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REVIEW

Regulation of neuronal migration, an emerging topic in autism spectrum disorders

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Abstract

Autism spectrum disorders (ASD) encompass a group of neurodevelopmental diseases that demonstrate strong heritability, however, the inheritance is not simple and many genes have been associated with these disorders. ASD is regarded as a neurodevelopmental disorder, and abnormalities at different developmental stages are part of the disease etiology. This review provides a general background on neuronal migration during brain development and discusses recent advancements in the field connecting ASD and aberrant neuronal migration.

Keywords: Astrotactin 2 *ASTN2*, Autism susceptibility candidate 2 *AUTS2*, Contactin-associated protein-like 2 *CNTNAP2*, Distal-less homeobox 1/2 *DLX1/2*, Neuronal migration, NudE nuclear distribution E homolog 1 *NDE1*.

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Autism spectrum disorders (ASD) encompass a group of neurodevelopmental diseases (review Chen *et al.* 2015). The symptoms of people with ASD fall on a continuum, with some individuals showing mild symptoms and others exhibiting more severe symptoms (Association 2013). The main symptoms include persistent social and communication deficits, and repetitive patterns of behavior, interests, or activities. In addition, patients may exhibit cognitive delay, intellectual impairment, and epilepsy. Family studies revealed a strong heritability component in ASD, with a 3–5% increased risk among first-degree relatives (International Molecular Genetic Study of Autism 2001), however, the inheritance is not simple. ASD exhibits a strong sex-bias, where far more males are affected than females (Kogan *et al.* 2009). However, the risk susceptibility of siblings of affected females is higher than that of affected males (Jorde *et al.* 1991; Zhao *et al.* 2007). Approximately five percent of patients microscopic cytogenetic abnormalities can be observed (review Vorstman *et al.* 2006). Smaller structural variations, or commonly referred to as copy number variations (CNV), are found in 10% of patients as either inherited or *de novo* mutations (Sebat *et al.* 2007; Marshall *et al.* 2008; Levy *et al.* 2011; Sanders *et al.* 2011; Girirajan *et al.* 2013). A similar proportion of patients exhibit genetic intellectual disability syndromes such as Fragile X syndrome, Rett's syndrome, tuberous sclerosis, Joubert's syndrome, and more (review Geschwind 2008). Over the last decade, mainly because of the advent of exome sequencing, several thousands of genes have been implicated in this disease (Iossifov *et al.* 2012; Neale *et al.* 2012; O'Roak *et al.* 2012a,b; Pagnamenta *et al.* 2012; Sanders *et al.* 2012; Talkowski *et al.* 2012; Casanova 2014; Fromer *et al.* 2014; Iossifov *et al.* 2014; Stessman *et al.* 2014; Butler *et al.* 2015; Turner *et al.* 2015; Michaelson *et al.* 2012) (reviews Beaudet 2007; Abrahams and Geschwind 2008; Geschwind 2008; van de Lagemaat and Grant 2010; Stankiewicz and Lupski 2010; Miles 2011; Schaaf and Zoghbi 2011; Murdoch and State 2013; Stessman *et al.* 2014; Ronemus *et al.* 2014; Jeste and Geschwind 2014). The discovery of many genes has been facilitated by the Simons Simplex Collection (Fischbach and Lord 2010), and the accumulating data can be found in the Simons Foundation Autism Research Initiative (SFARI) web site (http://sfari.org/). The genetics revealed that not only multiple genes contribute to ASD but also that the same mutations can show tremendous

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Abbreviations used: ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorders; ASTN1, astrotactin 1; CNV, copy number variations; *Dlx*, *distal-less homeobox*; MGE, medial ganglionic eminence.

phenotypic variability ranging beyond the definition of the ASD group of diseases. Patients with the same mutations can exhibit different degrees of social disability but also may exhibit schizophrenia, intellectual disability, language impairment, epilepsy, and delayed development (Cross-Disorder Group of the Psychiatric Genomics *et al.* 2013). With the expanding number of candidate genes for ASD, how will a disease gene be defined is an important challenge.

ASD is regarded as a neurodevelopmental disorder, thus, it can be assumed that abnormalities at different developmental stages may be part of the pathophysiology. This notion has been put forward, where possible roles of stem cell proliferation and neuronal migration in ASD has been discussed (review Casanova 2014). However, when we consider the field as a whole, a strong emphasis has been laid on defective synaptogenesis, synapse maintenance, and neuronal activity (Glessner *et al.* 2009; Gilman *et al.* 2011; Baudouin *et al.* 2012; Berkel *et al.* 2012; Clement *et al.* 2012, 2013; Gai *et al.* 2012) (reviews Geschwind 2008; Walsh *et al.* 2008; Toro *et al.* 2010; van Bokhoven 2011; Grant 2012; Spooren *et al.* 2012; Zoghbi and Bear 2012). Here, recent advancements in the field connecting ASD and aberrant neuronal migration will be discussed.

