都留文科大学大学院紀要　第21集（2017年 3 月）
THE TSURU UNIVERSITY GRADUATE SCHOOL REVIEW,
No.21（March, 2017）

Autism Spectrum Disorder and High Confidence Gene Factors

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Abstract

Autism spectrum disorder (ASD) is a neurological developmental disorder whose mechanism is yet unclear. However, recent ASD studies, which employ exome- and genome-wide sequencing, have identified some high-confidence ASD genes. Those ASD studies have revealed that *CHD8* is likely associated with ASD. In this article, we highlight that *CHD8* may regulate other candidate ASD risk genes. Current research indicates that there exist some thousand autism susceptibility candidate genes. Moreover, we suggest that symptom variations of ASD is also related to complicated interactions with those genes.

Keywords: Autism Spectrum Disorder, language disorder, *CHD8, FOXP2, CNTNAP2, PAX6*

0. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder whose mechanism is unclear. Recently the autism susceptibility candidate genes are extensively annotated for their relevance to ASD. This article shows interaction with autism susceptibility candidate genes and ASD. We also suggest that a significant number of single-gene disorders are involved in ASD. In section 1, we will briefly discuss communication deficit and language disorders that are typical ASD symptoms. In section 2, we will explore the relation between ASD and autism susceptibility candidate genes. Section 3 discusses implications of recent studies and makes some proposals. Section 4 offers a conclusion and suggests a future perspective.

1. Communication Deficit and Language Disorders with ASD

Autism Spectrum Disorder (ASD) is a neurological developmental disorder. Autistic symptoms emerge in early brain development. On average, the male to female ratio is estimated to be 4.3:1 (Fombonne 2005). One of the most visible signs of autism emerges between two and three years of age. Major symptoms include communication deficits, language disorders, repetitive behavior, and highly-focused interests. In particular, communication deficits and language

disorders are most strongly characteristic of ASD.

Most children with ASD have difficulty communicating nonverbally, such as through gesture, eye contact, and facial expression. Moreover, most individuals with ASD have language disorders in both receptive and expressive language. Children with ASD have differences in early language acquisition compared with children with typical development (TD). They have (1) deficiencies in joint attention behaviors (Mundy et al. 1986), (2) delay in speaking their first words (Charman et al. 2003), and (3) engage in "echolalia".

Joint attention is often referred to as a triadic relation between the self, other people, and an object (Bakeman and Adamson 1984). Joint attention behaviors of children with TD emerge between 6 and 12 months of age (Charman 2003). In research on autism, a few of the joint attention skills such as, 'gaze following,' 'pointing behavior,' and , 'mutual gazing' or 'joint visual attention,' are reported (Carpenter et al. 2002). It is argued that these shared attention behaviors are mainly related to the development of language (Charman 2003). To acquire a language, the child has to understand the link between words and objects and to interpret communicative gestures of others as intentional acts (Tager-Flusberg 2000). Children with ASD have deficits in joint attention, i.e. deficits in understanding the meaning of gestures such as pointing and looking, which may, therefore, be linked to delays in receptive language and overall language acquisition (Naber et al. 2007).

Children with ASD have been also reported to be delayed in speaking their first words. Therefore, studies which have measured the size of young autistic children's expressive vocabularies have often indicated that young children with ASD have smaller expressive vocabularies than same-age TD children (Charman et al. 2003). Eigsti et al. (2007) reported that ASD children producing their first words at an age of 38 months compared to TD children who first speak at an age of somewhere between 12 and 18 months.

"Echolalia" is the immediate or delayed imitation of the language they have heard from conversational partners or media (Tager-Flusberg et al. 1990). Over 33% of the echolalic utterances produced by children in their sample had a turn-taking function, and 25% had a declarative function (Prizant and Duchan 1981). Based on these findings, we can say that children with ASD have some differences compared with TD children.

