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Identification of Arx targets unveils new candidates for controlling cortical interneuron migration and differentiation

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Mutations in the homeobox transcription factor *ARX* have been found to be responsible for a wide spectrum of disorders extending from phenotypes with severe neuronal migration defects, such as lissencephaly, to mild forms of intellectual disabilities without apparent brain abnormalities, but with associated features of dystonia and epilepsy. Arx expression is mainly restricted to populations of GABA-containing neurons. Studies of the effects of *ARX* loss of function, either in humans or mutant mice, revealed varying defects, suggesting multiple roles of this gene in brain patterning, neuronal proliferation and migration, cell maturation and differentiation, as well as axonal outgrowth and connectivity. However, to date, little is known about how Arx functions as a transcription factor or which genes it binds and regulates. Recently, we combined chromatin immunoprecipitation and mRNA expression with microarray analysis and identified approximately 1000 gene promoters bound by Arx in transfected neuroblastoma N2a cells and mouse embryonic brain. To narrow the analysis of Arx targets to those most likely to control cortical interneuron migration and/or differentiation, we compare here our data to previously published studies searching for genes enriched or down-regulated in cortical interneurons between E13.5 and E15.5. We thus identified 14 Arx-target genes enriched (*Cxcr7*, *Meis1*, *Ppap2a*, *Slc12a5*, *Ets2*, *Phlda1*, *Egr1*, *Igf1*, *Lmo3*, *Sema6*, *Lgi1*, *Alk*, *Tgfb3*, and *Napb*) and 5 genes specifically down-regulated (*Hmgn3*, *Lmo1*, *Ebf3*, *Rasgef1b*, and *Slit2*) in cortical migrating neurons. In this review, we present these genes and discuss how their possible regulation by Arx may lead to the dysfunction of GABAergic neurons, resulting in mental retardation and epilepsy.

Keywords: ARX, GABA, epilepsy, interneurons, neuronal migration, basal ganglia

INTRODUCTION

The cerebral cortex is formed of two broad classes of neurons: excitatory projection neurons, which primarily use glutamate as a neurotransmitter, and inhibitory GABA-containing interneurons. Whereas projection neurons are generated directly from radial glial cells in the germinal ventricular zone (VZ; reviewed in Nadarajah and Parnavelas, 2002; Kriegstein and Noctor, 2004) or indirectly from intermediate progenitors in the subventricular zone (SVZ; Noctor et al., 2001, 2004), the majority of interneurons are generated in the ventral forebrain and reach the cortex by tangential migration along well-defined streams, guided by a combination of chemoattractive and repulsive cues (reviewed by Marín and Rubenstein, 2003; Métin et al., 2006). In rodents, cortical interneurons have been reported to arise predominantly from the medial ganglionic eminences (MGE) or caudal ganglionic eminences (CGE) and, to a smaller extent, from the embryonic preoptic area (Lavdas et al., 1999; Nery et al., 2002; Yozu et al., 2005; Gelman et al., 2009). They then, display diverse migratory behaviors before establishing themselves in an inside-out manner in the cortical plate (CP), similar to pyramidal neurons (Corbin et al., 2001; Ang Jr. et al., 2003; Tanaka et al., 2006, 2009). In addition, a few studies have suggested that, at least in primates and humans, a significant number of cortical GABAergic neurons may also be generated from progenitors of the VZ and SVZ in the dorsal forebrain (Letinic et al., 2002; Petanjek et al., 2009; Jakovcevski et al., 2011; Zecevic et al., 2011). Over the last 15 years, mutant mouse analysis and RNAi-mediated gene knock-down studies have identified several genes encoding transcription factors such as *Dlx1*, *Dlx2*, *Dlx5* (*Distal-less*), *Arx* (*Aristaless-related homeobox*), *Nkx2.1* (*NK2 homeobox 1*), or *Lhx6* (*LIM homeobox protein 6*) important for the correct generation, migration or differentiation of these GABAergic neurons (reviewed by Hernandez-Miranda et al., 2010).

Over the past decade, numerous studies have demonstrated that a dysfunction of the GABAergic system is responsible for a large variety of neurodevelopmental disorders (Baulac et al., 2001; Levitt et al., 2004; Di Cristo, 2007). In particular, it is now well accepted that there is a connection between altered neuronal

positioning, usually due to defects in migration, and susceptibility to epilepsy. Moreover, subtle alterations in interneuron position and/or function have been reported to contribute to disorders such as dyslexia, schizophrenia, autism, and mental retardation (Galaburda et al., 2006; Nakazawa et al., 2011). It is thus important to better characterize the molecular mechanisms involved in interneuron generation, migration and differentiation through, for example, the analysis of genes important for interneuron development.

The ARX gene was first identified in 2002 as being responsible for a rare and severe cortical malformation in human, the X-linked lissencephaly associated with abnormal genitalia (XLAG), typically characterized by severe congenital or postnatal microcephaly, complete disorganization of cortical layers (lissencephaly), agenesis of the corpus callosum, midbrain malformations, and neonatal-onset intractable epilepsy (Kitamura et al., 2002). Interestingly, a complete absence of interneurons was described in the cortex of these patients (Bonneau et al., 2002; Forman et al., 2005; Okazaki et al., 2008; Marcorelles et al., 2010). Similarly, aberrant migration and differentiation of GABAergic interneurons in the ganglionic eminences and neocortex were described in male embryonic *Arx* mutant mice (Kitamura et al., 2002; Colombo et al., 2007). Since then, *ARX* has been associated with no less than 10 different syndromes ranging from phenotypes characterized by severe neuronal migration defects, to mild or moderate forms of intellectual disability without apparent brain abnormalities, but often with dystonia and epilepsy (reviewed in Friocourt and Parnavelas, 2010; Shoubridge et al., 2010).