Neuronal production and migration

In the cerebral cortex, there are two main types of neurons; the excitatory or the glutaminergic neurons which compose the majority of the neurons in the cerebral cortex, and the inhibitory or the GABAergic interneurons constitute the minority. These two types of neurons are born in physically distinct areas of the brain; therefore, phenomenon of their migration is especially important (reviews Lambert de Rouvroit and Goffinet 2001; Hatten 2002; Nadarajah and Parnavelas 2002; Kriegstein and Noctor 2004; Ayala *et al.* 2007; Reiner 2013). The pyramidal or the excitatory neurons which contribute to the majority of population in the cerebral cortex and are born either within the ventricular zone or the subventricular zone (reviews Gotz and Huttner 2005; Hevner 2006; Fietz and Huttner 2011; Lehtinen and Walsh 2011; Shitamukai and Matsuzaki 2012). During early development neuroepithelial cells proliferate mainly to generate additional progenitors (reviewed Gotz and Huttner 2005; Fietz and Huttner 2011). Later, two types of progenitors in the ventricular zone are defined; most of them are the radial glial cells that span the entire neocortical wall, and the minority are the short neural precursors (Gal *et al.* 2006; Stancik *et al.* 2010). The radial glia are the major population of neural progenitor cells occupying the proliferative ventricular zone in the developing mammalian neocortex (Malatesta *et al.* 2000; Miyata *et al.* 2001; Noctor *et al.* 2001; Kosodo *et al.* 2004; Reugels *et al.* 2006; Wakamatsu *et al.* 2007; Konno *et al.* 2008; Noctor *et al.* 2008; Alexandre *et al.* 2010; Shitamukai *et al.* 2011). Asymmetric divisions will result in self-renewal of the progenitors, and will also produce intermediate progenitor cells (also known as basal progenitors), outer subventricular zone progenitors, or post-mitotic neurons (Noctor *et al.* 2004) (review Shitamukai and Matsuzaki 2012). During development, there is a gradual shift from proliferative divisions to neurogenic divisions, which is accompanied by progressive lengthening of the cell cycle (Takahashi *et al.* 1995).

The second proliferative area for excitatory neurons of the cerebral cortex is the subventricular zone, where progenitors usually divide in a symmetrical way (Smart 1973; Haubensak *et al.* 2004; Miyata *et al.* 2004; Noctor *et al.* 2004) (reviews Gotz and Huttner 2005; Shitamukai and Matsuzaki 2012; Tabata *et al.* 2012). In primates and humans the subventricular zone is widely expanded and they develop an additional proliferative region known as the outer subventricular zone (Smart *et al.* 2002; Zecevic *et al.* 2005; Fish *et al.* 2008). Similar progenitors have also been observed in non-primates, such as ferrets (Fietz *et al.* 2010) and mice (Shitamukai *et al.* 2011; Wang *et al.* 2011).

The inhibitory neurons, or the GABAergic neurons, are born in the ventral part of the telencephalon, in the subpallium (Anderson *et al.* 1997) (for reviews see Wonders and Anderson 2005; Wonders and Anderson 2006; Gelman and Marin 2010). In contrast to rodent models, there is evidence that in the human cortex, the majority of GABAergic neurons are born in the Subventricular zone, followed by radial migration (Letinic *et al.* 2002). More specifically, the medial ganglionic eminence (MGE) and the caudal aspect of the lateral ganglionic eminence (also known as the dorsal aspect of the caudal ganglionic eminence) generate most of the cortical GABAergic interneurons (Xu *et al.* 2004). However, additional sources of cortical GABAergic interneurons are the rostral lateral ganglionic eminence, the subpallial septum, and the embryonic pre-optic area (Jimenez *et al.* 2002; Taglialatela *et al.* 2004; Gelman *et al.* 2009) (Fig. 1). Radial glia cells are progenitors for inhibitory neurons as well as for excitatory neurons (Anthony *et al.* 2004) (for reviews see Campbell and Gotz 2002; Mori *et al.* 2005; Tan and Shi 2012). These progenitors not only share structural similarities, but the ventral progenitors in the MGE were shown to also undergo asymmetric cell divisions to produce neocortical interneurons (Brown *et al.* 2011). Furthermore, neocortical inhibitory interneurons were produced as spatially organized clonal units in the developing ventral telencephalon. However, although the radial glia cells in different areas of the cerebral cortex appear morphologically similar, they do not share the same molecular identity. In addition to proliferating radial glial cells, the ventral telencephalon contains multiple intermediate progenitors, which divide symmetrically to produce interneurons (Sheth and Bhide 1997; Malatesta *et al.* 2003). These proliferating progenitors are an important source of the interneurons since

