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MicroRNAs as the cause of schizophrenia in 22q11.2 deletion carriers, and possible implications for idiopathic disease: a mini-review

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The 22q11.2 deletion is the strongest known genetic risk factor for schizophrenia. Research has implicated microRNA-mediated dysregulation in 22q11.2 deletion syndrome (22q11.2DS) schizophrenia-risk. Primary candidate genes are *DGCR8* (DiGeorge syndrome critical region gene 8), which encodes a component of the microprocessor complex essential for microRNA biogenesis, and *MIR185*, which encodes microRNA 185. Mouse models of 22q11.2DS have demonstrated alterations in brain microRNA biogenesis, and that *DGCR8* haploinsufficiency may contribute to these alterations, e.g., via down-regulation of a specific microRNA subset. *miR-185* was the top-scoring down-regulated microRNA in both the prefrontal cortex and the hippocampus, brain areas which are the key foci of schizophrenia research. This reduction in *miR-185* expression contributed to dendritic and spine development deficits in hippocampal neurons. In addition, *miR-185* has two validated targets (RhoA, Cdc42), both of which have been associated with altered expression levels in schizophrenia. These combined data support the involvement of *miR-185* and its down-stream pathways in schizophrenia. This review summarizes evidence implicating microRNA-mediated dysregulation in schizophrenia in both 22q11.2DS-related and idiopathic cases.

Keywords: 22q11.2 deletion syndrome, schizophrenia, microRNA, *MIR185, DGCR8,* copy number variants, genetic risk factor

INTRODUCTION

The 22q11.2 deletion syndrome (22q11.2DS), also known as the velocardiofacial/DiGeorge syndrome, is a phenotypically heterogenous disease which is caused by a hemizygous microdeletion on the long arm of chromosome 22 in the region q11.2. The overall prevalence is 1 in 2,000–4,000 live births (Murphy et al., 1999; Botto et al., 2003; Robin and Shprintzen, 2005). The disorder is associated with a high risk for psychiatric disorder.

In particular, 22q11.2DS patients have an estimated 20–25% risk for schizophrenia or related psychotic disorders such as schizoaffective disorder (Murphy et al., 1999; Chow et al., 2006; Bassett and Chow, 2008; Philip and Bassett, 2011). The deletion is therefore the strongest known genetic risk factor for schizophrenia (odds ratio = 20.3; Levinson et al., 2011), and accounts for approximately 1–2% of all schizophrenia cases (Karayiorgou et al., 1995, 2010; Bassett and Chow, 2008; International Schizophrenia Consortium, 2008; Stefansson et al., 2008). Individuals with 22q11.2DS have variable cognitive and behavioral deficits (Karayiorgou et al., 2010) including relative impairments in social judgment, motor skills, verbal learning, and executive functioning (Chow et al., 2006; Philip and Bassett, 2011). In addition, adults with a 22q11.2 microdeletion have a two- to threefold increase in the risk of generalized anxiety disorder compared to the general population (Philip and Bassett, 2011). The major clinical features of 22q11.2DS-related schizophrenia are largely indistinguishable from those of the idiopathic disease (Murphy et al., 1999; Chow et al., 2006; Bassett and Chow, 2008). Identification of schizophrenia-risk gene/s in the 22q11.2DS deletion region may therefore generate insights into the pathophysiology of schizophrenia in general (Earls et al., 2012).

The size of the 22q11.2 deletion varies. The majority of 22q11.2 deletions (around 90%) are 3 Mb in size and span approximately 60 known genes, while the remaining 10% are 1.5 Mb in size and encompass around 35 genes (Edelmann et al., 1999; Shaikh et al., 2000). Both the larger and the smaller 22q11.2 microdeletions usually result from non-allelic homologous recombination, which is mediated by flanking low-copy repeats (Edelmann et al., 1999). Although the 22q11.2DS phenotype is highly variable, its severity is not correlated with the size of the deletion. This suggests that the minimal 1.5 Mb deletion region is crucial in terms of etiology (Carlson et al., 1997; Karayiorgou et al., 2010).