Although Arx is expressed in several structures including the brain, pancreas, developing testes, heart, skeletal muscle, and liver (Bienvenu et al., 2002; Collombat et al., 2003; Biressi et al., 2008), the most striking consequences of its loss of function concern the brain and testes in both mouse and human. During development, Arx is expressed early in telencephalic structures, and more specifically in the mantle zones of the developing lateral ganglionic eminences (LGE) and MGE in the basal forebrain. In the developing cortex, its expression is observed in progenitor cells of the VZ as well as in migrating interneurons, but not in radially migrating cells (Colombo et al., 2004; Poirier et al., 2004; Friocourt et al., 2006). The extensive cellular co-localization between Arx and GABA in mouse and human brain, as well as the absence of interneurons documented in the cortex of XLAG patients and *Arx* mutant mice have led to propose "interneuronopathy" as a new term to describe the group of pathologies *ARX* is responsible for (Kato and Dobyns, 2005).

Arx encodes a homeobox transcription factor that has been found to contribute to most fundamental processes of brain development: patterning, neuroblast proliferation, neuronal migration and differentiation as well as axonal outgrowth and connectivity (Kitamura et al., 2002; Cobos et al., 2005; Colombo et al., 2007; Colasante et al., 2008; Friocourt et al., 2008), but the signaling pathways controlled by this gene are still unknown. Although two gene expression profile analyses comparing E14.5 wild-type and *Arx* mutant ventral telencephalic tissues have been published in mouse, very few targets for this transcription factor have been described, and only three (*Lmo1*, *Ebf3*, and *Shox2*) were found to be direct (Fulp et al., 2008; Colasante et al., 2009). For this reason, we recently performed chromatin immunoprecipitation in Arx-transfected neuroblastoma cells (N2a) or E15.5 mouse embryonic brain, followed by hybridization to mouse promoter arrays (ChIP-chip) in order to identify new direct targets of Arx (Quillé et al., 2011). We then examined by transcriptomic experiments whether these genes were differently regulated following the ectopic expression of Arx in N2a cells or its knock-down in mouse ventral telencephalon (Quillé et al., 2011). For the latter, we used the publicly available microarray data generated by Fulp et al. (2008) and Colasante et al. (2009), comparing gene expression between basal telencephalon of E14.5 *Arx* knock-out and wild-type mice. Out of a total of 1006 genes which promoters were found to be enriched in Arx-immunoprecipitates, approximately 24% showed expression changes following Arx overexpression or knock-down (Quillé et al., 2011).

In order to provide novel insights into genetic networks regulated by Arx and specifically controlling the development of GABAergic neurons, we took advantage of previously published studies comparing the level of expression of genes between, on one hand, cortical interneurons (*Dlx5/6*-derived cells) and cortical non-interneurons (non-*Dlx5/6*-derived cells) in the telencephalon of E13.5, E14.5, and E15.5 mice (Batista-Brito et al., 2008; Marsh et al., 2008) and, on the other hand, genes expressed by GABAergic neurons (*Gad67*-positive cells) in the ganglionic eminence versus those migrating in the cortex at the same stages (Marsh et al., 2008; Faux et al., 2010). As Arx is strongly expressed in cortical migrating interneurons, we decided to compare these datasets with ours and present here a list of ChIP-positive (Arx-bound) and regulated genes (Quillé et al., 2011) that are enriched or down-regulated in migrating cortical interneurons and, thus, are good candidates to control, positively or negatively, molecular mechanisms involved in interneuron migration and/or differentiation (**Table 1**).

IDENTIFICATION OF CANDIDATE GENES POSITIVELY REGULATING CORTICAL INTERNEURON MIGRATION AND/OR DIFFERENTIATION

As shown in **Table 2**, we identified 14 ChIP-positive genes (genes whose promoters were enriched in Arx-immunoprecipitates) that showed deregulation, either following Arx overexpression in N2a cells or in *Arx* mutant subpallium (Quillé et al., 2011), and appeared enriched in migrating cortical interneurons (Batista-Brito et al., 2008; Marsh et al., 2008; Faux et al., 2010). Thus, these genes are good candidates to positively control molecular mechanisms involved in cortical interneuron migration and/or differentiation.

In vitro and *in vivo* studies have previously demonstrated that Arx can act as both transcriptional repressor and activator (Seufert et al., 2005; McKenzie et al., 2007; Fullenkamp and El-Hodiri, 2008). Accordingly, eight of Arx putative direct targets presented in **Table 2** (*Egr1*, *Igf1*, *Lmo3*, *Sema6a*, *Lgi1*, *Alk*, *Tgfb3*, and *Napb*) show either a significant reduction in expression as a consequence of increased Arx levels or increased expression in *Arx* knock-out brains (**Table 2**). However, four genes (*Ppap2a*, *Slc12a5*, *Ets2*, and *Phlda1*) show similar changes in expression following Arx overexpression or knock-down, thus making it difficult to determine whether Arx normally activates or represses these genes

Table 1 | List of candidate genes regulated by Arx and controlling cortical interneuron migration and/or differentiation.

Gene symbol	Gene name	Human CNS disease	Mouse endophenotype
Cxcr7	Chemokine (C-X-C motif) receptor 7	NA	Interneuron migration defects
Meis1	Meis homeobox 1	Restless legs syndrome	NA
Ppap2a	Phosphatidic acid phosphatase type 2A	NA	NA
Slc12a5	Solute carrier family 12, member 5	NA	Severe motor deficits
Ets2	E26 avian leukemia oncogene 2	May contribute to Down syndrome	NA
Phlda1	Pleckstrin homology-like domain, family A, member 1	NA	NA
Egr1	Early growth response 1	NA	Learning and memory defects
Igf1	Insulin-like growth factor 1	Growth retardation, deafness, and mental retardation	Defects in neurologic development
Lmo3	LIM domain only 3	NA	NA
Sema6a	Semaphorin 6A	NA	Impaired development of thalamocortical projections
Lgi1	Leucine-rich repeat LGI family, member 1	Lateral temporal epilepsy	Increased excitatory synaptic transmission
Alk	Anaplastic lymphoma kinase	Susceptibility to neuroblastoma	NA
Tgfb3	Transforming growth factor, beta 3	NA	NA
Napb	*N*-ethylmaleimide-sensitive factor attachment protein, beta	NA	NA
Hmgn3	High mobility group nucleosomal binding domain 3	NA	NA
Lmo1	LIM domain only 1	NA	NA
Ebf3	Early B-cell factor 3	NA	Interneuron migration defects
Rasgef1b	RasGEF domain family, member 1B	Candidate for the 4q21 deletion syndrome	NA
Slit2	Slit homolog 2 (*Drosophila*)	NA	Abnormal axonal projections

