# Autism and the Scaffolding Protein Neurobeachin

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**Abstract**

Autism is a group of early-onset, diverse, lifelong, neurodevelopmental conditions that affect social interaction, verbal and nonverbal communications, and behavior. It is a multifactorial condition, which results from the interaction of environmental and genetic factors. A number of proteins are identified as autism-related proteins such as neurobeachin (NBEA), a large multi-domain scaffolding protein belonging to BEACH domain-containing proteins (BDCPs), which is a family of proteins found in all eukaryotes. The human's BDCP family includes nine proteins that share the characteristic of containing BEACH and WD repeat domains. Mutation of each one of the genes encoding these proteins leads to a distinct disease condition. NBEA mutations includes deletion, translocation, inversion, or duplication and is associated with autism spectrum disorders (ASD).

**Keywords**

Autism · ASD · Neurobeachin · Scaffolding proteins · Membrane protein trafficking · Neuronal junction · Synapses · Neural development

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## 11.1 Introduction

The term autism was used for the first time in 1912 by Paul Eugen Bleuler, a Swiss psychiatrist, to describe the symptoms of schizophrenia. In 1938, Hans Asperger used "autistic psychopathy" to define a group of children with abnormal behavior and unusual movements, later known as Asperger's syndrome. The term autism in the modern sense was used for the first time in 1943 by the child psychiatrist Dr. Leo Kanner. Autism can be defined as a group of early-onset (mostly at the age of 2–3 years), diverse, lifelong neurodevelopmental conditions that can substantially affect social interaction, communication (both verbal and nonverbal), as well as behavior. Autism, Asperger's syndrome, Rett syndrome, and pervasive developmental disorder-not otherwise specified (PDD-NOS) are generally known as autism spectrum disorders (ASDs) (Park et al. 2016; Hodges et al. 2020; Styles et al. 2020).

Autism is a multifactorial condition, which results from the interaction of genetic and environmental factors such as exposure to teratogenic medications like thalidomide and valproic acid during pregnancy. ASD is reported globally with no overall differences between racial, ethnic, and socioeconomic groups. However, it affects more males than females with a ratio of 4.3:1 and a higher risk of severe disease condition is seen in male patients. When autism was first recognized, patients mainly were diagnosed with mental retardation of different severities or learning disabilities. The outcome for such individuals has improved tremendously, especially with early and intensive individual therapy. Today, some autistic children can attend regular schools (Styles et al. 2020; Levy et al. 2009; Chaste and Leboyer 2012; Baio et al. 2018; Begovac et al. 2009; Howlin et al. 2004; Freitag 2007).

While there is no exact known etiology for ASD, a number of risk factors associated with its development have been identified. The risk factors include genetic, epigenetic, and environmental factors, in addition to neuroanatomical abnormalities. Multiple studies have linked the development of ASD to brain protein mutations such as Shank3 protein, which usually acts as an information receiver protein. Researchers also showed that mutation of nSR100 protein leads to abnormal social and environmental interaction in mutated mice models. Major histocompatibility complex class I (MHC-I) is an essential cell surface protein for the adaptive immune system. This molecule was found to play a critical role in restricting the connection between brain cells and is linked to ASD in many studies. An interesting quantitative analysis study showed that the combination of a group of five proteins (complement C3, complement C5, integrin alpha-IIb (ITGA2B), talin-1 (TLN1), and vitamin D-binding protein GC) that were earlier found to be involved in different pathways linked to the pathophysiology of ASD was also validated by enzyme-linked immunosorbent assay (ELISA) and could distinguish children with ASD from normal controls. Mutations in the fragile X mental retardation 1 (FMR1) gene have been linked to the most common inherited type of ASD in humans. It has been found that mutated oocytes deficient in FMR1 typically result in embryos with severe neural defect conditions (Wieczorek et al. 2017; Alexiou et al. 2018; Shen et al. 2018; Greenblatt and Spradling 2018; Wang et al. 2017).

## 11.2 Scaffolding Proteins

Scaffold proteins are key regulators of several signaling cascades. They are also defined as adaptor or linker proteins. Several scaffolding protein groups are found naturally. Their function is not fully identified, but these proteins are known to bind and/or interact with multiple other proteins forming new complexes, known as signalsome or transducisome, in the signaling pathways. Scaffold proteins help to convey the messages between the nucleus and cell membrane in a faster manner (Fig. 11.1) (Hata and Iida 2009; Garbett and Bretscher 2014).