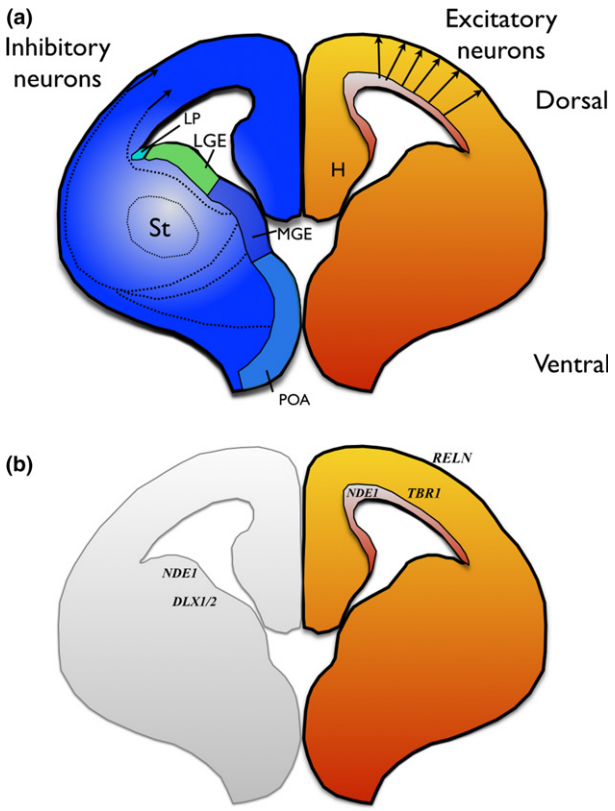

Fig. 1 (a) Schematic presentation of migratory routes of excitatory and inhibitory neurons in the developing brain (adapted from a review by Tan and Shi, WIREs Dev Biol 2012. doi: 10.1002/wdev.88). Inhibitory neurons are shown in the left side. Most of the GABAergic neurons are born in the ventral part of the telencephalon, in the subpallium, and more specifically in the medial ganglionic eminence (MGE) and the lateral ganglionic eminence, in the subpallial septum and the embryonic preoptic area (POA) and they migrate in a tangential way to the cortex. Excitatory neurons are shown in the right side, radially migrating into the cortex. St, striatum; LP, lateral palium; H, hippocampus. (b) Expression domains of some of the genes mentioned in this review. RELN is expressed mainly in Cajal–Retzius cells in the marginal zone of the cerebral cortex. TBR1 is expressed mainly in deep-layer neurons. NDE1 is mainly expressed in proliferating stem cells of both excitatory and inhibitory neurons. DLX1/2 genes are expressed in the progenitors of inhibitory neurons.

the subventricular zone in the ventral telencephalon is larger than that in the neocortex.

Neurons migrate using several types of cellular motility (reviewed Marin and Rubenstein 2003, 2001; Nadarajah and Parnavelas 2002; Kriegstein and Noctor 2004; Tsai and Gleeson 2005; Ayala *et al.* 2007; Reiner and Gerlitz 2013). The position of neurons within defined layers of the cerebral cortex is dependent upon their birth-date and their proper movement from their place of birth to their accurate placement. The six layers of the cerebral cortex are composed of neurons that are born in different areas but are subsequently organized according to their birth dates (Angevine and Sidman 1961; McConnell 1991). Neurons born relatively late during corticogenesis reside in more superficial layers on top of the older neurons, thus composing an inside-out organization. Early in development, multipolar neurons usually move using cellular locomotion. Later, neurons migrating along this route attach to radial glia, which provide a transient scaffold for directed migration (Rakic 1972; Hatten 1999, 2002; Kriegstein and Noctor 2004; Ayala *et al.* 2007). Neurons migrating along radial glia exhibit a bipolar structure. Once these cells reach the pial surface or their correct position, they detach from the radial glia and continue to move toward their correct laminar position, resulting in a layered organization of the cortex. Furthermore, daughter neuronal cells at different layers and of the same mother progenitor are radially aligned in minicolumnar structures, which become highly connected at later stages of development and are a fundamental part of brain circuitry.

A different mode of migration, known as tangential migration, is employed by the interneurons, which migrate tangentially across the plane of the glial fiber system (Lavdas *et al.* 1999; Marin and Rubenstein 2001; Nery *et al.* 2002; Kriegstein and Noctor 2004; Ayala *et al.* 2007). Once they reach the cerebral cortex, they employ the radial route and migrate along radial glia to their proper laminar position (de Carlos *et al.* 1996; Tan *et al.* 1998; Anderson *et al.* 1999, 2001; Ware *et al.* 1999; Wichterle *et al.* 2001; Jimenez *et al.* 2002; Polleux *et al.* 2002; Yozu *et al.* 2005; Miyoshi *et al.* 2010) (routes of migration are schematically shown in Fig. 1). Thus, even if only the radial route of migration is disrupted, the position of inhibitory neurons in the cerebral cortex will be affected, since they use both the tangential and the radial route. Here, we focused on the development of the cerebral cortex, for an excellent review summarizing the development of the cerebellum, which is also affected in ASD, please see Martinez *et al.* (2013).

Neuronal migration disorder and ASD – evidence from patients

A review of neuropathology studies reveal that migration-associated phenotypes can be detected in ASD patients including changes in neuronal density and volume, aberrant minicolumns, and heterotopias (reviews DiCicco-Bloom 2006; Casanova and Pickett 2013; Chen *et al.* 2015). A study with six autistic patients with severe intellectual disability revealed widespread cortical abnormalities (Bailey *et al.* 1998). In addition, a study of ASD patients revealed multiregional dysregulation of neurogenesis, neuronal migration, and maturation, which may contribute to the heterogeneity of the clinical phenotype (Wegiel *et al.* 2010). Two studies demonstrated evidence of cell clustering in lamina I and subplate with less distinct gray-white matter boundaries, which are suggestive of migrational abnormalities (Hutsler *et al.* 2007; Avino and Hutsler 2010). The typical organiza-

tion of cells in minicolumns was found to be disrupted in two studies (Casanova *et al.* 2002; Buxhoeveden *et al.* 2006). This finding may be because of impairments in neuronal migration. In another study, focal patches of abnormal laminar cytoarchitecture and cortical disorganization of neurons, but not glia, were detected in prefrontal and temporal cortical tissue the majority of ASD children brain samples (Stoner *et al.* 2014). The fact that there was disorganization of neurons but not glia, suggests abnormality at mid-gestation. There was evident heterogeneity between cases with respect to cell types that were most abnormal in the patches and the layers that were most affected by the pathological features. No cortical layer was uniformly spared, with the clearest signs of abnormal expression in layers 4 and 5. It has been demonstrated that a reduction in the number and in the size of the pyramidal neurons in ASD patients in the anterior midcingulate cortex, may also suggest neuronal migration abnormalities (Uppal *et al.* 2014).

Genes associated with ASD and neuronal migration abnormalities

Mutations in protein-coding genes participating in embryonic neuronal migration have been linked to the etiology of several neurocognitive disorders including ASD (review Valiente and Marin 2010). In this review, we are providing several examples of genes that are associated with regulation of neuronal migration and ASD, as well as additional brain-related pathologies (summarized in Table 1).