NA, not available.

in migrating interneurons. We had previously described similar results for some other genes and suggested that Arx may switch from repressor to activator depending on the developmental stage, the molecular context (posttranslational modifications such as phosphorylation or the presence of cofactors and/or chromatin-modifying enzymes) or the cellular model used (Quillé et al., 2011). On the contrary, two genes look positively regulated by Arx (**Table 2**).

One such gene positively regulated by Arx is *Cxcr7* (*CXC chemokine receptor 7*), which role in interneuron migration has recently been described (Sánchez-Alcañiz et al., 2011; Wang et al., 2011). Cxcr4 and Cxcr7 are receptors for the chemokine Cxcl12 (also called Sdf1, stromal cell-derived factor) expressed in tangentially migrating interneurons (Sánchez-Alcañiz et al., 2011; Wang et al., 2011). Cxcl12 binding to Cxcr4 triggers GαI protein-dependent signaling, whereas Cxcl12 binding to Cxcr7 activates the mitogen-activated protein kinase (MAPK) cascade (Wang et al., 2011). Cxcl12 expression in the marginal zone (MZ) and SVZ of the cortex attracts Cxcr4- and Cxcr7-expressing migrating interneurons, guiding them to tangential streams and controls the timing of the switch from tangential to radial migration to their destinations in the CP (Tiveron et al., 2006; Li et al., 2008; Lopez-Bendito et al., 2008; Wang et al., 2011). Loss of Cxcl12 signaling has been shown to induce defects in both interneuron motility and leading process morphology, as well as a premature entry into the CP, resulting in a significant decrease in their numbers in the migratory streams and an increase in the lower part of the CP (Stumm et al., 2003; Tiveron et al., 2006; Li et al., 2008; Liapi et al., 2008; Lopez-Bendito et al., 2008; Lysko et al., 2011; Sánchez-Alcañiz et al., 2011; Wang et al., 2011).

Interestingly, *Cxcr7* mRNA has been shown to be down-regulated in cortical interneurons and the GE of *Dlx1/2* knock-out mice (Long et al., 2009a,b). Similarly, Cxcr7 and Cxcr4 receptors are positively regulated by Lhx6 (Zhao et al., 2008). *Dlx1*, *Dlx2*, and *Lhx6* have all been shown to be important for tangential interneuron migration (Anderson et al., 1997; Alifragis et al., 2004; Liodis et al., 2007). Similarly, we found in previous work that Arx binds *Cxcr7* promoter (Quillé et al., 2011) and positively regulates its expression which, in turn, regulates Cxcr4 protein levels (Sánchez-Alcañiz et al., 2011). Accordingly, Cxcr4 expression was found down-regulated in *Arx* mutant subpallium (Fulp et al., 2008; Colasante et al., 2009). As *Arx* expression was shown to be regulated by several members of the *Dlx* family of homeobox proteins, particularly *Dlx2* (Cobos et al., 2005), we may hypothesize that interneuron migration defects observed in *Dlx1/2*, *Lhx6*, or *Arx* mutants are, at least in part, due to abnormal Cxcl12 signaling pathway. In addition, $Cxcr4^{-/-}$ and $Cxcr7^{-/-}$ mutants have been reported to have defects in leading process morphology during migration (Wang et al., 2011), which may also be related to the cell morphology defects observed in migrating interneurons in the absence of *Arx* (Colombo et al., 2007; Friocourt et al., 2008).

Table 2 | Examples of Arx-bound and regulated genes that are enriched in migrating cortical interneurons (IN) compared to neurons in ganglionic eminences (GE) and cortical non-interneurons (non-IN).