Scaffold proteins can act in several ways. Its key function is to tether the signaling components increasing the signaling pathway efficiency and specificity by enhancing the physical assembly and effective concentration of the relevant components in the scaffold complex, which avoids the unwanted interaction between other proteins in the pathway. Another function is to localize the signaling components and target them to precise cell compartments. They also regulate the signal transduction by managing the positive and the negative feedback signals. Finally, they sequester the correct signaling proteins from other competing proteins and prevent the deactivation and/or degradation of the activated signaling components (Fig. 11.2). In short, scaffold proteins increase the efficacy and specificity of the signaling pathways and act as catalysts (Engström et al. 2010; Shaw and Filbert 2009; Locasale et al. 2007).

## 11.3 BEACH Domain-Containing Proteins

BEACH domain-containing proteins (BDCPs) are a group of related scaffolding proteins that belong to a new family, the Beige and Chediak-Higashi (BEACH) family. BDCPs were initially identified during a study to characterize the human type of Chediak-Higashi syndrome (CHS) using the *Beige* murine model. BEACH is conserved in all eukaryotes, including mammals, plant cells, and yeast. In humans,

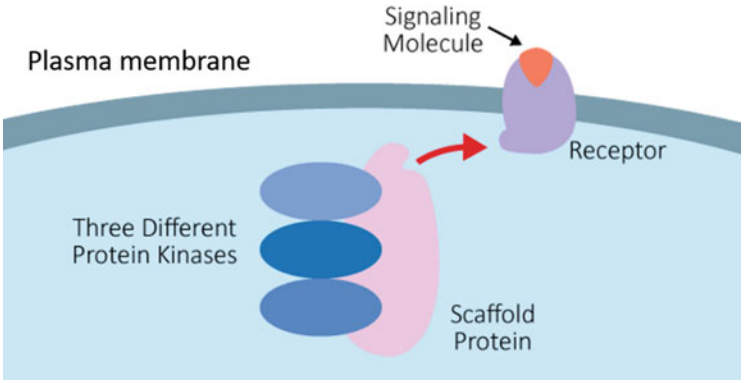


**Fig. 11.1** Scaffold proteins are proteins that bind multiple other proteins simultaneously, forming new complexes that enhance signaling efficiency and fidelity