2. Autism Spectrum Disorder and Genetic Factors

Identifying the genes involved in the faculty of language is necessary not only for understanding of disorders such as ASD, but also understanding the evolution of the human brain since the intricate system of language is only present in humans (Bowers 2012). Recent ASD studies, employing exome- and genome-wide sequencing, have identified some high-confidence ASD genes. More than 100 genes and genomic regions have been associated with ASD (Betancur 2011). Moreover, over 800 genes are believed to play roles in ASD (Neale et al. 2012). This article will explicate such genes as *CNTNAP2, FOXP2, PAX6* and *CHD8* in more detail

subsequently in the following sub-sections.

2.1 *CNTNAP2*

The contactin-associated protein-like 2 (*CNTNAP2*) gene on chromosome 7q35-7q36.1 (OMIM 604569) was the first gene to be associated with genetically complex forms of SLI. Recently, a homozygous mutation in this gene has been reported in Old Order Amish children from several families. Symptoms include seizures, language regression, and pervasive developmental disorder (Strauss et al. 2006). Copy Number Variants (CNVs) or chromosome rearrangements in *CNTNAP2* have been reported recently in a full spectrum of neuropsychiatric disorders such as autism, attention deficit hyperactivity disorder (ADHD), schizophrenia, epilepsy, Gilles de la Tourette, and mental retardation (Newbury et al. 2010). Moreover Alarcón et al. (2008) suggest that common variants of *CNTNAP2* may be involved in autism susceptibility: A single nucleotide polymorphism (SNP) rs2710102 showed an association with the, 'age at first-word,' trait in autistic patients. A recent study suggests that rs2710102 may influence early language acquisition in the general population (Whitehouse et al. 2011).

2.2 *FOXP2*

The forkhead box p2 (*FOXP2*) (7q31.1) may also be related to ASD. This gene is a member of the forkhead family of transcription factors and is highly homologous to two other forkhead transcription factors, *FOXP1*, and *FOXP4* (Li et al. 2004). *FOXP2* was the first found to be involved in a speech and language disorder. The disorder was first discovered in a British family known as the KE family. Various disruptions in the *FOXP2* gene have been reported, and the symptoms caused by disorders mentioned above tended to include a broad spectrum of deficits, including speech and language problems, verbal dyspraxia, low-performance IQ, developmental delay, and brain abnormalities (Nudel et al. 2013). A direct relationship between *FOXP1* and ASD has been uncovered recently (Bowers 2012). There is research that found mutations of *FOXP1* in individuals with ASD (Hamdan 2010). Almost all of the people with ASD have communication deficits; therefore, *FOXP2* may well be related to ASD.

2.3 *PAX6*

The paired box protein 6 (*PAX6*) gene is initially identified in chromosomal region 11p13 as one associated with WAGR (Wilm's tumor, Aniridia, Genitourinary malformations and mental Retardation) syndrome (Hanson et al. 1995). These disorders are rare genetic disorders caused by chromosomal deletion of the 11p12-p14 region. As an important point, more than 20% WAGR patients also have features of ASD (Fischbach et al. 2005). Moreover, chromosome 11p13, on which *PAX6* is located is implicated as a possible locus for ASD susceptibility (Szatmari et al. 2007) Besides, a mutation in *PAX6* was found in an autistic patient (Maekawa et al. 2009). These studies suggest that *PAX6* mutations are involved in phenotypes of autism.