Gene	Arx knock-out mice (Quillé et al., 2011)	Arx-transfected N2a cells (Quillé et al., 2011)	Expression in cortical migrating interneurons		
			Cells and stage	FC	Reference
Cxcr7	↓ KO subpallium (FC = 1.6, $p < 0.05$/Colasante et al., 2009)	No specific change	IN > GE at E13.5 and E15.5	2.2–2.3	Faux et al. (2010)
Meis1	No specific change	↑ N2a cells ($p < 0.005$)	GE > IN at E13.5 and E15.5	2.6–2.8	Faux et al. (2010)
			IN > non-IN at E13.5	2.6	Batista-Brito et al. (2008)
Ppap2a	↑ KO subpallium (FC = 1.4, $p < 0.05$)	↑ N2a cells ($p < 0.05$)	IN > non-IN at E13.5	2.2	Batista-Brito et al. (2008)
Slc12a5 = KCC2	↑ KO subpallium (FC = 1.8, $p < 0.005$)	↑ N2a cells ($p < 0.05$)	IN > non-IN at E13.5 and E15.5	7.7	Batista-Brito et al. (2008)
Ets2	↑ KO subpallium (FC = 1.8, $p < 0.001$)	↑ N2a cells ($p < 0.005$)	IN > non-IN at E13.5	2.7	Batista-Brito et al. (2008)
Phlda1	↑ KO subpallium (FC = 2.2, $p < 0.05$/Fulp et al., 2008)	↑ N2a cells ($p < 0.01$)	IN > non-IN at E13.5 and E15.5	3.2–3.7	Batista-Brito et al. (2008)
			IN > non-IN at E14.5	NA	Fulp et al. (2008)
Zif268 = Egr1	↑ KO subpallium (FC = 3.1, $p < 0.05$)	No specific change	IN > GE at E13.5 and E15.5	1.9–2.5	Faux et al. (2010)
			IN > non-IN at E13.5	6.4	Batista-Brito et al. (2008)
Igf1	↑ KO subpallium (FC = 1.5–5, $p < 0.001$)	No specific change	IN > non-IN at E15.5	6.9	Batista-Brito et al. (2008)
Lmo3	↑ KO subpallium (FC = 3.3, $p < 0.001$/Fulp et al., 2008/ Colasante et al., 2009)	No specific change	IN > non-IN at E14.5	6.9	Fulp et al. (2008)
Sema6a	↑ KO subpallium (FC = 1.6, $p < 0.01$)	No specific change	IN > GE at E15.5	1.9	Faux et al. (2010)
Lgi1	No specific change	↓ N2a cells ($p < 0.005$)	IN > non-IN at E13.5 and E15.5	2.7–26.2	Batista-Brito et al. (2008)/ Marsh et al. (2008)
Alk	No specific change	↓ N2a cells ($p < 0.05$)	IN > GE at E13.5 and E15.5	1.8–2.2	Faux et al. (2010)
			IN > non-IN at E13.5 and E14.5	2.5	Batista-Brito et al. (2008)/ Marsh et al. (2008)
Tgfb3	No specific change	↓ N2a cells ($p < 0.005$)	IN > GE at E13.5 and E15.5	3.4–4.5	Faux et al. (2010)
			IN > non-IN at E13.5 and E15.5	5.3–5.5	Batista-Brito et al. (2008)
Napb	No specific change	↓ N2a cells ($p < 0.05$)	IN > GE at E15.5	2	Faux et al. (2010)
			IN > non-IN at E13.5	2.6–3	Batista-Brito et al. (2008)

FC, fold change; NA, not available.

Another gene enriched in cortical migrating interneurons and positively regulated by Arx is *Meis1* (*murine ecotropic integration site 1*), a transcription factor involved in cell proliferation in retina and hematopoietic stem cell development. Although the function of this gene has not been studied in interneurons, its expression is consistent with a role in GABAergic neuron development. First detected around E10.5 in mouse ventrolateral telencephalon, it is expressed at later stages at high levels in the CGE and developing amygdala and more weakly in the MGE and LGE (Toresson et al., 2000). Interestingly, a recent paper on the effect of *Meis1* knock-down in a human precursor B-cell leukemic line RS4;11 reported an impairment of cell migration, possibly due to a defect in the CXCR4/SDF-1 axis (Orlovsky et al., 2011). Further studies should be undertaken in interneurons to assess whether this gene is also important for their migration and/or differentiation. This may be a worthwhile pursuit, as this gene has been linked to the restless legs syndrome (RLS), a common neurological disorder characterized by an irresistible urge to move the legs at night. RLS is generally considered to be a central nervous system-related disorder due to reduced intracortical inhibition and is often treated by benzodiazepines, a class of sedative drugs affecting the GABA receptors.

Among the genes that appear negatively regulated by Arx is *Egr1* (*early growth response 1*), a transcription factor that has been implicated in synaptic plasticity underlying learning and memory in mouse (Bozon et al., 2003). A recent study has reported that Egr1 overexpression in rat brain hippocampus and primary cultures of neurons regulates cytoskeleton dynamics by inactivating the

phosphatase PP1 and activates cyclin-dependent kinase 5 (Cdk5) to promote phosphorylation of Tau, a microtubule-associated protein (Lu et al., 2011). This is of particular interest, as both Cdk5 and PP1 are involved in neuronal migration (Gilmore et al., 1998; Shmueli et al., 2006; Rakić et al., 2009). The observed enrichment of this gene in cortical migrating interneurons suggests that it may positively control interneuron migration and/or differentiation. Accordingly, angiopoietin-1 (Ang-1) was found to stimulate cell migration in endothelial cells by increasing expression of Egr1 (Abdel-Malak et al., 2009). In addition, it has been reported that Reelin, produced by the mitral cells of the olfactory bulb (OB), activates the MAPK/extracellular signal-regulated kinase (ERK) pathway and induces Egr-1 transcription, which in turn promotes the shift from tangential/chain to radial/individual neuronal migration, and the detachment of neurons in the rostral migratory stream (RMS; Simó et al., 2007). These findings are particularly relevant as Reelin, produced by Cajal–Retzius cells, is also important for neuronal migration in the cortex. It is thus possible that fine regulation of Egr1 expression may be necessary to control cortical interneuron migration and the switch from tangential to radial mode into the CP.

Interestingly, *Egr1* expression was found up-regulated in *Arx* mutant mice (**Table 2**), suggesting that Arx normally represses its expression in the subpallium. This is somewhat contradictory with its putative positive role in cell migration. This discrepancy may be explained by the fact that Arx is expressed in different cell types in the forebrain during development (cortical neuronal progenitors, subpallial postmitotic cells, and cortical migrating interneurons) and may thus differentially regulate the same gene depending on the developmental stage, the biological context or the molecular environment. It is thus possible that Arx normally down-regulates *Egr1* in the subpallium in order to keep these cells undifferentiated, but up-regulates it in cortical migrating interneurons. Alternatively, *Egr1* up-regulation in *Arx* mutant mice may just be the result of the accumulation of cells that failed to exit the subpallium in the absence of *Arx*.