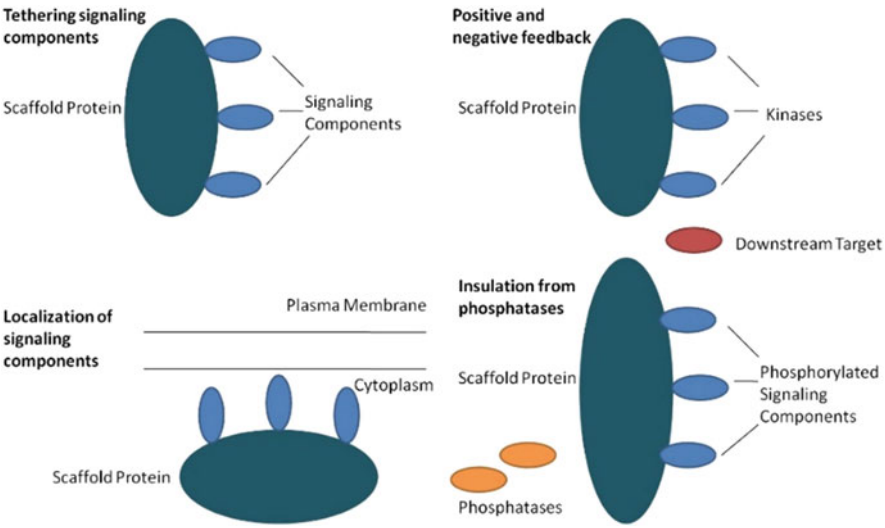


**Fig. 11.2** Scaffolding protein main functions (Shaw and Filbert 2009)

BDCP family includes nine proteins. Lysosomal trafficking regulator protein (LYST) is the first member with the BEACH domain to be discovered, followed by the identification of the other family members, lipopolysaccharide-responsive, beige-like anchor protein (LRBA), neurobeachin (NBEA), neurobeachin-like 1 (NBEAL1), neurobeachin-like 2 (NBEAL2), WD repeat domain 81 (WDR81), neutral sphingomyelinase activation-associated factor (NSMAF), WD and FYVE zinc finger domain-containing protein 3 (WDFY3), and WD and FYVE zinc finger domain-containing protein 4 (WDFY4). The proteins belonging to this family are mostly large in size and share the presence of PH-like domain in their C-terminal for membrane association, followed by the BEACH domain, which is vital for their functions in vesicle trafficking, membrane dynamics, and receptor signaling. The WD sequence repeats are thought to facilitate protein-protein interactions and regulate various cellular functions such as division, determination of cell fate, gene transcription, cell transmembrane signaling, mRNA adjustment, and vesicle formation and trafficking. The sequence of N-terminal of most proteins in this family is unrelated and is consistent with the different cellular functions they perform. Therefore, mutations in individual BEACH family proteins can cause different disorders (Repetto et al. 2018; Volders et al. 2011; Albers et al. 2011; Barbosa et al. 1996; Teh et al. 2015).

## 11.4 Neurobeachin

Neurobeachin (NBEA) is a cytosolic multi-domain scaffold protein with no less than seven different protein motifs. The mammalian neurobeachin is a neuron-specific polypeptide of 327 kDa with 38% of hydrophobic amino acids. It is characterized by the presence of the PH-BEACH sequence in its C-terminal followed by multiple WD40 repeats. In addition to BEACH, PH-like (pleckstrin homology) domain, and four C-terminal tryptophan-aspartic acid WD repeats, the NBEA protein domains uniquely include an A-kinase anchoring protein (AKAP) motif that binds to protein kinase A (PKA), which is essential in establishing cell microdomains. It contains in its N-terminal a Concanavalin A-like lectin (ConA-like) CALL domain, which is thought to play a role in intracellular sorting due to the similarity to the clostridial neurotoxin N-terminal heavy chain and also contains an armadillo repeat domain which was presented as a domain of unknown function 4704 (DUF4704). Another DUF domain (DUF1088) with assumed nuclear localization signals is also present (Fig. 11.3).

Neurobeachin is concentrated at the trans-Golgi complex, post-Golgi vesicles, and synaptic contacts. NBEA is expressed throughout the cell of many tissues but at different levels. It is largely expressed in human brain tissues, mostly in the plasma membrane of the postsynaptic area. It can be expressed at medium levels in the tissues of the spleen, thymus and prostate glands, testis, and ovaries. Lower levels of

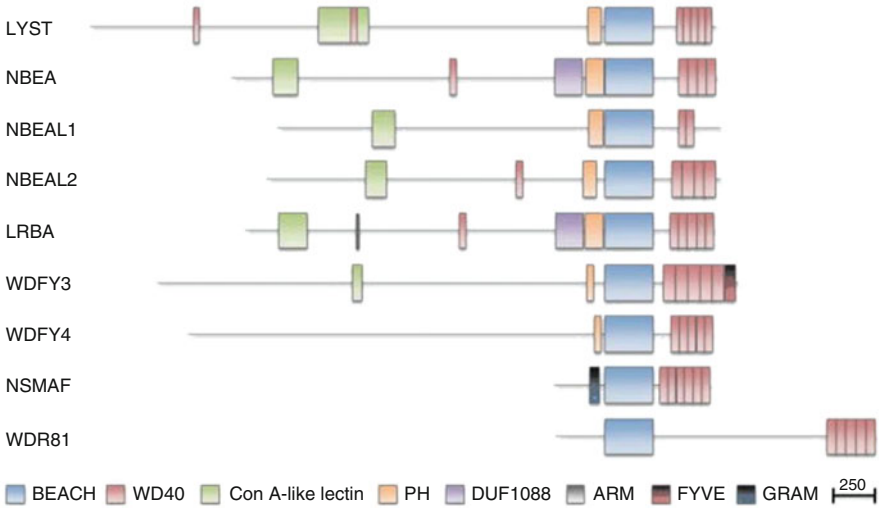


**Fig. 11.3** Schematic diagram displaying standard protein domains in human BDCPs. The BEACH domain is aligned for all nine proteins, and the drawing is to scale, where the scale bar represents 250 amino acids. Note the similarity in number and positions of the WD40 repeat domains following and the PH domains preceding the BEACH domain in 7 out of the 9 proteins. Other recognized domains include ConA-like lectin, DUF1088, ARM, FYVE, and GRAM domains (Cullinane et al. 2013)