T-Brain-1 (*TBR1*) was identified as a causative gene in ASDs (Neale *et al.* 2012; O'Roak *et al.* 2012a,b; De Rubeis *et al.* 2014; Deriziotis *et al.* 2014). It is considered as a high confidence gene because in addition to functional analysis, independent studies have shown recurrent and convincing mutations in this gene. *TBR1* was also suggested as a likely candidate to be involved in developmental delay and intellectual impairment (Traylor *et al.* 2012; Burrage *et al.* 2013; Palumbo *et al.* 2014). The gene encodes for a brain-specific T-box transcription factor, with important roles in the developing brain and in regulation of neuronal migration and is associated with the differentiation of intermediate progenitors to post-mitotic early-born neurons (Dwyer and O'Leary 2001; Hevner *et al.* 2001, 2002; Englund *et al.* 2005; Kolk *et al.* 2005; Bayatti *et al.* 2008; Bedogni *et al.* 2010a; Han *et al.* 2011; McKenna *et al.* 2011; Mendez-Gomez *et al.* 2011). TBR1 is highly expressed in deep layers of the cerebral cortex, which have been suggested to participate in ASD pathology (Willsey *et al.* 2013). TBR1 target genes include multiple other autism risk factors (Chuang *et al.* 2015), and in particular TBR1 activates AUTS2 (Bedogni *et al.* 2010a; Srinivasan *et al.* 2012). Pathogenic *de novo* truncating and missense mutations disrupted multiple aspects of TBR1 function, including subcellular localization, interactions with co-regulators and transcriptional repression (Deriziotis *et al.* 2014). $Tbr1^{-/-}$ mice did not express markers of Cajal–Retzius, subplate, or layer 6 neurons and exhibited reduction in Reelin expression, whereas later-born cortical layers were relatively normal (Hevner *et al.* 2001; Neuron). $Tbr1^{-/+}$ mice were used to investigate whether the loss of one allele results in autism-like phenotypes. *Tbr1* haploinsufficiency resulted in reduced social interaction and vocalization, cognitive inflexibility and impaired associative memory (Huang *et al.* 2014).

A well-known neuronal migration regulator is Reelin (*RELN*) (reviews Folsom and Fatemi 2012; Sekine *et al.* 2014). RELN is a signaling glycoprotein, secreted by Cajal–Retzius cells in the marginal zone. It controls neuronal cell-adhesiveness during different stages of migration and in particular, during the transition from multi-polar to bipolar neurons at the initial step of migration as well as migration termination and neuronal layering. RELN is considered as a strong candidate for ASD, with several studies demonstrating an association between specific alleles and ASD (Persico *et al.* 2001; Zhang *et al.* 2002; Bonora *et al.* 2003). A meta-analysis provided a comprehensive and systematic evaluation of the roles of RELN variants in ASD susceptibility and found a significant association between a specific single nucleotide polymorphism (SNP) and ASD risk (Wang *et al.* 2014b). In addition, a *de novo* loss of function allele and two *de novo* potentially damaging mutant allele were identified in large scale sequencing studies (Iossifov *et al.* 2012; De Rubeis *et al.* 2014). Postmortem samples from ASD patients suggested abnormalities in Reelin signaling (Fatemi *et al.* 2005). Severe mutations of this gene in humans cause a type of lissencephaly, which is characterized by cerebellar hypoplasia, abnormal cerebral cortical neuronal migration and abnormal axonal connectivity (Hong *et al.* 2000). Neuronal migration abnormalities are well characterized in Reelin-deficient mice, which have roughly inverted neuronal layers (Falconer 1951; Caviness 1982; Goffinet *et al.* 1984; D'Arcangelo *et al.* 1995; Hirotsune *et al.* 1995). These mice display abnormal behavior as judged by tests of gait, emotionality, social aggression, spatial working memory, novel-object detection, fear conditioning, and sensorimotor reflex modulation (Salinger *et al.* 2003).

A genetic defect causing autism and epilepsy involving the contactin-associated protein-like 2 gene (*CNTNAP2*) has been discovered in a selected cohort of Amish children (Strauss *et al.* 2006). *CNTNAP2* is considered a strong candidate for ASD, however, several of the observed features in patients are not required for an ASD diagnosis (therefore the SFARI category is 2S). Several studies on large cohorts of patients substantiated the identity of *CNTNAP2* as an ASD gene (Alarcon *et al.* 2008; Arking *et al.* 2008; Bakkaloglu *et al.* 2008; Anney *et al.* 2012). *CNTNAP2* was also linked to seizures, epilepsy and attention-deficit hyperactivity disorder (ADHD), pathologies which are found in high