Another gene that may have a similar role is *Igf1* (*Insulin-like growth factor-1*), which encodes a growth factor highly expressed in embryonic brain. It has been implicated in several processes such as projection neuron growth, dendritic arborization, synaptogenesis, and adult hippocampal neurogenesis. In human, mutations in this gene are responsible for intrauterine and postnatal growth retardation with sensorineural deafness and intellectual deficit (Woods et al., 1996). In mouse, disruption of *Igf1* results in reduced brain size, hypomyelination, and loss of hippocampal granule and striatal parvalbumin-containing neurons (Beck et al., 1995). More recently, this gene was found to promote neuronal migration and positioning in the OB and the incorporation of neuroblasts from the SVZ to the RMS (Hurtado-Chong et al., 2009). *Igf1*$^{-/-}$ mice display altered pattern of OB layering with, in particular, a misplacement of glutamatergic neurons in the mitral cell layer (ML) and the external plexiform layer (EPL), a depletion of several populations of interneurons in the glomerular layer and the EPL, and an accumulation of neuroblasts in the postnatal and adult SVZ (Hurtado-Chong et al., 2009). Interestingly, these authors observed that a number of misplaced glutamatergic neurons in the ML had failed to radially re-orient their cell bodies, maintaining a relatively tangential orientation. These results suggest that, in the absence of *Igf1*, there was a defect in the switch from tangential to radial migration in the ML of the OB (Hurtado-Chong et al., 2009). In addition, they showed that Dab1 activity was necessary for Igf1 action suggesting that, similar to Egr1, its role in interneuron migration may, at least partly, intersect with the Reelin signaling pathway (Hurtado-Chong et al., 2009). Finally, a role for Igf1 has also been demonstrated in the GABAergic differentiation of neural precursors through the activation of the Pdk1/Akt pathway, which induces *Mash1* expression (Oishi et al., 2009). The fact that *Pdk1* was found repressed in Arx-overexpressing N2a cells (Quillé et al., 2011) confirms the involvement of Arx in this pathway and may explain the reason why some GABAergic neurons, and especially NPY^{+} and ChAT^{+} populations, were found strongly reduced in *Arx* mutant forebrains (Kitamura et al., 2002, 2009; Colombo et al., 2007; Price et al., 2009).

Similar to *Egr1* and *Igf1*, *Arx* knock-out mice display increased expression of the *Sema6a* (*semaphorin 6a*) gene in the subpallium (**Table 2**). Like other semaphorins, Sema6a is better known for its function in thalamocortical axon guidance, but it has also been reported to play a role in cell migration during cerebellum development. This protein is selectively expressed by postmitotic granule cells during their tangential migration in the deep external granule cell layer, but not during their radial migration (Kerjan et al., 2005). The analysis of granule cell migration and neurite outgrowth in cerebellar explants of mutant mice for *Sema6a*, or for its receptor *Plexin a2*, revealed that Sema6a controls the switch from tangential to radial migration by regulating centrosome–nucleus coupling and cellular translocation (Kerjan et al., 2005; Renaud et al., 2008). The role of Sema6a in cortical interneuron migration has never been studied, but this gene is probably a good candidate as other members of the semaphorin family have been shown to be important for the guidance of cortical interneurons as they migrate in the ventral telencephalon (Marín et al., 2001; Hernandez-Miranda et al., 2011).

Although no change of *Lgi1* (*leucine-rich, glioma-inactivated*) was detected in *Arx* mutant subpallium, this gene was found to be down-regulated following *Arx* transfection in N2a cells. Interestingly, mutations of this gene result in autosomal dominant lateral temporal epilepsy (Kalachikov et al., 2002). Enhanced excitatory synaptic transmission through increased release of glutamate has been suggested as a basis for the seizure phenotype. *Lgi1*, which encodes a secreted protein involved in postnatal glutamatergic synapse development, has not been studied in interneurons, but its strong enrichment in these cells compared to cortical non-interneurons (**Table 2**, fold change = 26.2 at E13.5), suggests an important role in interneuron development and possibly migration, as Lgi1 has been shown to regulate cell mobility through the formation of stress fibers in glioblastoma cells (Kunapuli et al., 2010).

At the start of corticogenesis, GABAergic interneurons enter the neocortex at the level of the preplate layer (PPL) and IZ. Loss of the upper stream(s) was reported at E14.5 and E18.5 in *Arx* knock-out mice, but the stream in the IZ/SVZ looked intact (Kitamura et al., 2002; Colombo et al., 2007). Interestingly,

Lgi1 has recently been found up-regulated in cortical migrating interneurons of the PPL compared to the IZ layer at E14.5 (Antypa et al., 2011). It is thus possible that regulation of *Lgi1* expression by Arx may explain the loss of the PPL migratory stream, but not the IZ stream in *Arx* mutant cortex (Kitamura et al., 2002).

Tgfb3 (*transforming growth factor, beta 3*) encodes a member of the TGF-β family of proteins. They act by stimulating specific membrane serine/threonine receptor complexes resulting in the phosphorylation and activation of Smad transcription factors (regulatory Smad, R-smad). Smad1, Smad5, and Smad8 are mainly activated by bone morphogenetic protein (BMP) and growth differentiation protein (GDF) receptors, while Smad2 and Smad3 are substrates for TGF-β, activin, and Nodal receptors. Once activated, the R-Smads accumulate in the nucleus where they associate with Smad4, a common partner for all R-Smads to form transcription complexes. Interestingly, in addition to *Tgfb3*, we found that Arx binds to *Smad1* and *Smad4* regulatory sequences in both neuroblastoma cells and E15.5 mouse embryonic brain, and that Arx overexpression in N2a cells results in *Smad1* down-regulation (Quillé et al., 2011), confirming a possible involvement of Arx in the TGF-β signaling pathway. Maira et al. (2010) have recently investigated a possible role for the TGF-β superfamily pathway in telencephalic GABAergic neuron development. They first showed that *Smad1*, *Smad2*, *Smad4*, and *Smad5* are expressed in the subpallium at E15.5, where they exhibit expression levels similar to those of *Dlx* genes. They also observed the presence of activated Smad1 and Smad2 in the developing basal ganglia and in cortical migrating interneurons. In addition, inhibition of TGF-β signaling by the use of dominant-negative forms of Smad proteins in the basal ganglia, impairs tangential migration of cortical interneurons: Smad1 or Smad2 dominant negative mutants only partially blocked migration, whereas inhibition of Smad4 completely abrogated the migration of electroporated cells to the cortex, thus providing evidence that both branches of the TGF-β signaling pathway are important for cortical interneuron migration (Maira et al., 2010).

