in peripheral lymphocytes of autism, ADHD, and ID patients via quantitative real-time reverse transcriptase PCR (qRT-PCR) to explore lncRNA expression and regulation pattern in different neurodevelopmental disorder condition.

Results

i. General demographic information of study subjects

A total of 244 blood samples, which consisted of four groups of clinically characterized autism, ADHD, ID, and normal control, were used for quantitative measurement of transcripts (Table 1). There groups showed no statistical significance among their ages.

Group	Male		Female		P value
	Number	Age (yrs.)	Number	Age (yrs.)	
Autism	35	3.8±0.8	18	3.9±0.2	> 0.05
ADHD	33	4.6±0.5	30	4.0±0.7	> 0.05
ID	28	4.2±0.8	30	4.7±0.4	> 0.05
Control	35	4.0±0.5	35	4.0±0.3	> 0.05
Subtotal	131		113		

Table 1: The age and gender composition of study subjects.

ii. Differential expression of mRNAs of SYT15, BDNF, PKNOX2, SHANK2, HOXB5, HOXA6 and HOXA13 in different neurological disorders

qR-T-PCR analysis of expression of mRNAs of SYT15, BDNF, PKNOX2, SHANK2, HOXB5, HOXA6 and HOXA13 genes indicated the differential expression pattern in different neurological disorders (Table 2). The expressions of mRNAs of BDNF, SHANK2, HOXB5 and HOXA6 genes were down-regulated significantly in ADHD group when compared to the control group. For group of autism, a significantly down-regulated expression of mRNAs of HOXA6 and HOXA13 gene was found as compared to the control group. A differential mRNA expression pattern was revealed for ID subjects of different genders. As for the male ID, there were significantly down-expressed mRNAs of HOXB5 and HOXA13 genes. The mRNAs of HOXB5 and HOXA6 genes were significantly downregulated in female ID as compared to the control group.

Group	HOXA6	HOXA13	HOXB5	BDNF	SYT15	SHANK2	PKNOX2
Autism	2.85E+00*	1.20E+00*	9.63E-02	3.77E+00	5.97E+00	8.65E+00	4.28E+00
ADHD	1.59E+00*	4.53E-01	3.28E-01*	5.37E+00*	8.71E+00	1.08E+01*	9.16E+00
ID_Male	6.24E-03	4.71E-01*	7.03E-01*	3.69E+00	-5.69E+00	-1.97E+00	-7.92E-01
ID_Female	8.92E-02*	4.26E-02	1.22E+00*	-1.95E+00	-4.39E+00	-1.42E+00	-9.65E-01
Control	-1.05E+00	-6.44E-01	-1.96E+00	-6.62E-01	-9.71E-01	-1.22E+00	-4.25E-01

*: significantly differential expression when compared to control group ($p < 0.05$).

Table 2: Differential expression of mRNAs of selected genes in developmental disabilities.

iii. Differential expression of lncRNAs which targeting mRNAs of SYT15, BDNF, PKNOX2, SHANK2, HOXB5, HOXA6 and HOXA13 in different neurological disorders

qR-T-PCR analysis of expression of lncRNAs which targeting mRNAs of SYT15, BDNF, PKNOX2, SHANK2, HOXB5, HOXA6 and HOXA13, found inconsistency in different neurological disorders (Table 3). No differential expression was identified for the selected lncRNAs in autism and ADHD with compared to the control group, except for a down-regulated expression of lncRNA that targets mRNA of HOXA13 in autism. Conversely, the expression of lncRNAs that target mRNAs of SYT15, PKNOX2, SHANK2, HOXB5, HOXA6 and HOXA13 was shown to be differentially decreased in male ID as compared to the control group. For female ID, a significantly down-regulated expression for lncRNAs targeting mRNAs of BDNF, PKNOX2, HOXB5 and HOXA6 as well as a differentially increased expression of lncRNAs targeting mRNAs of SYT15 and SHANK2 was found.