Initial research to identify schizophrenia-risk genes in the 22q11.2 deletion region proved unsuccessful. The identification of heterozygous loss-of-function mutations in non-deleted schizophrenia patients would be the most obvious human genetic evidence for the involvement of a specific gene in disease susceptibility. Hopes were raised by the identification of heterozygous point mutations in the T-box 1 gene (*TBX1*), which encodes a T-box transcription factor, that resulted in the characteristic

abnormal facies and cardiac defects of 22q11.2DS in patients without a 22q11.2 deletion (Yagi et al., 2003; Zweier et al., 2007). However, no such mutation has yet been identified in schizophrenia patients.

In contrast, recent research in the *Df(16)A*$^{+/-}$ mouse model has generated breakthroughs in our understanding of the underlying biological mechanisms of 22q11.2DS schizophrenia-risk. This engineered mouse strain carries a heterozygous chromosomal deletion which spans a segment syntenic to the human 22q11.2 locus. *Df(16)A*$^{+/-}$ mice show deficits in the synaptic connectivity of hippocampal neurons, including a lower density of dendritic spines and glutamatergic synapses (Mukai et al., 2008). In addition, *Df(16)A*$^{+/-}$ mice display hyperactive behavior and deficits in spatial working memory-dependent learning (Stark et al., 2008). Further characterization of this animal model has suggested that the 22q11.2 microdeletion results in alterations in the biogenesis of brain microRNAs (Stark et al., 2008; Xu et al., 2010). Primary candidate genes in the region are the DiGeorge syndrome critical region gene 8 (*DGCR8*), which encodes a component of the microprocessor complex essential for microRNA biogenesis (Tomari and Zamore, 2005), and the *MIR185* gene (Karayiorgou et al., 2010), which encodes microRNA 185. Both genes are located within the minimal 1.5 Mb deletion region at 22q11.2 (Karayiorgou et al., 2010).

The microRNAs are a class of 21–25-nucleotide small non-coding RNAs. They control the expression of their target genes by binding to target sites in messenger RNAs (mRNAs), typically in their 3′ untranslated regions (He and Hannon, 2004; Meola et al., 2009). In most cases, microRNAs negatively regulate target gene expression through a combination of repression of mRNA translation and promotion of mRNA decay. Each microRNA usually controls up to several hundred target mRNAs, while one mRNA target can be synergistically regulated by multiple microRNAs (Sathyan et al., 2007; Didiano and Hobert, 2008; Drew et al., 2011). This allows microRNAs to integrate different intracellular signals and to regulate various signaling pathways (Johnston and Hobert, 2003; Choi et al., 2007). Accumulating evidence suggests that microRNAs contribute to the basic mechanisms underlying brain development and plasticity (**Table 1**; Fineberg et al., 2009; Schratt, 2009; Im and Kenny, 2012). Neural microRNAs play an important role at various stages of synaptic development, including dendritic arborization (Vo et al., 2005; Yu et al., 2008), synapse formation, and synapse maturation (Caygill and Johnston, 2008; Siegel et al., 2009). Arguably the two most extensively studied examples in the context of synapse development are *miR-132* and *miR-134*. CREB-induced *miR-132* promotes dendritogenesis and spine growth by down-regulating p250GAP (Wayman et al., 2008; Magill et al., 2010). *miR-134* on the other hand is required for activity-dependent dendritic arborization and the restriction of spine growth by targeting Pumilio-2 and Lim-domain containing protein kinase (Limk1), respectively (Schratt et al., 2006; Fiore et al., 2009). Furthermore, investigation of a mouse model displaying conditional knock-out of the microRNA biogenesis enzyme *Dicer* (Schratt, 2009) revealed disrupted morphogenesis of the hippocampus and cortex (Davis et al., 2008), suggesting that undisturbed microRNA processing might be necessary for normal brain development (Xu et al., 2010). These data suggest the possible involvement of microRNA-dependent dysregulation in the pathogenesis of various psychiatric disorders (Forero et al., 2010; Xu et al., 2010), including schizophrenia (Beveridge et al., 2008).