It is interesting to note that Arx transfection of N2a cells induces down-regulation of *Smad1*, but that the level of expression of *Smad1* and *Smad4* was unchanged in *Arx* knock-out, similar to *Dlx1/2* mutant mice (Maira et al., 2010). It had thus been suggested that expression of most TGF-β superfamily genes was not downstream of Dlx. Interestingly, we found that Arx up-regulates two more components of the TGF-β superfamily, *Smad3* and *Bmper* (BMP binding endothelial regulator). The latter was recently identified as a Dlx5 direct target in inner ear (Sajan et al., 2011). As *Arx* expression is ectopically induced by forced expression of *Dlx1*, *Dlx2*, or *Dlx5* in mouse dorsal thalamus (Cobos et al., 2005), it appears very likely that the Dlx and Arx genes act through the same components of the TGF-β pathway to regulate interneuron migration and/or differentiation.

The *Slc12a5* gene (*solute carrier family 12, member 5*, also called *KCC2*, *potassium/chloride cotransporter 2*) was found up-regulated in both *Arx* mutant subpallium and transfected N2a cells, confirming that it is a direct target of Arx. Up-regulation of Slc12a5 by migrating interneurons results in the termination of their tangential migration and allows the radial sorting of different populations of tangentially migrating interneurons, resulting in their layer-specific integration into the emerging cortical network (Bortone and Polleux, 2009; Miyoshi and Fishell, 2011). It is thus likely that Arx, through *Slc12a5* expression, regulates the timing of migration and the final organization of interneurons in cortical layers.

There is little information available concerning the other genes found enriched in migrating cortical interneurons. As *Slc12a5*, the *Phlda1* (*pleckstrin homology-like domain, family A, member 1*) gene was found up-regulated in both *Arx* mutant subpallium and transfected N2a cells (**Table 2**). This gene encodes a proline–histidine rich nuclear protein which is specifically induced by Igf1. Although it has never been studied in interneuron development, it has recently been reported that siRNA-mediated suppression of *Phlda1* in colon cancer cells inhibited cell migration (Sakthianandeswaren et al., 2011). Similarly, *Ppap2a* (*phosphatidic acid phosphatase type 2A*) encodes an enzyme that converts phosphatidic acid to diacylglycerol and functions in *de novo* synthesis of glycerolipids. Ppap2a has been shown to reduce platelet-derived growth factor (PDGF)- and lysophosphatidic acid-induced migration of embryonic fibroblasts (Long et al., 2006). Concerning Ets2 (*E26 avian leukemia oncogene 2*), this gene encodes a transcription factor located on chromosome 21 which has been suggested to contribute to Down syndrome's phenotype. Its role is not yet well understood. Finally, the *Lmo3* (*LIM-only protein 3*) gene was consistently found up-regulated in *Arx* mutant subpallium (Colasante et al., 2008; Fulp et al., 2008; this study). Forced expression of this gene in the MGE of E14.5 brain slices has no effect on neuronal migration (Colasante et al., 2009), suggesting that Lmo3 expression is not required for the initiation of migration. However, to exclude a definite role in migration, it would be interesting to knock down this gene specifically during migration. In addition, Lmo3 has been reported to form a complex with HEN2 and induce *Mash1* expression (Isogai et al., 2011). Although these observations were made in neuroblastoma cells, this is potentially relevant as *Mash1* is known to be specifically expressed in the ventral part of the telencephalon and contributes to the generation of GABAergic neurons.

In contrast, the *Alk* (*Anaplastic lymphoma kinase*) gene seems to be repressed by Arx. This gene encodes a receptor tyrosine kinase (RTK) that has been shown to concentrate in postsynaptic domains. Its role in interneuron development has never been studied. Similarly, *Napb* encodes soluble *N*-ethylmaleimide-sensitive factor (NSF) attachment protein beta (beta Snap) involved in SNAP receptor (SNARE)-mediated vesicle trafficking and synapse formation. The mode of migration used by cortical interneurons is very similar to that of other types of migrating cells. They first extend a leading process in the direction of migration, followed by nuclear translocation and the retraction of the trailing process (Métin et al., 2006). During migration, interneurons show highly dynamic branching with changes in the orientation of the leading process, migration in all directions within streams and the use of different substrates. The role of vesicular trafficking in processes such as endocytosis to regulate substrate attachment or detachment, or membrane cycling from the leading and trailing process is thus very important (Skalski et al., 2010; Shieh et al., 2011).

IDENTIFICATION OF CANDIDATE GENES NEGATIVELY REGULATING CORTICAL INTERNEURON MIGRATION AND/OR DIFFERENTIATION

We found five Arx-bound genes specifically down-regulated in migrating cortical interneurons compared to neurons of the GE or cortical non-interneurons (**Table 3**). Thus, these genes may be necessary for cortical progenitor proliferation and/or pyramidal neuron development. Alternatively, as Arx negatively regulates most of these genes, they may repress interneuron migration and/or differentiation.

Only one gene, *Hmgn3* (*high mobility group nucleosomal binding domain 3*) appears to be positively regulated by Arx (**Table 3**). This gene encodes a nucleosome binding protein that affects chromatin function. It has been reported to induce the expression of the glycine transporter 1 gene (Glyt1), a membrane transporter that regulates glycine concentration in synaptic junctions (West et al., 2004). In addition, Hmgn3 expression is very similar to that of the glial fibrillary acidic protein (GFAP), suggesting that it might play a role in astrocyte function.