2.4 *CHD8*

Mutations in chromodomain helicase DNA-binding protein 8 (*CHD8*) have been associated with ASD (Neale et. al 2012). *CHD8* (14q11.2) encodes an ATP-dependent chromatin remodeler and binds to histone H3 di- and trimethylated on lysine 4 (Yuan et al. 2007). Also, it has been shown to bind promoters of E2 adenovirus promoter binding factor-target genes and is required for their expression during the G1/S transition of the cell cycle (Subtil-Rodríguez et al. 2013). Cotney et al. (2015) found that *CHD8* targets are strongly enriched for other ASD risk genes in both human and mouse neurodevelopment, and converge in ASD-associated co-expression networks in the human midfetal cortex. Furthermore, their results suggest that loss of *CHD8* contributes to ASD by perturbing an ancient gene regulatory network during human brain development (Cotney et al. 2015). In other research, Katayama et al. (2016) suggest that *CHD8* haploinsufficiency is a highly penetrant risk factor for ASD, with disease pathogenesis probably resulting from a delay in neurodevelopment. This study indicates that mice heterozygous for *Chd8* mutations manifest ASD-like behavioral characteristics including increased anxiety, repetitive behavior, and altered social behavior. Moreover, reduced expression of *CHD8* was associated with abnormal activation of RE-1 silencing transcription factor (REST), which suppresses the transcription of many neuronal genes (Katayama et al. 2016). As a consequence, *CHD8* might be an essential gene for ASD.

2.5 Genes Connected with Autism Spectrum Disorder

As mentioned earlier, more than 100 genes and genomic regions have been associated with ASD (Betancur 2011) and over 800 genes have been suggested to play a role in ASD (Neale et al. 2012). Though gene connections are so complex, there are several links among ASD high confidence genes.

First, the connection is *FOXP2* and *CNTNAP2*. These are genes that are associated with language as we have observed in sections 2.1 and 2.2. Both genes map to chromosome 7q, where several linkage studies reported positive results in autism (Abrahams and Geschwind 2008, Vernes et al. 2008, Reader et al. 2014 among others). *FOXP2* encodes a transcription factor involved in the regulation of numerous genes, including *CNTNAP2* (Vernes et al. 2008). In addition, these genes have a direct connection themselves among other possible genes related to ASD (Figures.1 and 3). As a consequence, it may be the case that these genes are associated with ASD.

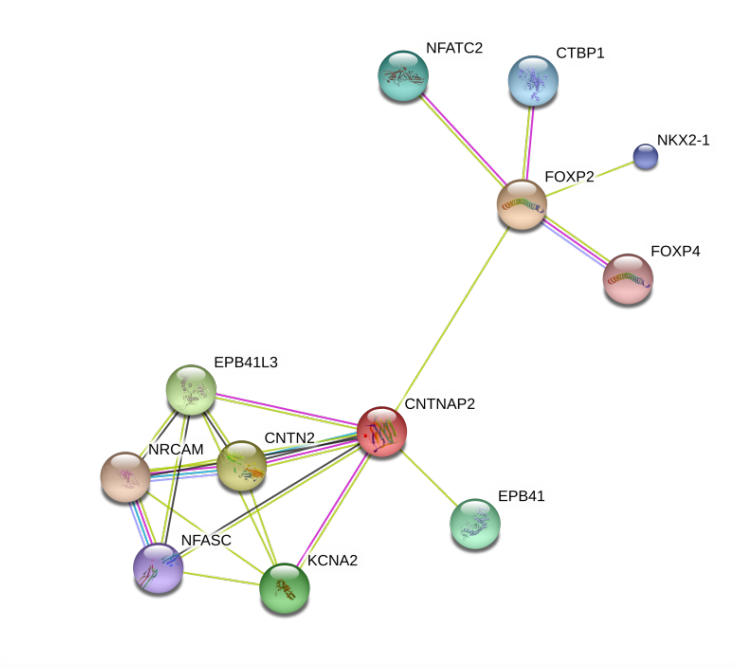

Figure1. *FOXP2* and *CNTNAP2* networks (STRING ver.10)

A recent study, however argues that common variants of *FOXP2* are not involved in susceptibility to autism (Toma et al. 2013). Furthermore, it is reported that the same group of researchers failed to replicate positive results of two common variants of *CNTNAP2* related to autism and language (Toma et al. 2013). As a consequence, further research is necessary to elucidate the role of *CNTNAP2* as well as *FOXP2* in autism.