The present review summarizes the various lines of evidence implicating microRNAs as the causal factor for schizophrenia in 22q11.2DS carriers and emerging evidence from expression studies and genome-wide association studies (GWAS) that these mechanisms may also be involved in the development of idiopathic schizophrenia.

THE ROLE OF *DGCR8*

Investigation of *Dgcr8*$^{+/-}$ mice confirmed that heterozygous *Dgcr8* deficiency was responsible for the reduced biogenesis of microRNAs observed in *Df(16)A*$^{+/-}$ mice (Stark et al., 2008; Schofield et al., 2011). *Dgcr8*$^{+/-}$ mice displayed 22q11.2DS-associated cognitive and behavioral deficits, and altered short-term plasticity in the prefrontal cortex (PFC; Stark et al., 2008). This indicates that *DGCR8* heterozygosity, and the resulting alterations in microRNA expression, are sufficient to produce some of the neural deficits observed in 22q11.2DS (Schofield et al., 2011). On the neuronal cell level, *Dgcr8* deficiency resulted in structural changes in dendritic spines and reduced dendritic complexity in the hippocampus (Stark et al., 2008). Schofield et al. (2011) identified alterations in the electrical properties of layer V pyramidal neurons in the medial PFC of *Dgcr8*$^{+/-}$ mice, as well as a decrease in the complexity of the basal dendrites and reduced excitatory synaptic transmission. These functional results suggest that precise microRNA expression is critical for the development of PFC circuitry (Schofield et al., 2011), circuitry which has been reported to be altered in schizophrenia patients (Ursu et al., 2011).

Dgcr8$^{+/-}$ mice also displayed a decrease in the number of cortical neurons, structural deficits in dendritic spines in the PFC, and alterations in synaptic potentiation and short-term plasticity (Fenelon et al., 2011). These alterations might influence functional connectivity (Schreiner et al., 2013), and could be implicated in the observed cognitive and behavioral deficits. In particular, they may explain observed alterations in prepulse inhibition (Stark et al., 2008), which have also been reported in schizophrenia patients (Powell et al., 2009).

Ouchi et al. (2013) showed that heterozygous *Dgcr8* deficiency in mice led to reduced progenitor cell proliferation and neurogenesis in the adult hippocampus. This is of particular interest since alterations in the anatomy, histology, and function of the hippocampus have been consistently reported in schizophrenia patients (Tamminga et al., 2010). Several schizophrenia-associated genes were down-regulated in the hippocampus of *Dgcr8*$^{+/-}$ mice (Ouchi et al., 2013), including the insulin-like growth factor 2 (IGF2), which was recently found to play a crucial role in hippocampal functions such as memory consolidation and fear extinction (Agis-Balboa et al., 2011; Chen et al., 2011a). Interestingly, restoration of IGF2 expression in the hippocampus rescued the observed spatial working memory deficits in *Dgcr8*$^{+/-}$ mice, suggesting that IGF2 contributes – at least in part – to the learning and spatial working memory deficits that are associated with 22q11.2DS-related schizophrenia (Ouchi et al., 2013).

Table 1 | List of individual microRNAs involved in neural development and synapse development/plasticity and their mRNA targets in mice and men.