iv. Differential expression ratio of lncRNAs and mRNAs of BDNF, SYT15, SHANK2, PKNOX2, HOXB5, HOXA6 and HOXA13 in different neurological disorders

The differential expression ratio of lncRNAs and targeted mRNAs for BDNF, SYT15, SHANK2, PKNOX2, HOXB5, HOXA6 and HOXA13 was calculated in different neurological disorders when compared to control (seen in Figure 1). In ADHD, the decreased expression of mRNAs accompanied by increased lncRNAs expression for all seven selected genes was presented. The largest differential expression ratio of lncRNA and mRNA was for PKNOX2 and SYT15 respectively.

Group	HOXA6	HOXA13	HOXB5	BDNF	SYT15	SHANK2	PKNOX2
ADHD	-1.36E+00	-2.54E-01	-1.44E+00	-1.34E+00	-2.91E+00	-2.29E+00	-1.32E+00
Autism	7.42E-01	1.66E+00*	-4.73E-02	2.13E-01	-4.45E-01	9.18E-02	-4.85E-02
ID_Male	7.55E-01*	1.01E+00*	1.02E+00*	4.32E-01	1.44E+00	1.69E+00*	1.05E+00*
ID_Female	5.84E-01*	1.83E-01	8.92E-01*	1.35E 01*	1.03E+00Δ	1.24E+00Δ	6.28E-01*
Control	-8.63E-01	-4.95E-01	-8.46E-01	-1.13E+00	-5.18E-01	-6.56E-01	-8.90E-01

*: significantly decreased expression when compared to control group ($p < 0.05$); Δ: significantly increased expression when compared to control group ($p < 0.05$).

Table 3: Differential expression of lncRNAs targeting mRNAs of selected genes in developmental disabilities.

In autism, the mRNA expression of BDNF, SYT15, SHANK2, PKNOX2, HOXB5, HOXA6 and HOXA13 was all decreased, with the largest differential expression ration for SHANK2. The lncRNA expression of BDNF, SHANK2, HOXA6 and HOXA13 was also decreased, whereas an increased expression for lncRNAs of SYT15, PKNOX2 and HOXB5 was found. The largest differential expression ratio of lncRNA and mRNA was for SYT15 and SHANK2. In male ID, the lncRNA expression of BDNF, SYT15, SHANK2, PKNOX2, HOXB5, HOXA6 and HOXA13 was all decreased, with an increased expression for mRNAs of BDNF, SYT15, SHANK2, PKNOX2 and decreased expression for HOXB5, HOXA6 and HOXA13. The largest expression ratio for mRNA of SHANK2 and lncRNA of SYT15 was found in male ID. In female ID, the same expression trend for mRNAs of seven selected genes was indicated with the male ID, with the largest expression ratio was for SHANK2. For lncRNAs, a decreased expression for HOXB5, HOXA6, HOXA13, BDNF and PKNOX2 was similar to that in male ID, but the expression for SYT15, SHANK2 was increased inversely.