Table 1 ASD-associated genes discussed in this review

Gene	Gene symbol	SFARI score	Brain-related pathologies	Genetic mutation
T-Brain-1	*TBR1*	1	ASD	De novo mutation (Neale *et al.* 2012; O'Roak *et al.* 2012a,b; De Rubeis *et al.* 2014; Deriziotis *et al.* 2014)
			Developmental delay and Intellectual impairment	Micro Deletion (Traylor *et al.* 2012; Burrage *et al.* 2013; Palumbo *et al.* 2014)
REELIN	*RELN*	2	ASD	Polymorphism, missense mutation (Persico *et al.* 2001; Zhang *et al.* 2002; Bonora *et al.* 2003; Wang *et al.* 2014b)De novo mutations (Iossifov *et al.* 2012; De Rubeis *et al.* 2014)
			Lissencephaly	Severe mutations (Hong *et al.* 2000)
Contactin-associated protein-like 2	*CNTNAP2*	2S	ASD	Homozygous mutation (Strauss *et al.* 2006) SNP (Alarcon *et al.* 2008; Arking *et al.* 2008; Bakkaloglu *et al.* 2008; Anney *et al.* 2012) De novo inversion (Bakkaloglu *et al.* 2008),
			Seizures, epilepsy, and ADHD	SNP (Jackman *et al.* 2009; Elia *et al.* 2010; Mefford *et al.* 2010)
			Abnormal social interactions and language processing	SNP (Stein *et al.* 2011; Whalley *et al.* 2011; Al-Murrani *et al.* 2012; Toma *et al.* 2013; Condro and White 2014)
Autism susceptibility candidate 2	*AUTS2*	3	ASD	Translocation breakpoint (Sultana *et al.* 2002), (Huang *et al.* 2010) CNV (Pinto *et al.* 2010; Ben-David *et al.* 2011; Talkowski *et al.* 2012; Cheng *et al.* 2013; Nagamani *et al.* 2013; Egger *et al.* 2014; Liu *et al.* 2015)
			Intellectual impairment	Exon deletion (Beunders *et al.* 2015) Balancd translocation (Kalscheuer *et al.* 2007)
			ADHD	Exon deletion (Beunders *et al.* 2015) CNV(Elia *et al.* 2010)
			Speech disorders	De novo exon deletion (Amarillo *et al.* 2014)
			Developmental delay	Exon deletion (Beunders *et al.* 2015) Intragenic deletion (Jolley *et al.* 2013)
			Intellectual disability	Exon deletion (Beunders *et al.* 2013, 2015) CNV(Asadollahi *et al.* 2014) De novo mutation (Kalscheuer *et al.* 2007; Hamshere *et al.* 2009; Elia *et al.* 2010; Mefford *et al.* 2010; Talkowski *et al.* 2012; Beunders *et al.* 2013; Amarillo *et al.* 2014; Asadollahi *et al.* 2014; McCarthy *et al.* 2014; Zhang *et al.* 2014; Beunders *et al.* 2015; Jolley *et al.* 2013)
			Microcephaly	Exon deletion (Beunders *et al.* 2015)
			Epilepsy	CNV (Mefford *et al.* 2010)
			Schizophrenia	SNP (Hamshere *et al.* 2009; Zhang *et al.* 2014)
			Heroin addiction	SNP (Chen *et al.* 2013; Dang *et al.* 2014)
			Alcohol consumption	SNP (Schumann *et al.* 2011; Kapoor *et al.* 2013) Review (Edenberg and Foroud 2013)
			Risk for suicide	SNP(Chojnicka *et al.* 2013; Coon *et al.* 2013)
Astrotactin 2	*ASTN2*	3	ASD	CNV (Glessner *et al.* 2009)
			ADHD, speech delay, anxiety, obsessive compulsive disorder (OCD)	CNV (Lionel *et al.* 2014)
			Alzheimer	SNP (Fulp *et al.* 2008)

(continued)

Table 1. (continued)

Gene	Gene symbol	SFARI score	Brain-related pathologies	Genetic mutation
WD repeat and FYVE domain containing 3	*WDFY3*	3	ASD	De novo mutations (Iossifov *et al.* 2012, 2014) CNV (Jacquemont *et al.* 2006)
Distal-less homeobox 1/2	*DLX1/2*	4	ASD	SNP (Liu *et al.* 2009) SNP/microsatellite (International Molecular Genetic Study of Autism, C 2001)
			Epilepsy	
NudE nuclear distribution E homolog 1	*NDE1*	NA	ASD,intellectual disabilities, speech and language delay, schizophrenia, epilepsy, and attention-deficit hyperactivity disorder (ADHD).	CNV (Ullmann *et al.* 2007; Nagamani *et al.* 2011; Ramalingam *et al.* 2011; Girirajan *et al.* 2013; Tropeano *et al.* 2013)
			Microlissencephaly	Frame shift mutations (Alkuraya *et al.* 2011; Bakircioglu *et al.* 2011)
			Microhydranencephaly	Exon deletion (Guven *et al.* 2012)
			ADHD	Duplication (Williams *et al.* 2010)
			Seizures	Deletions (Heinzen *et al.* 2010; de Kovel *et al.* 2010; Mefford *et al.* 2010)

SFARI score: 1, High confidence. 2, Strong candidate. S, Mutations are associated with a substantial degree of increased risk and are consistently associated with additional features not required for an ASD diagnosis. 3, Suggestive evidence. 4, Minimal evidence. NA, not applicable.