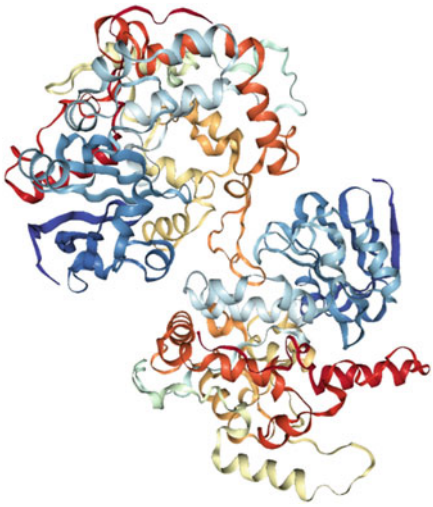

**Fig. 11.4** Crystal structure of the PH-BEACH domain of human neurobeachin. Blue is the N-terminus, and red is the C-terminus. Source: Protein Data Bank (PDB, https://www.rcsb.org)

expression are found in the heart, kidneys, pancreas, skeletal muscle tissues, and intestine. Neurobeachin and more than ten other mammalian proteins belonging to the same family were also found in invertebrates, plants, yeasts, and protozoa. This includes beige-like protein (BGL), which is an isoform of neurobeachin but does not bind to the regulatory subunit of protein kinase (Repetto et al. 2018; Wang et al. 2000; Dyomin et al. 2002; Gaudet et al. 2011) (Fig. 11.4).

## 11.5 Neurobeachin, an Autism Candidate Protein

Neurobeachin is located on chromosome q13 and recently was identified as a nonfamilial autism spectrum disorder-related protein. It was first recognized in a boy from a family with negative history of ASD or any other psychiatric or developmental disorders as balanced de novo translocation t(5;13)(q12.1;q13.2) and in three other patients as a monoallelic deletion. In patients with ASD, the NBEA gene is found to be either deleted or translocated (the breakpoint is located in intron 2 distal to the promoter), resulting in the absence of its expression. In a number of studies on ASD patients using genome-wide assessment (GWAS) and whole-genome comparative microarray, multiple other structural variations and autism-specific copy number variants (CNVs), including inversion and duplication, were also identified in some cases but with no known, precise causative mechanism (Odent et al. 2021; Creemers et al. 2014; Castermans et al. 2003; Marshall et al. 2008; Christian et al. 2008).

## 11.6 Neurobeachin Studies in Animal Models

To understand the role played by NBEA in autism pathogenesis, few ASD-related features were studied using animal models. In a study on mice, the NBEA-deficient mice showed some behavioral alterations, such as changes in memory and learning, self-grooming, social responses, and fear reactions. The observed symptoms coincide with an increase in long-term potentiation (LTP) in their CA1 region. The noticed changes in memory and learning and hippocampal LTP are associated with decreased expression of the immediate-early gene zif268 in dorsomedial striatum and CA1 region of the hippocampus, and also increased CREB phosphorylation and increased hippocampal BDNF expression. Such changes in NBEA-deficient mice could underlie the ASD symptoms in NBEA mutant individuals. In another in vivo study also done in mice, data indicated that mice lacking one allele of the NBEA gene exhibited unusual and specific cell excitability changes, which may contribute to the behavioral abnormalities in NBEA-deficient mice and can be related to ASD symptoms in patients. In another study, two independent mouse models have demonstrated a role in neurotransmitter release and synaptic functioning. Rugose (RG) in *Drosophila* is a homolog of the mammalian, including human, NBEA gene. It encodes an A-kinase anchor protein (DAKAP 550) and interacts with the epidermal growth factor receptors (EGFR), and Notch-mediated signaling pathways. Protein-protein interaction with NOTCH 1 is most relevant for ASD pathogenesis because NOTCH signaling is essential for neural development. Data from a functional study of the larval neuromuscular junctions revealed abnormal neurodevelopmental synaptic physiology. Additionally, RG mutant adult Drosophila showed unusual social behavior, diminished acclimatization, changes of motion, and overactivity resembling human ASD. Furthermore, the NBEA homologue in *C. elegans*, SEL-2, was identified as a negative regulator of Notch activity. A separate study has shown that NBEA acts as an important regulator in the postsynaptic neurons of zebrafish and is required for electrical and chemical synapse formation. It also showed a correlation to abnormal behavior (Nuytens et al. 2013a; Muellerleile et al. 2020; Wise et al. 2015; Miller et al. 2015).