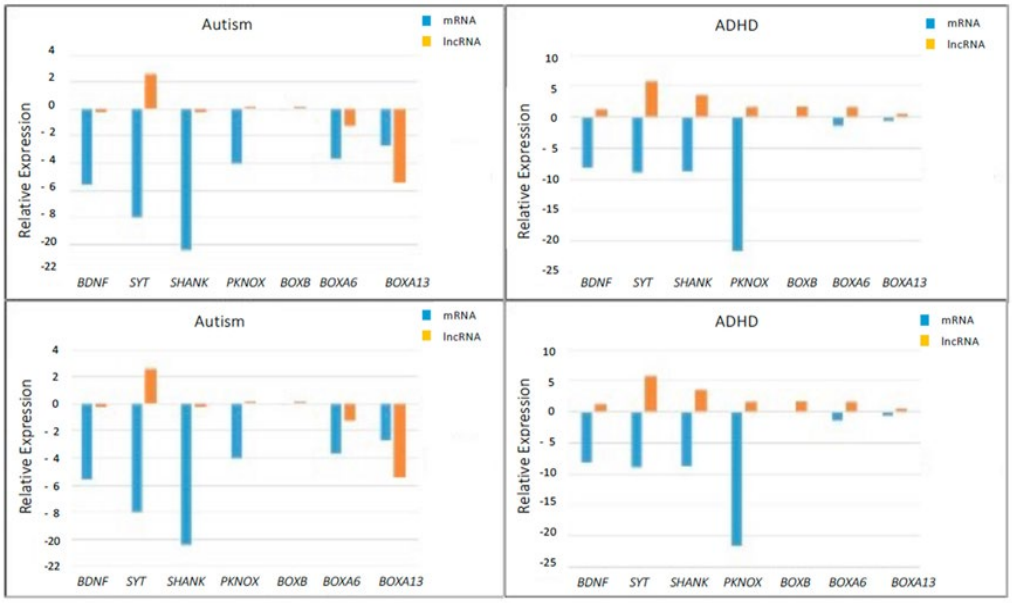

Figure 1: Different expression ratio of lncRNAs and mRNAs of SYT15, BDNF, PKNOX2, SHANK2, HOXB5, HOXA6 and HOXA13 in different neurological disorders: (A). Autism; (B). ADHD; (C). ID for male; (B). ID for female.

Discussion

Due to the significantly negative influence on the individual and family caused by neurodevelopmental and neuropsychiatric disorders such as Autism, ADHD and ID, the vast amount of efforts have been invested in the exploration of the pathogenesis and identification and intervention for these diseases. However, there was no generally accepted biomarkers for early screening or/ and diagnosis of Autism, ADHD and ID till now. Because of the examination of samples from brain tissues and related structures during the early stage are not practical in clinical practice, we attempted to investigate the possible changes in the peripheral blood lymphocytes related to or involved in the occurrence and development of central nervous system diseases. The participation and functional importance of lncRNA in neurodevelopmental disorders has been widely identified and proved through research studies with human subjects and animal models. Presently, we examined differentially expressed lncRNAs and targeted mRNAs of seven development-related genes HOXB5, HOXA6, HOXA13 SYT15, BDNF, PKNOX2, and SHANK2 in the peripheral blood lymphocytes of autism, ADHD and ID children. Our results indicated a different expression pattern of selected lncRNAs and targeted mRNAs for different neurological disorders.

In this study, we identified a consistently significant decrease trend for expression of lncRNAs and the targeted mRNAs of HOXA13 in autism, HOXB5 in ID of both genders, HOXA13 in male ID and HOXA6 in female ID. There was a significantly downregulated expression of mRNAs of HOXA6 in autism and HOXA6-targeted lncRNA in male ID. Also, a significantly down-regulated expression of mRNAs of HOXB5 and HOXA6 without change of corresponding lncRNAs in ADHD was found. However, no significant difference for lncRNA and the targeting mRNA of HOXA13 in female ID was indicated by our results. HOXB5 and HOXA6 genes encoding the class of transcription factors called homeobox (HOX) genes found in clusters named B or A, respectively, on two separate chromosomes. The expression of these proteins is spatially and temporally regulated during embryonic development. HOX gene family is known to be a classic example of the intimate relationship between embryogenesis and tumorigenesis. A study has suggested that HOXB5 acted as a positive modulator most likely by promoting cell proliferative response and invasiveness in ER-positive breast cancer [26]. HOXA6 was demonstrated directly involved in fundamental processes of hemopoietic progenitor cell development [27]. Similar to HOXA6, HOXA13 is a member of homeobox genes that encode transcription factors regulating embryonic development and cell fate. Dysregulation of HOXA13 has been implied in the oncogenesis and development of gastric cancer and hepatocellular carcinoma [28,29]. Several studies have linked the disordered proliferation of brain neural cells such as cortical neural progenitor cells, glial cells with the pathogenesis of autism and ID [30-32]. The differential expression of HOXB5, HOXA6 and HOXA13 which involved in the proliferation of cell growth may have play a specific role in the neurodevelopmental disorder. These HOX-gene family members were almost all affected in autism, ADHD, and ID, either it was in a separate or combined manner of differential