The four other genes seem to be repressed by Arx (**Table 3**) and may thus normally inhibit cortical interneuron migration and/or differentiation. Accordingly, a recent study has shown that ectopic expression of one of these genes, *Ebf3* (*early B-cell factor 3*), in basal ganglia severely interferes with tangential migration of GABAergic interneurons to the cortex. On the opposite, knock-down experiments targeting this gene in *Arx* mutant mice were found to rescue, at least partially, neuronal migration defects (Colasante et al., 2009). These results confirm the implication of this transcription factor in neuronal migration, although the underlying mechanisms are still unknown. Ebf3 is also known to be expressed in the developing hindbrain and spinal cord where it promotes neuronal differentiation and radial migration (Garcia-Dominguez et al., 2003). This gene is normally not (or only marginally) expressed in the developing telencephalon, but it was found strongly misexpressed in the MGE and present in the LGE of *Arx* mutant mice (Colasante et al., 2009). Interestingly, it was also found up-regulated in *Dlx1/2* mutant subpallium (Fulp et al., 2008), suggesting that Ebf3 may belong to a pathway that is common to *Dlx* and *Arx* genes (Cobos et al., 2005).

The *Rasgef1b* (*RasGEF domain family, member 1b*) gene encodes a guanine nucleotide exchange factor (GEF) for Ras family proteins, and several members have been reported as key regulators of actin and microtubule dynamics during dendrite or spine structural plasticity. GEF proteins stimulate the intrinsic GDP/GTP exchange activity of Ras and promote the formation of active Ras-GTP, which in turn controls diverse signaling networks important for the regulation of cell proliferation, survival, differentiation, vesicular trafficking, or gene expression. Rasgef1b has been shown to function as a very specific exchange factor for Rap2, which is implicated in the regulation of cell adhesion, the establishment of cell morphology, and the modulation of synapses in neurons (Yaman et al., 2009). Normally located in the differentiated striatal mantle, *Rasgef1b* was found misexpressed in the SVZ of the basal ganglia of *Arx* mutant mice (Colasante et al., 2009). Interestingly, it is present in some migrating cortical interneurons, at least in the IZ layer, compared to the PPL (Antypa et al., 2011) suggesting that, contrary to *Ebf3*, the expression of this gene is compatible with migration. In addition, whereas it was found up-regulated in *Arx* mutant subpallium, it appeared down-regulated in *Dlx1/2* mutants (Fulp et al., 2008), suggesting that the role of this gene in neuronal migration may be more complex than just the control of cell motility. However, since this gene has been linked to severe mental retardation, absent speech, distinctive facial features, and severe growth delay (Bonnet et al., 2010), the study of this gene is probably worth pursuing.

Table 3 | Examples of Arx-bound and regulated genes that are down-regulated in migrating cortical interneurons (IN) compared to neurons in the ganglionic eminences (GE) and cortical non-interneurons (non-IN).

Gene	Arx knock-out mice (Quillé et al., 2011)	Arx-transfected N2a cells (Quillé et al., 2011)	Expression in cortical migrating interneurons		
			Cells and stage	FC	Reference
Hmgn3	↓ KO subpallium (FC = 1.3, $p < 0.001$)	No specific change	GE > IN at E15.5	2.1	Faux et al. (2010)
			Non-IN > IN at E13.5	2.6–2.9	Batista-Brito et al. (2008)
Lmo1	↑ KO subpallium (FC = 1.6, $p < 0.001$/ Fulp et al., 2008/Colasante et al., 2009)	↓ N2a cells ($p < 0.05$)	GE > IN at E13.5 and E15.5	3.0–5.3	Faux et al. (2010)
			Non-IN > IN at E13.5 and E15.5	3.3–5.6	Batista-Brito et al. (2008)/ Fulp et al. (2008)
Ebf3	↑ KO subpallium (FC = 1.6, $p < 0.001$/ Fulp et al., 2008/Colasante et al., 2009)	No specific change	GE > IN at E13.5 and E15.5	2.0–2.3	Faux et al. (2010)
			Non-IN > IN at E13.5	5.5	Batista-Brito et al. (2008)/ Fulp et al. (2008)
Rasgef1b	↑ KO subpallium (Fulp et al., 2008/ Colasante et al., 2009)	No specific change	GE > IN at E13.5	3	Faux et al. (2010)
			Non-IN > IN at E14.5	NA	Fulp et al. (2008)
Slit2	↑ KO subpallium (FC = 1.4, $p < 0.005$)	No specific change	GE > IN at E13.5 and E15.5	2.1–2.2	Faux et al. (2010)
			Non-IN > IN at E13.5	3.5	Batista-Brito et al. (2008)

FC, fold change; NA, not available.

Similarly, *Lmo1* (*LIM domain only 1*) gene, consistently found repressed by Arx in several previous studies (Fulp et al., 2008; Colasante et al., 2009; Quillé et al., 2011), is found down-regulated in migrating cortical interneurons (**Table 3**). Interestingly, we found that Arx also regulates other members of this family of LIM-containing transcription factors. Arx directly binds to *Lmo3* and *Lmo4* promoters and down-regulates their expression in N2a-transfected cells as shown by gene expression profile analysis and quantitative RT-PCR (Quillé et al., 2011 and data not shown). Accordingly, *Lmo1*, *Lmo3*, and *Lmo4* genes were found up-regulated in *Arx* mutant subpallium (Fulp et al., 2008; Colasante et al., 2009). These three genes are normally never, or only marginally, transcribed in the ventral telencephalon, but were found strongly expressed in *Arx* mutant MGE and LGE/CGE (Colasante et al., 2009). It is thus possible that they play important roles in interneuron differentiation.