Next, consider *CHD8* and several high confidence genes of ASD. Transcription and *CHD8* binding site profiles from cell and primary tissue models of early development indicate that *CHD8* may also positively regulate other candidate ASD risk genes through both direct and indirect means (Barnard et al. 2015).

3. Discussion

The mechanism of ASDs is unclear and displays many symptoms that may influence daily living and health. The scientific literature suggests that a significant number of autism susceptibility candidate genes may be associated with ASD. Consequently, mutations in autism susceptibility candidate genes can be responsible for variations in an individual symptom. There is a hierarchy of ASD associated genes. In the recent studies of ASD, *CHD8* is a high-risk factor and it can be a master gene of other high confidence genes of ASD because ASD is caused by mutations in *CHD8* and its bind genes are also affected. Therefore, ASD has a variation of symptoms. For example, they are language disorders of ASD. First, a mutation occurred in *CHD8*, and

subsequently, *CNTNAP2* is affected. Then, *CNTNAP2* affects *PAX6* and *FOXP2* among other genes. Therefore, language disorders are caused. While there is no direct connection between *CHD8* and *FOXP2* (Figure.2), there are indirect connections including *FOXP1*, *FOXP3*, *FOXP4*, *PAX6* and *CNTNAP2* (Figure.3). In addition, these genes relate to other ASD candidate genes[1] (Figure.4). Also, *CNTNAP2* relates to *CHD8*. Moreover, there is a relationship between *FOXP2* and *PAX6*. As a consequence, we can say that multiple genes would be associated with ASD. Other symptoms can occur in the same mechanism. Finally, more research needs to be carried out on more complex interactions of possible genes for ASD.

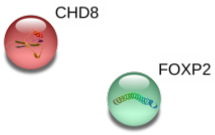

Figure 2. There is no direct connection between *CHD8* and *FOXP2*. (STRING ver.10)

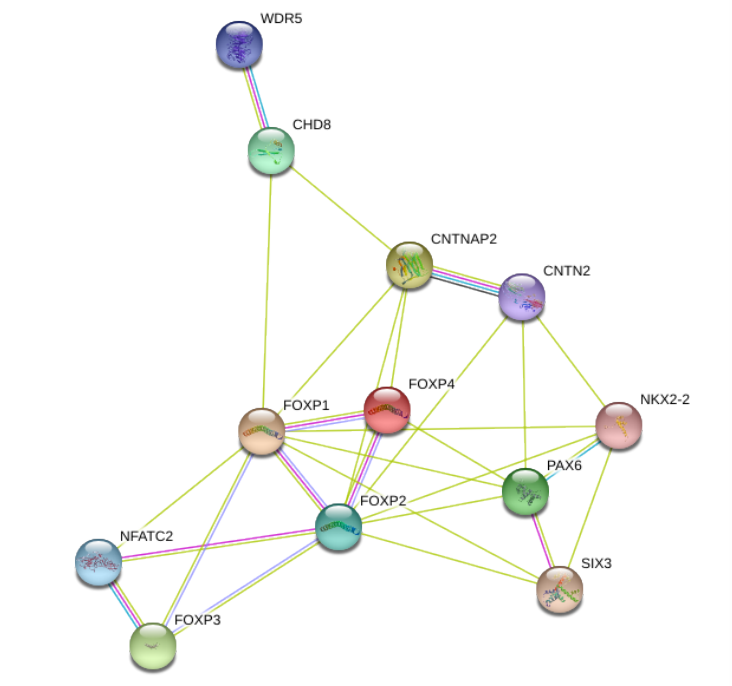

Figure 3. *CHD8* and *FOXP2* networks including *FOXP1*, *FOXP3*, *FOXP4*, *PAX6* and *CNTNAP2*. (STRING ver.10)