MicroRNA	Function	Target/s	Reference
microRNAs involved in neural development			
let-7	Promotes neuronal differentiation	HMGA, LIN28, TLX	Nishino et al. (2008), Rybak et al. (2008), Zhao et al. (2010)
	Neural tube closure	MLIN41	Maller Schulman et al. (2008)
miR-7a	Inhibits differentiation of forebrain dopaminergic neurons	PAX6	de Chevigny et al. (2012)
miR-9	Promotes neuronal differentiation	FOXG1, TLX, STAT3, REST, FGF8, FGFR1, FOXP2	Krichevsky et al. (2006), Leucht et al. (2008), Packer et al. (2008), Shibata et al. (2008, 2011), Zhao et al. (2009), Yoo et al. (2011), Clovis et al. (2012)
	Promotes proliferation of early human embryonic stem cell-derived neural progenitor cells	STMN1	Delaloy et al. (2010)
miR-9*	Promotes neuronal differentiation	BAF53a	Yoo et al. (2009, 2011)
	?	coREST	Packer et al. (2008)
miR-17	Inhibits neural differentiation	?	Beveridge et al. (2009)
miR-17/92	Promotes axonal outgrowth in embryonic cortical neurons	PTEN	Zhang et al. (2013)
	Controls spinal neural progenitor patterning	Olig2	Chen et al. (2011b)
miR-34a	Antagonizes neuronal differentiation	Numbl	Fineberg et al. (2012)
	Promotes neuroblastoma and medulloblastoma differentiation	?	Agostini et al. (2011), de Antonellis et al. (2011)
miR-92b	Limits the production of intermediate cortical progenitors	?	Nowakowski et al. (2013)
miR-124	Promotes neuronal differentiation	SCP1, PTBP1, SOX9, DLX2, JAG1, BAF53a, RhoG, Lhx2	Makeyev et al. (2007), Visvanathan et al. (2007), Cheng et al. (2009), Yoo et al. (2009, 2011), Sanuki et al. (2011), Akerblom et al. (2012), Franke et al. (2012)
miR-125	Promotes neuronal differentiation	GLI1, SMO, LIN28, SMAD4	Ferretti et al. (2008), Rybak et al. (2008), Boissart et al. (2012)
miR-128	Inhibits NSC proliferation	BMI1	Godlewski et al. (2008)
miR-132	Promotes synaptic integration and survival of newborn dentate gyrus and olfactory bulb neurons	Nurr1, FoxP2	Luikart et al. (2011), Clovis et al. (2012), Pathania et al. (2012)
	Promotes differentiation of dopamine neurons	Nurr1	Yang et al. (2012)
miR-133b	Modulates maturation of dopaminergic neurons	PITX3	Kim et al. (2007)
miR-137	Promotes neural differentiation of embryonic stem cells	Klf4, Tbx3	Jiang et al. (2013)
miR-200	Promotes olfactory progenitor differentiation	SOX2, ETF3	Choi et al. (2008), Peng et al. (2012)
miR-324-5p	Promotes neuronal differentiation	GLI1, SMO	Ferretti et al. (2008)
miR-326	Promotes neuronal differentiation	GLI1, SMO	Ferretti et al. (2008)
miR-541	Promotes neurite outgrowth of PC12 cells	Synapsin-1	Zhang et al. (2011)
microRNAs involved in synapse development/plasticity			
miR-29a/b	Inhibits spine maturation	Arpc3	Lippi et al. (2011)
miR-34c	Negative constraint of memory consolidation	SIRT1	Zovoilis et al. (2011)

(Continued)