frequency in ASD patients (Jackman *et al.* 2009; Elia *et al.* 2010; Mefford *et al.* 2010). *CNTNAP2* has been associated with abnormal social interactions as well as to language processing (Stein *et al.* 2011; Whalley *et al.* 2011; Al-Murrani *et al.* 2012; Toma *et al.* 2013; Condro and White 2014). Imaging evidence indicates that the language-associated SNP alters functional connectivity in the cerebral cortex (Vernes *et al.* 2008; Scott-Van Zeeland *et al.* 2010). CNTNAP2 (also known as Caspr2) is a transmembrane scaffolding protein and a member of the Neurexin family, and members of this protein family were found to interact with protein products of genes associated with ASD (Jamain *et al.* 2003; Comoletti *et al.* 2004). The possible role of CNTANP2 in the regulation of neuronal migration was suggested because of the presence of ectopic neurons in patients with *CNTNAP2* mutations (Strauss *et al.* 2006). *Cntnap2*$^{-/-}$ mice demonstrated neuronal migration impairment, including the presence of ectopic neurons in the corpus callosum and abnormal distribution of Cux1 upper layer neurons in deep layers V–VI, as well as a reduced number of GABAergic neurons (Penagarikano *et al.* 2011). The interneuron niche in the cerebral cortex and its defects in ASDs have been receiving a lot of coverage in scientific literature. In the postnatal brain, CNTNAP2 is involved in neuron-glia adhesion complex with contactin 2 (CNTN2, also known as TAG-1) and clustering of K+ channels in myelinated axons (Poliak *et al.* 1999, 2003). Interestingly, Tag-1 is an adhesion molecule present on corticofugal fibers and required for GABAergic interneurons tangential migration (Denaxa *et al.* 2001; Morante-Oria *et al.* 2003).

Distal-less homeobox (Dlx) genes play a crucial role in controlling the tangential migration of GABAergic neurons from the MGE to the cortex. *Dlx1/2* are widely expressed in the ganglionic eminences with their prominent expression being in the MGE of the developing brain. The single *Dlx1* knockout mice exhibited a reduction in inhibitory neurons and develop late-onset epilepsy, which is a common feature among ASD patients (Cobos *et al.* 2005). The migratory stream of GABAergic neurons is completely disrupted in *Dlx1*$^{-/-}$*; Dlx2*$^{-/-}$ double knockout mice and the neuronal precursors accumulate in the ganglionic eminences (Anderson *et al.* 1997; Ghanem *et al.* 2007). The activity of DLX in migrating tangential neurons may be in part through its immediate downstream target, *Arx* (Colasante *et al.* 2008). Interestingly, a subset of patients with a mutation of the X-linked homeobox gene *ARX* exhibits autistic features (Stromme *et al.* 2002; Turner *et al.* 2002). Linkage analysis suggested the *DLX1/2* bi gene cluster located in 2q32 and their paralogs *DLX5/6* located in 7q22 as ASD candidate genes (International Molecular Genetic Study of Autism, C 2001). Sequence analysis of the *DLX1/2* and *DLX5/6* genes revealed three non-synonymous variants in *DLX2* and two non-synonymous variants in *DLX5* that were either very rare or not present in other populations. A number of other SNPs were identified in all four genes (Hamilton *et al.* 2005). Another association analysis suggested the existence of

functional SNPs near or in *DLX1/2* that may contribute to ASD susceptibility (Liu *et al.* 2009).

Autism susceptibility candidate 2 (AUTS2) was first implicated in ASD following the finding of a translocation within this gene (Sultana *et al.* 2002), later detected also in another patient (Huang *et al.* 2010), and further strengthened by other findings in the same gene (Pinto *et al.* 2010; Ben-David *et al.* 2011; Talkowski *et al.* 2012; Cheng *et al.* 2013; Nagamani *et al.* 2013; Egger *et al.* 2014; Liu *et al.* 2015) (review Oksenberg and Ahituv 2013). *AUTS2* was further implicated in other diseases sharing co-morbidity with ASD such as intellectual impairment, ADHD, speech disorders, developmental delay, microcephaly, epilepsy, and schizophrenia (Kalscheuer *et al.* 2007; Hamshere *et al.* 2009; Elia *et al.* 2010; Mefford *et al.* 2010; Talkowski *et al.* 2012; Beunders *et al.* 2013; Jolley *et al.* 2013; Amarillo *et al.* 2014; Asadollahi *et al.* 2014; McCarthy *et al.* 2014; Zhang *et al.* 2014; Beunders *et al.* 2015). In addition, *AUTS2* has been associated with heroin addiction (Chen *et al.* 2013; Dang *et al.* 2014), alcohol consumption (Schumann *et al.* 2011; Kapoor *et al.* 2013) (review Edenberg and Foroud 2013), as well as with a risk for suicide (Chojnicka *et al.* 2013; Coon *et al.* 2013).

A role for AUTS2 for cell proliferation and neuronal cell survival in the developing brain has been suggested following functional studies where the knockdown of *Auts2* resulted in microcephaly and reduction in neurons in zebrafish embryos (Beunders *et al.* 2013; Oksenberg *et al.* 2013), as well as in the mouse (Hori *et al.* 2014). Most of the AUTS2 protein is nuclear and it has been suggested to participate in regulation of gene expression in the developing brain (Bedogni *et al.* 2010b; Srinivasan *et al.* 2012; Gao *et al.* 2014) (review Oksenberg *et al.* 2013). The association of AUTS2 with polycomb repressive complex 1 leads to transcription activation, in contrast to the canonical role of polycomb repressive complex 1 in gene repression (Gao *et al.* 2014). However, there is also a cytoplasmic pool of the AUTS2 protein, which acts as a regulator of Rho family GTPases (Hori *et al.* 2014). This function is involved in regulation of cortical neuronal migration and neuritogenesis in the developing brain (Hori *et al.* 2014).