The last gene found to be down-regulated in migrating cortical interneurons is *Slit 2* (*slit homolog 2*, *Drosophila*). This chemorepulsive ligand and its receptors of the Robo family are expressed in the developing and adult brain and have been reported to regulate commissural axon guidance and axonal branching as well as cell migration. Double labeling experiments have shown that the vast majority of cortical interneurons express Robo1 and Robo2 and that Slit proteins are present in a complementary manner in the proliferative zones of the ventral telencephalon and in the septum during early and mid-phases of corticogenesis (Andrews et al., 2008). Evidence from *in vitro* experiments indicates that migration of Robo-expressing interneurons is initiated by the chemorepulsive activity of Slit secreted from the VZ of the LGE. In the developing cortex, Slit1 is robustly expressed in the CP, Slit3 is restricted to the MZ, while Slit2 is weakly expressed in the VZ. The presence of a putative Slit gradient along the interneuron migratory routes suggests that Slit/Robo signaling may also play a role in the positioning of the different tangential migratory paths within the developing cortex. However, it has been reported that migration of cortical interneurons is normal in *Slit1*/*Slit2* double knock-out mice, prompting speculation that Slits do not play a major role in tangential migration, although they seem to be important regulators of neuronal positioning within the basal telencephalon (Marín et al., 2003). Nevertheless, the Slit/Robo signaling pathway has also been shown to regulate cell division and interneuron morphology (Andrews et al., 2008).

CONCLUSION

The *Arx* gene has been shown to play different roles in brain development: patterning, cell proliferation, migration and differentiation as well as axonal outgrowth and connectivity (Kitamura et al., 2002; Cobos et al., 2005; Colombo et al., 2007; Colasante et al., 2008; Friocourt et al., 2008). Accordingly, we recently identified a high number of putative direct targets for this transcription factor (Quillé et al., 2011), several of them being involved in cell proliferation, cytoskeleton dynamic regulation, axonal guidance, or neurotransmission. To narrow the analysis of Arx targets to those most likely to control cortical interneuron migration, we compared our data to previously published studies in search of genes enriched or down-regulated in cortical migrating interneurons. We found several Arx-bound and regulated genes that may be good candidates to explain the severe defects of interneuron migration observed in the absence of *Arx* in both human and mice. In particular, we identified a few genes (*Igf1*, *Egr1*, *Cxcr7*, *Sema6a*, and *Slc12a5*) involved in the control of the mode of migration or the switch from tangential to radial migration. This is of particular interest in the light of our previous observation, that Arx overexpression in radially migrating cells promotes tangentially orientated migration in the SVZ and lower IZ, although these cells do not express GABAergic markers (Friocourt et al., 2008; Friocourt and Parnavelas, 2010).

As previously reported (Marsh et al., 2008), several of the genes that were enriched in migrating cortical interneurons are involved in synaptic transmission (*Egr1*, *Igf1*, *Lgi1*, *Alk*, *Napb*, *Glyt1*,. . .), probably due to the fact that migration is known to be partly controlled by paracrine transmitter release requiring synaptic vesicle proteins. One of these genes, Slc12a5, has been identified as a direct target for Arx (Quillé et al., 2011), thus implicating Arx in the control of the capacity for migrating cells to respond to GABA and switch from depolarization to hyperpolarization (Ben-Ari, 2002), resulting in a voltage-sensitive, calcium-mediated reduction of interneuron motility. Interestingly, we identified several putative direct targets for Arx which are related to calcium release (*Caln1*, *Calu*, *Cacng4*, *Camkv*, *Cacna2d1*, the latter being specifically down-regulated in cortical migrating interneurons) that may be good candidates for a role during interneuron migration.

It is not always clear whether the genes we identified are normally activated or repressed by Arx as a few genes in **Tables 2 and 3** showed the same the type of regulation in Arx-overexpressing N2a cells and in knock-out brains. These apparent discrepancies may have several explanations. First, it is important to note that the microarray experiments on Arx knock-out brains were performed from ventral telencephalon (Fulp et al., 2008; Colasante et al., 2009), thus leaving out possibly different gene expression changes during interneuron migration and differentiation in the cortex. Second, some changes in gene expression may be too low to be detected in microarray experiments. We previously observed that some Arx-bound genes such as *Gabrb3*, *Lmo3*, or *Cdh2* showed a change of expression in qRT-PCR experiments following Arx expression in N2a cells but not on microarrays (Quillé et al., 2011). Third, Arx is expressed in different cell types during brain development and in adult, and it is thus possible that, depending on the presence or the absence of specific cofactors it may activate one gene at some stage and repress the same gene at a different time or in a different cell. Fourth, changes or the absence of change in a given gene expression may be the result of some compensatory effect of *Arx* knock-out or overexpression.

In addition, the disadvantage of using transfected N2a cells is that, as *Arx* is normally not expressed in these cells, it may lack binding partners and/or cofactors necessary to regulate the expression of certain genes. On the other hand, as we performed gene expression analysis relatively shortly (2 days) after Arx transfection in N2a cells, it is likely that the changes we see are a direct effect of *Arx* expression. For example,

important genes for cortical development such as *Dab1* or *Dclk1* were found repressed following Arx transfection in N2a cells (Quillé et al., 2011). Dab1 is an intracellular adaptor which is expressed in cells that respond to Reelin and is required for correct radial migration of cortical pyramidal neurons (Howell et al., 1997; Ware et al., 1997). Expression of *Dab1* in early-born interneurons has also been shown to be required for correct cortical layering (Hammond et al., 2006). Similarly, *Dclk1* (doublecortin-like kinase 1) is necessary for correct migration of both pyramidal cells and interneurons (Deuel et al., 2006; Koizumi et al., 2006; Friocourt et al., 2007). Thus, gene expression in transfected N2a cells brings new and complementary information to expression studies performed in *Arx* mutant subpallium (Fulp et al., 2008; Colasante et al., 2009).

In conclusion, we identified here a set of candidate genes important for cortical interneuron migration and/or differentiation. Some of these genes have already been described to play a role in neuronal migration, but others have never been investigated in this context. Further studies will definitely bring new information about their function and how their possible regulation by Arx may lead to the dysfunction of GABAergic neurons, resulting in mental retardation and epilepsy.

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