## 11.7 Functions of Neurobeachin

The functions of neurobeachin have not been fully understood. It is characterized by its high binding affinity to the regulatory unit type II of protein kinase A (R II PKA) and targeting the cell membrane. NBEA deficiency or its absence can disturb protein kinase A (PKA)-mediated phosphorylation. NBEA has been shown to regulate the nucleus transcriptional process. It plays a not fully known role in spine formation, which includes small actin-rich protrusions from dendrites where most excitatory synapses are located, and it has an influence on actin distribution. It has been shown that deletion of the NBEA gene in cultured neurons from knockout mice and its deletion in cortical tissue from heterozygous mice lead to reduced numbers of spinous synapses and change the miniature postsynaptic currents (mEPSCs).

Neurobeachin has also been proved to target the postsynaptic neurotransmitter receptor in other species such as Drosophila and zebrafish. In addition, a novel interaction between NBEA, which is a nucleus transcriptional regulator, and NOTCH1, which is an essential protein-coding gene for neural development, was identified as the most relevant pathogenesis for ASD. NBEA haploinsufficiency was found to affect the morphological structure of dense granules in blood platelets leading to insufficient secretion regulation, a possible endophenotype in autism. In addition, it can affect receptor trafficking and synaptic structure (Repetto et al. 2018; Miller et al. 2015; Tuand et al. 2016; Niesmann et al. 2011; Nuytens et al. 2013b).

## 11.8 Lysosomal Trafficking Regulator Protein (LYST)

LYST is the first protein to be discovered in the BEACH family. It is a large cytosolic protein of 3801 amino acids (430 kDa). LYST gene contains PH-BEACH domain, ConA-like lectin domain, and WD40 repeats. The human LYST gene or CHS1 is located on chromosome 1 (1q42-43) and is believed to be related to material trafficking into lysosomes. Lysosomes help to recycle processes within the cells. LYST gene disruption, including nonsense and missense mutations, deletions, and insertions, leads to Chediak-Higashi syndrome (CHS), which is a rare, autosomal recessive condition that affects various body systems. Patients with CHS are characterized by severe immunodeficiency and frequent infections; hypopigmentation of the hair, skin, and eyes (albinism); poor blood coagulation leading to easy bruising; and prolonged bleeding time in addition to neurologic problems, such as neuropathies and ataxia, which accelerate with age (Cullinane et al. 2013; Ward et al. 2002; Ajitkumar et al. 2021).

## 11.9 WDFY3 and WDFY4

WD and FYVE zinc finger domain-containing protein 3 or autophagy-linked FYVE (Alfy) is a large scaffold protein that belongs to the human BDCP family. It is known to be the only protein in BDCP family that contains zinc finger domain FYVE, which is a domain also found in several other human proteins and exhibits a selective autophagy function, especially under unusual conditions such as starvation. It plays a vital role in mitochondrial homeostasis as well. It is localized near organelle membranes, making it easier to interact directly with the PtdIns(3)P phospholipids. The PH-like domain presence binds other phosphorylated inositides, but normally not PtdIns(3)P. In addition to the classical presence of ConA-like lectin and BEACH domains, the WD repeats found in the C-terminal are thought to be responsible for the co-localization of WDFY3. The human WDFY3 gene is located on chromosome 4 (4q21.23) and is expressed in developing as well as in the adult central nervous system. Its mutations are recently linked in animal models to conditions of decreased intellectual abilities, neurodevelopmental delay, familial microcephaly, and

psychiatric conditions like attention-deficit hyperactivity disorder (ADHD) and ASD with macrocephaly (Napoli et al. 2018; Isakson et al. 2013).

WD and FYVE zinc finger domain-containing protein 4 (WDFY4) is a large protein of 3184 amino acids belonging to the human BDCP family. Like other proteins of this family, it contains multiple functional domains, including WD40 and BEACH. However, despite its name and unlike WDFY3, WDFY4 does not encode the FYVE domain. WDFY4 gene is located on chromosome 10 (10q11.23) and is highly expressed in immune tissues like lymph nodes, tonsils, thymus gland, and spleen. Studies strongly suggest the relation between WDFY4 mutation and the autoimmune disease systemic lupus erythematosus (SLE) pathogenesis; however, its exact function is not fully identified (Cullinane et al. 2013; Yuan et al. 2018).

## 11.10 Neurobeachin-Like 1 and Neurobeachin-Like 2

Based on the presence of the BEACH domain, neurobeachin-like 1 (NBEAL1) and neurobeachin-like 2 (NBEAL2) as BEACH domain-containing proteins (BDCPs) have been identified as mammalian homologues of NBEA. NBEAL1 is a typical large BDCP with a total of 2694 amino acids. The human NBEAL1 gene is located on chromosome 2 (2q33-2q34); in addition to a ConA-like lectin, a PH-like, BEACH, and WD domain, it contains a vacuolar-targeting peptide motif ILPK, which suggests the possible protein localization in the lysosome. However, this has to be confirmed by cellular localization studies. Biopsies from different grades of glioma patients showed upregulation of the NBEAL1 gene, especially in the lower grade gliomas, which suggests their possible correlation. Studies also suggested the correlation of NBEAL1 to several other tumors like ovarian serous adenocarcinoma and metastasis of specific mammary gland breast cancer (Volders et al. 2011; Chen et al. 2004).