1 It is listed in Bowers et al. (2012) pp 225, Table1.

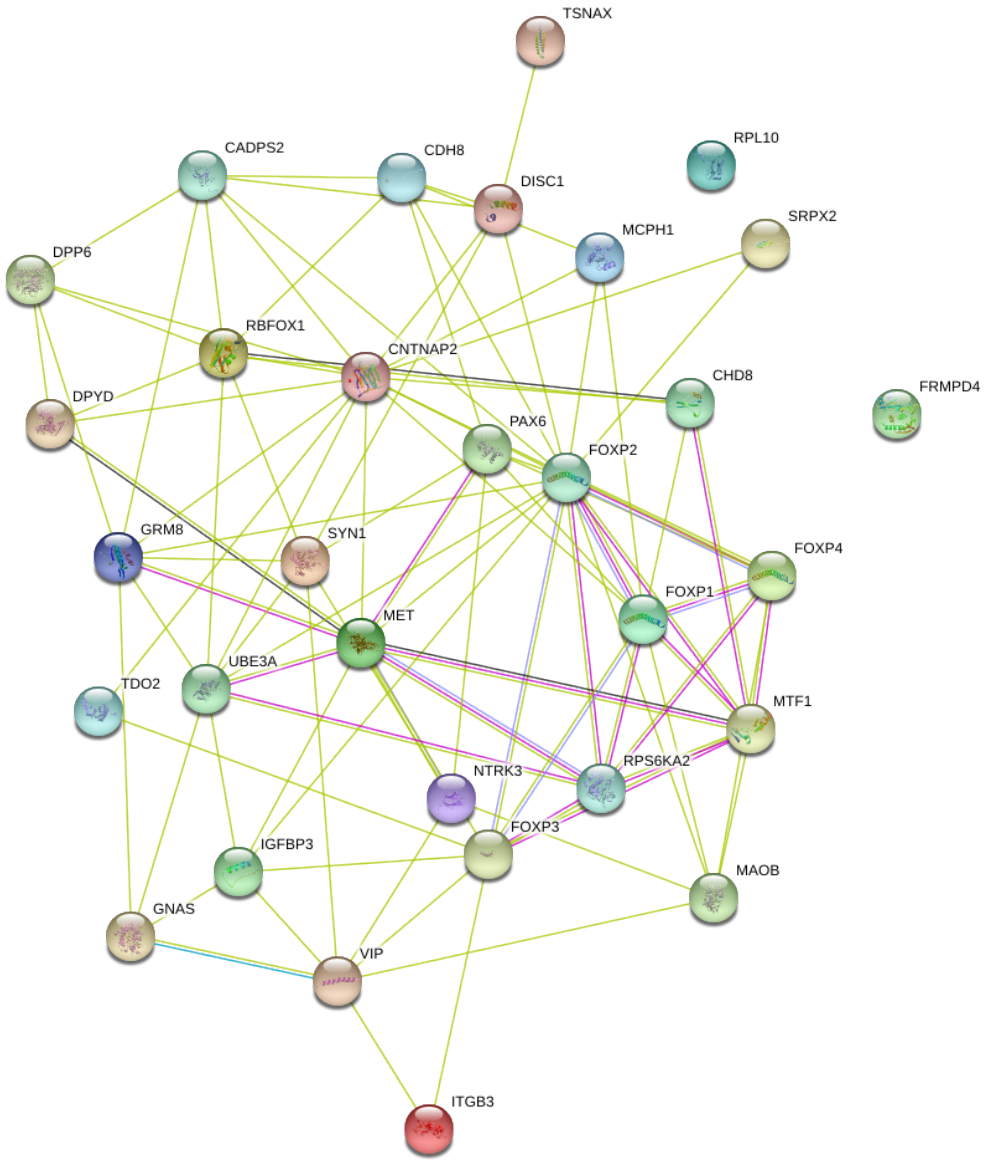

Figure 4. Genes in Figure 3 and other ASD candidate genes. (STRING ver.10)

This network is composed by unifying genes in Figure 3 and other ASD candidate genes (Bowers et al. (2012)). *FRMPD4* and *RLP10* are not related to this network. *FOXP2* has many connections. *CNTNAP2* also has several connections. Therefore, the genes that relate to language may be strongly connected to ASD.