expression for lncRNA and targeted mRNA. Which indicated a fundamental role for HOX genes in neurodevelopmental and neuropsychiatric diseases. The exact function for lncRNA and targeted mRNA of HOXB5, HOXA6 and HOXA13 in autism, ADHD, and ID deserved further exploration.

BDNF gene encodes a member of the nerve growth factor family of proteins. Binding of this protein to its cognate receptor promotes neuronal survival in the adult brain. Expression of this gene is reduced in Alzheimer's, Parkinson's, and Huntington's disease patients. This gene has been demonstrated possibly involved in the regulation of stress response and in the biology of mood disorders [33,34]. It has been hypothesized that BDNF is involved in the pathogenesis of ADHD, although the study results were controversial. An increase of plasma BDNF levels in untreated ADHD patients had a significant positive correlation with the severity of inattention symptoms [35]. However, BDNF serum levels were found significantly lower in adults with ADHD compared to healthy controls ($p < 0.0001$) [36]. Another report, however, indicated there was no alteration of serum BDNF levels in untreated patients with ADHD [37]. The different outcome among these studies may be partly due to the difference in study subject's composition. Our finding suggested a decreased mRNA of BDNF in the peripheral blood lymphocytes of ADHD, which may be in accordance with the possible change in neuron cells in brain correlating to the regulation of secretion of BDNF without the involvement of lncRNA. Although no difference in the expression of mRNA of BDNF in both genders, a decreased regulation of BDNF-targeted lncRNA was found for female ID which may reveal the discrepancy of the implication of BDNF in different sex. We found no correlation between differential expression of lncRNA or overlapped mRNA of BDNF in peripheral blood lymphocytes with the occurrence of autism, which may imply a different pathogenesis for autism without the involvement of BDNF gene.

We found no significant difference of mRNAs of SYT15 and SHANK2 in peripheral blood lymphocytes in autism and ID, with a significantly decreased expression for mRNAs of SHANK2 in ADHD. However, a significantly down-regulated expression of SYT15-targeted lncRNA in male ID was presented accompanied by an opposite expression pattern in female ID. Also, a significantly up-regulated expression for SHANK2-targeted lncRNA was found in female ID. No significant difference was found for both lncRNAs which targeted mRNAs of SYT15 and SHANK2 in autism and ADHD. SYT15 gene encodes a member of the Synaptotagmin (Syt) family of membrane trafficking proteins. Study has demonstrated that most synaptotagmins are expressed in the rodent brain is highly distinctive expression patterns, and that individual neuron expresses variable subsets of different synaptotagmins [38]. Synaptotagmins-1, -2, and -9, are known to have an essential role as calcium sensors for fast synaptic release. Synaptotagmin-7 is a major calcium sensor for the exocytosis of large secretory vesicles in endocrine cells. Unlike related family members, SYT15-a is classified as a non-neuronal, but Ca^{2+}-independent Syt [39]. Synaptotagmins have been implied in relation to psychiatric disorders susceptibility such as ADHD and autism [40,41]. But no significant difference for lncRNA and targeted mRNA of SYT15 were found in the peripheral lymphocytes of autism, ADHD, and ID child in our study, the function of SYT15 in these disorders deserves future clarification. The expression of SYT15-targeting lncRNA was significantly decreased in male but increased in female ID, with no expression difference in mRNA level for both genders, was an interesting finding. Whether this indicated a distinct mechanism underlined the development of ID between different gender needs further investigation. SHANK2 gene encodes a protein that is a member of the Shank family of synaptic proteins that function as molecular scaffolds in the postsynaptic density of excitatory synapses [42]. SHANK2 gene has been identified in patients with autism and ID [43,44]. No difference of the mRNA of SHANK2 in autism and ID, with an increased expression of SHANK2-targeting lncRNA in male ID, was shown in this study. This may reflect a different expression pattern in different cells for SHANK2.