NBEAL2 is a protein with 2754 amino acids, which belongs to the same family and like other members in this protein family, it contains a BEACH domain and multiple WD40 repeats. Human NBEAL2 is a gene with previously unknown functions until its involvement in granule development was noticed. It is located in chromosome 3 (3p21-3q31) and was found to be related to thrombopoiesis and thought to interfere with megakaryocyte alpha-granule biogenesis. Its mutation is identified as the cause of gray platelet syndrome (GPS), which is a rare congenital autosomal recessive disorder caused by the decrease or complete absence of alpha-granules in blood platelets, leading to mild-to-moderate bleeding tendency, thrombocytopenia, and a marked reduction or lack of platelet alpha-granules and the proteins contained in them. Many patients tend to develop myelofibrosis later in life. Unlike neurobeachin, NBEAL2 is highly expressed in blood cells, mainly megakaryocytes (MKs) and granulocytes, and NBEAL2 expression levels increase during granulocyte maturation. It has low expression in the brain tissues (Albers et al. 2011; Fabbro et al. 2011).

Other members of this family are also connected to different disorders when mutated. LPS-responsive and beige-like anchor gene (LRBA) is generally involved

in the immune response and cell apoptosis and proliferation and is required for several pathways such as regulation of EGFR and PKA pathways. LRBA deficiency in humans was found to be related to some immunodeficiency conditions. It is observed to be more expressed in several cancer types, e.g., breast cancer related to estrogen and p53 mutation, melanoma, and gastric cancer (Bratanič et al. 2017; Wang et al. 2004). The neutral sphingomyelinase activation-associated factor (NSMAF) protein or factor associated with N-Smase activation (FAN) is a unique member of the BDCPs. NSMAF is comparatively not very large, and it consists of 948 amino acids only. It contains BEACH, and WD repeat domains, but not the ConA-like lectin domain. It is the only member with a membrane-associated GRAM domain instead of the membrane-associated PH-like domain found in a number of other BDCPs. For NSMAF to function, it has to bind phospholipids like PtdIns(4,5) P and be localized in the plasma membrane. It is required for TNF-mediated activation of neutral sphingomyelinase, and it is believed to have a role in regulating cellular inflammatory responses induced by TNF (Haubert et al. 2007). A WD repeat domain 81 (WDR81) is a transmembrane protein belonging to BDPCs, and similarly, the WD repeat domains precede the BEACH domain, but unlike most other BDCPs, WDR81 does not contain a PH-like or ConA-like lectin domain. It is expressed mainly in the corpus callosum and cerebellum, particularly in the cerebellar Purkinje cells. Mutation of WDR81 is linked with posture and gait abnormalities in humans. It has been demonstrated to be associated with neurological disorders. This needs further studies to be well identified (Cullinane et al. 2013; Gulsuner et al. 2011; Wang et al. 2021).

## 11.11 Conclusions

The NBEA is one of the several ASD candidate genes, which has been identified in a patient with a de novo chromosomal translocation. In animal models, NBEA gene loss was found to mimic autism as the defect affects signaling at neuronal junctions (synapses). The NBEA gene encodes a large multi-domain scaffolding protein that functions in neuronal post-Golgi membrane trafficking. NBEA possesses several domains that mediate protein-protein interactions. NBEA protein plays a diverse biological role. NBEA deficiency affects regulated secretion [negative regulator of secretion of large dense-core vesicles (LDCVs)], receptor trafficking, synaptic architecture [synaptic transmission is a fundamental step in brain function], and PKA-mediated phosphorylation [PKA is virtually a universal cellular component in eukaryotes, where diminished PKA-mediated phosphorylation of proteins thus leads to abnormalities in cellular signaling].

As a putative regulator of membrane protein trafficking to synaptic contacts, NBEA presumed function is consistent with the “excitatory-inhibitory imbalance” model of autism. While NBEA seems to be relevant to ASD social behavior, further investigation is warranted to understand how alterations in NBEA function might contribute to the pathogenesis of ASD.

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