4. Conclusion

Multiple genes are associated with the onset and risk of ASD. Also, those variations are related to multiple symptoms of ASD. Over the past 10 years, interest in genetic studies of ASD has steadily increased. Moreover, research on mutations or variations of animal models with high confident genes of ASD is extremely useful and plays a significant role in research on ASD. To identify a gene playing a role in the complex system of autism cannot provide a simple explanation for ASD. There will be more discoveries about the mechanism of ASD in the future. Consequently, there is some hope that we will discover new genes that may be related to the faculty of language.

Acknowledgements

I am grateful to the anonymous reviewer and especially Takashi Imai for many constructive suggestions and comment on earlier drafts of this article. I am also grateful to Hywel Evans for useful suggestions for editing.

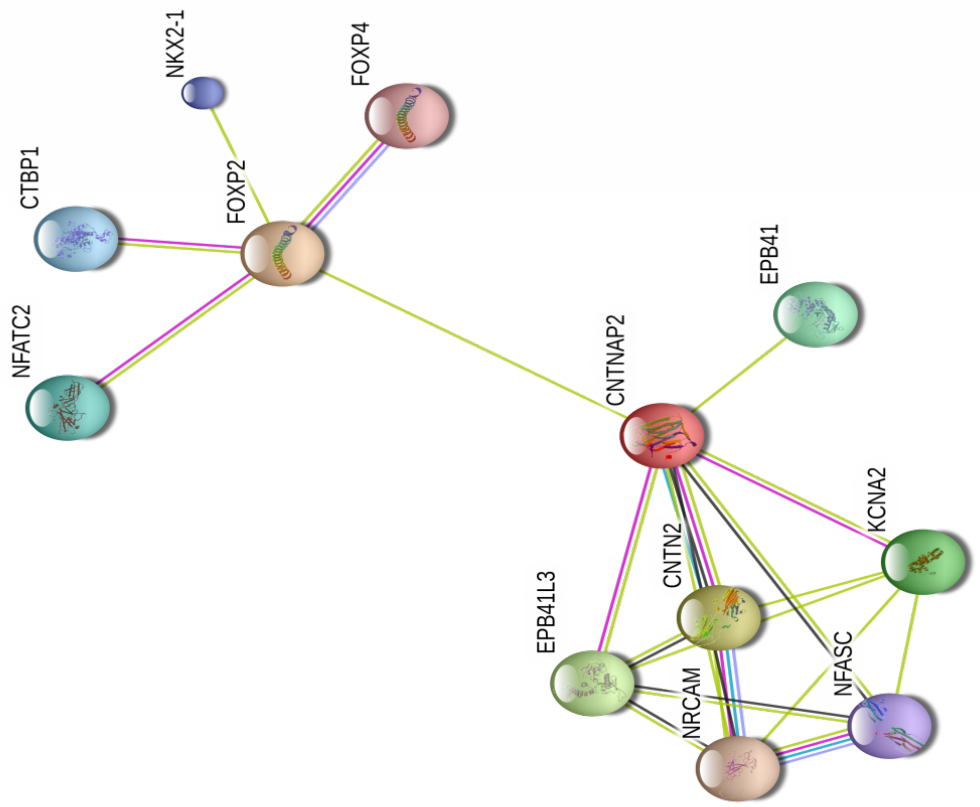
NKX2-1
FOXP4
CTBP1
FOXP2
NFATC2
EPB41
CNTNAP2
KCNA2
CNTN2
EPB41L3