Table 1 | Continued

MicroRNA	Function	Target/s	Reference
miR-124	Regulates neuronal process complexity	RhoG, Cdc42	Yu et al. (2008), Franke et al. (2012)
miR-125a	Reduces number of branched spines	PSD-95	Muddashetty et al. (2011)
miR-125b	Negatively regulates spine morphology	NR2A	Edbauer et al. (2010)
miR-129	Reduces intrinsic neuronal excitability	Kv1.1	Sosanya et al. (2013)
miR-132	Promotes dendritogenesis	P250RhoGap, MeCP2, RFX4	Vo et al. (2005), Cheng et al. (2007), Wayman et al.
	Promotes spine growth		(2008), Edbauer et al. (2010), Impey et al. (2010),
	Facilitates memory acquisition		Mellios et al. (2011), Tognini et al. (2011), Scott et al.
	Positively regulates LTP		(2012), Hansen et al. (2013), Remenyi et al. (2013),
	Essential for experience-dependent plasticity in visual cortex		Wang et al. (2013)
	Negatively regulates circadian clock resetting		
miR-134	Necessary for activity-dependent dendritogenesis	Pum2	Fiore et al. (2009)
	Restricts spine growth	Limk1	Schratt et al. (2006)
	Interferes with memory formation and LTP	Creb1	Gao et al. (2010)
miR-137	Inhibits dendritic morphogenesis	Mib1	Smrt et al. (2010)
miR-138	Negatively regulates dendritic spine size	Apt-1	Siegel et al. (2009)
	Represses axon regeneration	SIRT1	Liu et al. (2013)
miR-146a	Inhibits AMPAR endocytosis	MAP1B	Chen and Shen (2013)
miR-181a	Reduces AMPAR expression and spine formation	GluA2	Saba et al. (2012)
miR-188	Controls dendritic plasticity	Nrp-2	Lee et al. (2012)
miR-219	Regulates circadian clock length	SCOP	Cheng et al. (2007)
miR-375	Reduces dendrite density	HuD	Abdelmohsen et al. (2010)
miR-483-5p	Rescues dendritic spine defects in MeCP2-overexpressing neurons	MeCP2	Han et al. (2013)
miR-485	Regulates presynaptic homeostatic plasticity	Synapsin-1	Cohen et al. (2011)

NSC, neural stem cell; LTP, long-term potentiation; ? – unknown.

The question now arises as to which specific microRNAs are regulated by *DGCR8*. The investigation of *Dgcr8*$^{+/-}$ mice identified 59 down-regulated microRNAs in the PFC and 30 down-regulated microRNAs in the hippocampus (Stark et al., 2008). These down-regulated microRNAs include *miR-185*, which is also located in the minimal 1.5 Mb deletion region at 22q11.2.

THE ROLE OF *MIR185*

Studies of 22q11.2DS mouse models have identified *miR-185* as the top-scoring down-regulated microRNA in schizophrenia-associated brain areas (Stark et al., 2008; Benetti et al., 2009). A recent study by Xu et al. (2013) confirmed the drastic reduction in *miR-185* expression levels in the hippocampus and PFC of *Df(16)A*$^{+/-}$ mice, and showed that this reduction contributed to deficits in dendritic complexity and spine development in hippocampal neurons. In addition, *Dgcr8* deficiency resulted in an approximately 20% reduction in *miR-185* expression in the hippocampus (Xu et al., 2013). This suggests that the pronounced reduction of *miR-185* expression in *Df(16)A*$^{+/-}$ mice – a reduction which is much more pronounced than would be expected by the 50% decrease in gene dosage – may be due to the combined effect of the hemizygosity of the *MIR185* gene and the impaired maturation of the *pri-miR-185* transcript secondary to reduced *Dgcr8* levels (**Figure 1**; Xu et al., 2013). The large reduction in *miR-185* expression renders *miR-185* unique among the genes that are affected by the 22q11.2 microdeletion (Xu et al., 2013).

A recent human study confirmed a down-regulation of *MIR185* expression to 0.4× normal levels in the peripheral blood of patients with 22q11.2DS (de la Morena et al., 2013). This finding suggests that pronounced *miR-185* down-regulation also occurs in patients with 22q11.2DS.

Previous research has shown that *MIR185* is present or enriched in synapses (Lugli et al., 2008; Earls et al., 2012). This may indicate that *MIR185* is of relevance to neural function, since a number of microRNAs have been shown to play a critical role in synaptic plasticity (Schratt, 2009).