Astrotactin 1 (ASTN1), which forms adhesions between neurons and astroglia as a neuronal cell-surface antigen, exhibits an important role in neuronal migration (Edmondson *et al.* 1988; Stitt and Hatten 1990; Fishell and Hatten 1991; Zheng *et al.* 1996). Astn1 null mice exhibit a slower migration rate of cerebellar granule cells, smaller cerebellar size, reduced glial-neuron binding, abnormal Purkinje cell morphology, and poorer balance and coordination in behavioral assays compared with wild-type (Adams *et al.* 2002). A second member of the astrotactin protein family, astrotactin 2 (ASTN2), interacts with ASTN1 and regulates its expression on the neuronal surface, thereby affecting neuronal-glial adhesions during migration (Wilson *et al.* 2010). There are suggestive data linking *ASTN2* to ASD. Rare CNVs disrupting *ASTN2* have been reported (Glessner *et al.* 2009). Genome wide association studies also implicated the involvement of *ASTN2* in ASD (Lesch *et al.* 2008). Individuals with ASTN2 deletions exhibit one or more of the following pathologies: ASD, ADHD, speech delay, anxiety, and obsessive compulsive disorder (Lionel *et al.* 2014). Patients with a specific SNP also exhibited early onset of Alzheimer disease (Wang *et al.* 2014a).

WD repeat and FYVE domain containing 3 (WDFY3) has been suggested to be an ASD causative gene following the detection of two *de novo* loss of function variants (Iossifov *et al.* 2012, 2014). In addition, earlier studies demonstrated linkage to the genomic locus (Yonan *et al.* 2003), and one patient with a CNV in this locus has been reported (Jacquemont *et al.* 2006). WDFY3 is a member of the BEACH (beige and CHS proteins) protein family and contains in addition to the BEACH domain five WD40 domains and a C-terminal FYVE (Fab1/YOTB/Vac1/EEA1) domain (Simonsen *et al.* 2004). WDFY3 has been shown to interact directly with the lipid membrane component phosphatidylinositol 3-phosphate through its FYVE domain (Simonsen *et al.* 2004), with Atg5 through its WD40 repeats (Filimonenko *et al.* 2010), and with P62 through its BEACH domain (Clausen *et al.* 2010). Mice carrying hypomorph alleles of the Wdfy3 gene, where only the longest isoform was missing exhibited a regionally enlarged cerebral cortex, which resembled the early brain outgrowth observed in many autistic children. The ventricular zone, and subventricular zone were smaller in mutant mice, leading to overall reduction in cortex thickness and suggesting aberrations in neural progenitor proliferation and neurogenesis. In addition, these mice exhibited local cortical dysplasia in which layer 5/6 cortical projection neurons locally 'over-migrated' into upper layers (Orosco *et al.* 2014).

NDE1 (nudE nuclear distribution E homolog 1) is a gene, which is involved in multiple brain diseases. NDE1 is part of the LIS1/NDE1/NDEL1/cytoplasmic dynein complex and as such participates in regulation of cell proliferation, migration, and intracellular transport (Efimov and Morris 1998, 2000; Feng *et al.* 2000; Kitagawa *et al.* 2000; Niethammer *et al.* 2000; Sasaki *et al.* 2000; Yan *et al.* 2003; Shu *et al.* 2004; Efimov *et al.* 2006; Stehman *et al.* 2007; Vergnolle and Taylor 2007; Bradshaw *et al.* 2008; Burdick *et al.* 2008; Lam *et al.* 2010; McKenney *et al.* 2010; Shmueli *et al.* 2010). *LIS1* (*Lissencephaly 1*) (officially known as *PAFAH1B1*) was the first gene to be identified which is involved in a neuronal migration disorder (Reiner *et al.* 1993) (reviews Reiner 2013; Reiner and Sapir 2013). Most of the known LIS1 activities relate to its interactions with the molecular motor cytoplasmic dynein. Many LIS1 interacting proteins are dynein regulators; these include NDE1, NDEL1, and CLIP-170 (Coquelle *et al.* 2002; review Reiner 2000). Cytoplasmic dynein is a large and complex microtubule-

associated molecular motor, which moves toward the minus ends of microtubules, and serves as the main retrograde motor in neurons (recent reviews: Kardon and Vale 2009; Allan 2011; Vallee *et al.* 2012). NDE1 and NDEL1 share 72% similarity and 57% identity; part of their functions are shared, whereas in others specialization can be noted (review Maher and LoTurco 2012). Rodent models have been used to study NDE1. *Nde1* mouse knockout revealed an important role of this protein in the regulation of proliferation of neuronal progenitors as well as neuronal migration retardation (Feng and Walsh 2004). Studies conducted in the mouse and rat revealed the importance of LIS1 in cell proliferation and neuronal migration. LIS1 affects cell proliferation in the developing brain at multiple stages (Gambello *et al.* 2003; Tsai *et al.* 2005; Hebbar *et al.* 2008; Bi *et al.* 2009; Youn *et al.* 2009; Pramparo *et al.* 2010, 2011; Silver *et al.* 2010). Neuronal progenitors, knocked down for LIS1 failed to proliferate (Tsai *et al.* 2005). In addition, mosaic analysis demonstrated the requirement of LIS1 for the proliferation of all neuronal lineages and astrocytes (Hippenmeyer *et al.* 2010). Abnormal interkinetic motility was observed in knockdown, knockout, and increased dosage of LIS1 (Tsai *et al.* 2005; Bi *et al.* 2009; Pramparo *et al.* 2010). LIS1 is essential for control of mitotic spindle orientation (Yingling *et al.* 2008). Multiple studies link LIS1 to regulation of neuronal migration in the developing brain (Hirotsune *et al.* 1998; Cahana *et al.* 2001; Shu *et al.* 2004; Tsai *et al.* 2005, 2007). *Nde1* mouse knockout combined with $Lis1^{-/+}$ resulted in a more severe phenotype where not only a striking reduction in brain size was observed, but also the morphology of the progenitors in the ventricular zone, the radial glia, was abrogated (Pawlisz *et al.* 2008). This activity was mediated through stabilizing the dystrophin/dystroglycan glycoprotein complex (Pawlisz and Feng 2011). Proliferation regulation in the developing brain was found to be in a spatiotemporally restricted pattern, where *Nde1-Lis1* deficiency resulted in a spatially dependent alteration of the MAPK scaffold protein Ksr and hyperactivation of MAPK (Lanctot *et al.* 2013).