PKNOX2 encodes a member of homeodomain proteins, which are sequence-specific transcription factors that share a highly conserved DNA-binding domain and play fundamental roles in cell proliferation and differentiation. PKNOX2 has been reported involved in the pathogenesis of schizophrenia and substance dependence formation [45,46]. Because of the similar clinical characteristics of cognitive disorder between ID and schizophrenia, a decreased PKNOX2-targeting lncRNA may involve in the development of ID. Our results revealed no significant difference of expression of mRNA of PKNOX2 in ADHD, autism and ID, although a significant decrease of PKNOX2-targeting lncRNA in ID of both genders was documented.

Materials and Methods

i. Study subjects

This study was approved by the Ethic Committee of Peking University Center of Medical Genetics and by the Institutional Biological Committee of New York State Institute for Basic Research in Developmental Disabilities. Blood samples were selected from prestored biobank. Totally, 244 children aged around 4years, who were diagnosed with autism, ADHD and ID with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [47]. The prebanked subjects were selected from a birth cohort with a criterium that the participant should not have a clinical history of having epilepsy, brain damage, or any other neurologic or genetic disorder. Informed consent was acquired from the parents of each subject. The Hospital Ethics Committee that administrates the biobank reviewed and approved the research project.

ii. Peripheral blood lymphocytes preparation

A sum of 3–5ml of heparinized peripheral venous blood was obtained from participant and then lymphocytes were isolated within 30 minutes by using the lymphocyte separation liquid. All lymphocyte samples were stored at 70°C until total RNA was extracted.

iii. RNA Isolation and Quality Control

Total RNA was extracted from lymphocyte samples with a Qiagen Mini kit (Qiagen, Valencia, CA) according to the manufacturer's protocol. RNA quantity was measured by NanoDrop ND-1000. Agilent Bioanalyzer 2100 was used to assess RNA integrity for each sample.

iv. Quantitative real-time PCR analysis

Two micrograms of total RNA extracted from leukocytes were used for the synthesis of first strand cDNA using the Superscript III First Strand cDNA Synthesis Kit (Invitrogen). qRT-PCR analysis was performed with the ABI7900 system (Life Technologies, Grand Island, NY) and SYBR green dye SuperArray PCR master mix (SABiosciences, Frederick, MD). mRNA of glyceraldehyde 3- phosphate dehydrogenase (GAPDH) was used as an internal control for quantitative analysis of lncRNA or mRNA. The lncRNA or mRNA values were normalized to GAPDH levels. Normalized, relative gene expression was calculated using standard ΔΔCt methods using Applied Biosystem RQ Manager Software (v1.2). Each qPCR reaction was run three separate times, with technical triplicates in each reaction. All data were given in terms of relative expression of the mean ± S.E. The data were subjected to one-way ANOVA followed by an unpaired, two-tailed t-test. Differences were considered significant at $p < 0.05$.

Conclusions

Altogether, through our work, we identified for the first time the differential expression pattern of lncRNAs and targeted mRNAs for several development related genes (HOXB5, HOXA6, HOXA13, SYT15, PKNOX2, SHANK2 and BDNF) in peripheral lymphocytes of autism, ADHD, and ID patients. Although the potential expression difference between peripheral blood lymphocytes and brain originated cells may weaken the strength of our finding and further study with more samples and more elaborate design was needed to validate these results, our investigation provided a new window for exploration the mechanism underlain neurodevelopmental and neuropsychiatric disorders and identification of biomarkers more practicable to apply in clinical practice.

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Author Contributions

WJ and XZ performed laboratory quantitative experiments and data analysis. NZ designed and supervised the study, and drafted and finalized the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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