NFASC
NRCAM

Figure 1

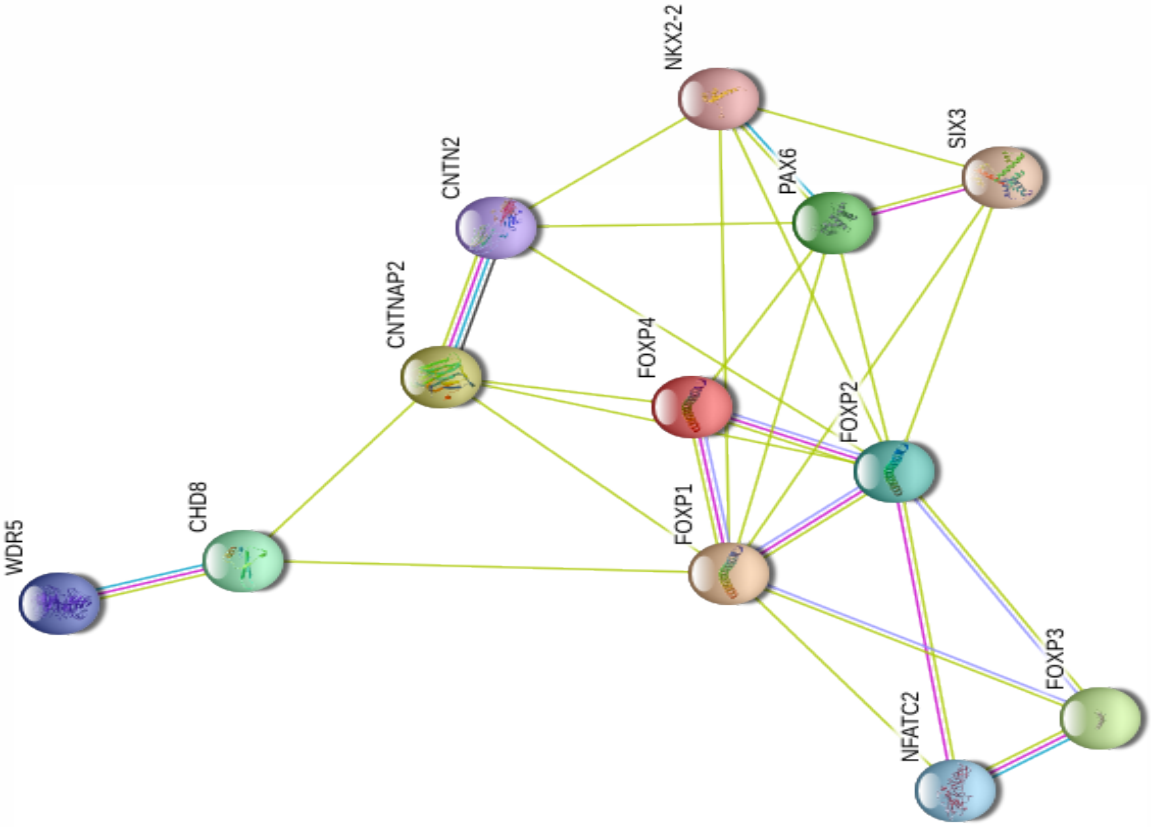
NKX2-2
SIX3
CNTN2
PAX6
CNTNAP2
FOXP4
FOXP2
CHD8
FOXP1
WDR5
FOXP3
NFATC2

Figure 3

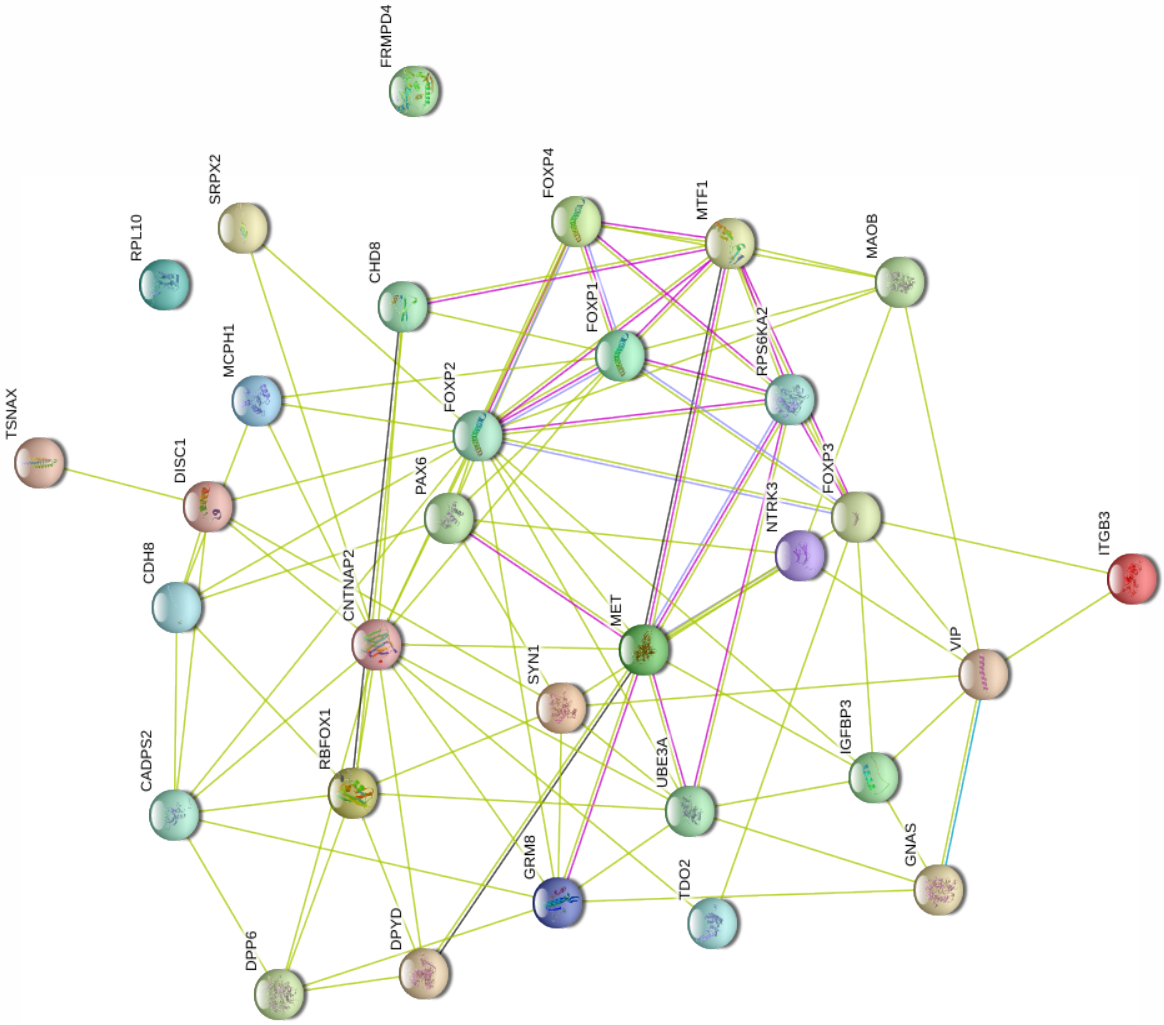
FRMPD4
SRPX2
RPL10
CHD8
FOXP4
MTF1
MAOB
FOXP1
RPS6KA2
MCPH1
TSNAX
FOXP2
DISC1
PAX6
FOXP3
NTRK3
ITGB3
CDH8
CNTNAP2
MET
VIP
SYN1
IGFBP3
CADPS2
RBFOX1
UBE3A
GRM8
GNAS
TDO2
DPP6
DPYD

Figure 4

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Received:October 26,2016
Revision received:November 22, 2016
Accepted:December 01, 2016