Some mutations in the *NDE1* locus resulted in microlissencephaly (small brain with a simplified gyral pattern) (Alkuraya *et al.* 2011; Bakircioglu *et al.* 2011), in these two studies three different mutations were identified; two were frameshifts, and the remaining was a splicing mutation. A more severe disruption of the brain structure, resulting in microhydranencephaly (extreme microcephaly, motor and intellectual disability and almost complete absence of the cerebral hemispheres) was observed in patients with a homozygous deletion of the exon containing the initiator methionine (Guven *et al.* 2012). Deletions of one allele and mutations in the second allele have been reported in cases of microcephaly (Paciorkowski *et al.* 2013). CNVs in the corresponding genomic locus were associated with a diverse array of neuropsychiatric disorders including intellectual disabilities, ASD, schizophrenia, epilepsy, and ADHD (Ullmann *et al.* 2007; Nagamani *et al.* 2011; Ramalingam *et al.* 2011; Girirajan *et al.* 2013; Tropeano *et al.* 2013). Most notably, both duplications and deletions were associated with a wide range of phenotypic manifestations (Tropeano *et al.* 2013). Most commonly detected were developmental delay/learning disability and physical dysmorphism, however, the majority of patients older than 2 years also presented with a specific neurologic/neuropsychiatric phenotype, including ASD, speech and language delay, seizures, behavioral problems, microcephaly, and attention-deficit hyperactivity disorder. In line with other reports, seizures were most commonly observed among deletion carriers (Heinzen *et al.* 2010; de Kovel *et al.* 2010; Mefford *et al.* 2010), whereas ADHD was only present in duplication carriers (Williams *et al.* 2010). It was noted that the sex of the person represents a major risk factor in the presentation of ASD. Interestingly, there was a male-biased autosomal effect of 16p13.11 duplications and deletions in a study which used a sample of more than 10 000 individuals with a neurodevelopmental condition (Tropeano *et al.* 2013).

Discussion

ASD is recognized by now as a neurodevelopmental disease, and in this review we have surveyed several genes associated with ASD and neuronal migration abnormalities. The reviewed genes are also associated with other pathologies such as schizophrenia and bipolar disorders, thus suggesting that these diseases lie on a continuum spectrum of neurodevelopmental disorders. Aberrant neuronal migration during development fits well with the overall pathology of ASD, which is characterized with brain heterotopia, disrupted neuronal minicolumns, and changes in neuronal density and volume. The role of the reviewed genes in cortex development is complex and involves both straightforward mechanical aspects, such as ASTN1, which forms adhesion between neuron and radial glia, as well as developmental regulation signaling as in the case of RELN. Other genes such as *WDFY3* have been shown to affect migration but their exact role remains unclear. The manifestation of abnormal migration greatly varies between genetic mutations, ranging from slower migration rate and reduced neuronal-glia binding appearing in ASTN1, to full deletion of Cajal–Retzius and layer 6 neurons in TBR1 null mice. Thus, it seems that there are many possible pathways from migration deficit to intellectual imparity including overall reduction in neuronal population, imbalance in excitatory and inhibitory neuronal population or malformation of neuronal circuits and minicolumnar structures because of layer mislocalization of neurons. These are complemented by additional ASD-related neurodevelopmental disorders affecting synapse formation and neuronal activity.

Overall, there is a gap between the huge advance in genetic information and the lagging of biochemical data, animal

model experiments and pathology evidence which is required to identify a pathophysiological mechanism for ASD. Several recent technological breakthroughs are expected to enable deeper investigation in the near future. The development of multiple Cre lines enables genetic fate mapping to understand the origin of specific cell types, their migration process, and final position and function (Taniguchi *et al.* 2011, 2013). This is especially important in Autism, where migration deficits may lead to erroneous connections and imbalance between different cell types in the brain. The CRISPR/Cas9 technology allows precise genomic editing and will facilitate study of specific mutations and deletions (Hsu *et al.* 2014). Reprogramming of patient cells for generation of pluripotent stem cells, and *in vitro* neuronal differentiation protocols will promote study of genetic disorders in human cell cultures (Takahashi *et al.* 2007; Lancaster *et al.* 2013; Kim *et al.* 2014). Finally, optogenetic tools in living animals will facilitate direct studies of the relation between genetics, neuronal activity and behavior (Yizhar *et al.* 2011).

Understanding the role of neuronal migration in ASD is also important for developing autism treatments, which to date has no pharmacological solution. There may be a time window in which disease phenotype may be ameliorated. This has been first demonstrated in pioneering work in mice mutated in *Mecp2,* which serve as a model for Rett syndrome, which is an early onset neuronal developmental disease (Guy *et al.* 2007). They showed that part of the neurological defects because of the absence of *Mecp2* can be rectified by delayed restoration of the gene. This study demonstrated the principle of reversibility in a mouse model and raise the possibility that neurological defects seen in this disease and related human disorders may be partially repaired. Along the same line, a successful time-sensitive postnatal rescue of subcortical band heterotopia in Doublecortin knockdown mice by using conditional postnatal re-expression of Doublecortin has been demonstrated (Manent *et al.* 2009). Further studies in additional disease models will be required to further investigate these exciting possibilities.

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