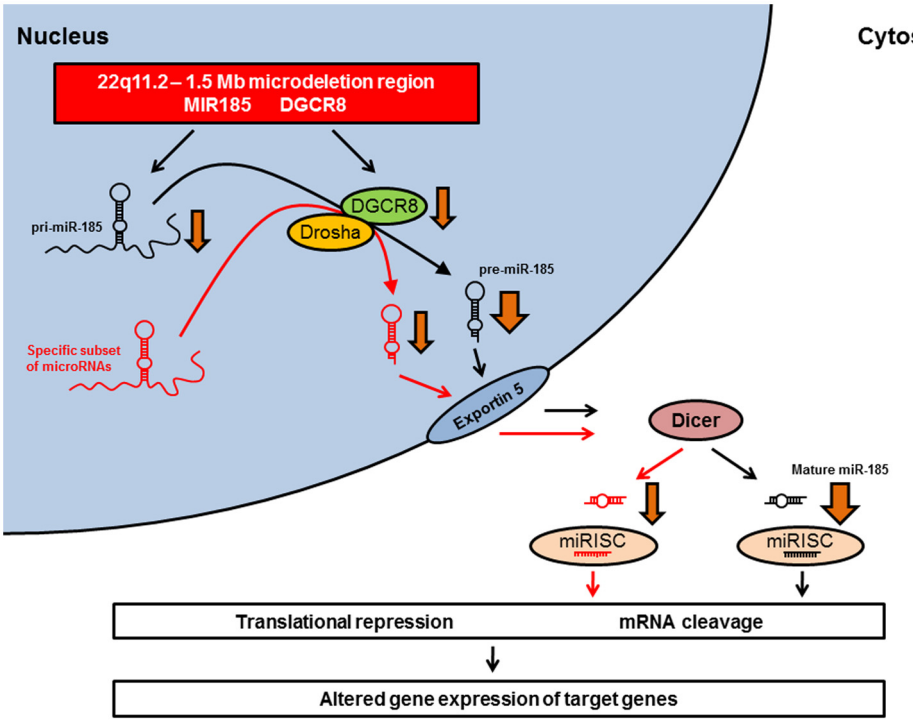

FIGURE 1 | Dysregulation of microRNA biogenesis in 22q11.2DS animal models. The *MIR185* and the *DGCR8* genes are located within the minimal 1.5 Mb microdeletion region on chromosome 22q11.2 and the equivalent region of mouse chromosome 16. The microdeletion leads to a hemizygosity of *MIR185* and *DGCR8*. The heterozygous *Dgcr8* deficiency is responsible for the reduced biogenesis of a specific subset of microRNAs (red) observed in *Df(16)A*$^{+/-}$ mice (Stark et al., 2008). These down-regulated microRNAs include *miR-185* (black). The pronounced reduction of *miR-185* expression (indicated by a broader arrow) may be due to a combined effect of the hemizygosity of the *MIR185* gene and the impaired maturation of the *pri-miR-185* transcript secondary to reduced *Dgcr8* levels (Xu et al., 2013). The resulting alterations in mature microRNA expression levels may lead to altered gene expression of target genes, which might produce some of the neural, cognitive, and behavioral deficits observed in 22q11.2DS. miRISC, microRNA-induced silencing complex.

Earls et al. (2012) identified *MIR185* as a regulator of sarco(endo)plasmic reticulum Ca(2+) ATPase (SERCA2) which maintains Ca^{2+} levels in the endoplasmatic reticulum. The depletion of *MIR185* contributes to SERCA2 upregulation and has been proposed as a mechanism leading to abnormal hippocampal synaptic plasticity in 22q11.2DS mouse models. The microRNA regulation of SERCA2 translation may also be implicated in the elevation of SERCA2 protein observed in the post-mortem brains of idiopathic schizophrenia patients (Earls et al., 2012). These results suggest that microRNA-mediated SERCA2 upregulation at central synapses might be a mechanistic link between 22q11.2DS and idiopathic schizophrenia (Earls et al., 2012).

Further support for the involvement of *MIR185* in schizophrenia is provided by findings that two of its validated targets (RhoA, Cdc42; Liu et al., 2011) are associated with altered expression levels in schizophrenia (Hill et al., 2006; Ide and Lewis, 2010). Cdc42 (cell division cycle 42) is a member of the RhoGTPase family (Hill et al., 2006) and promotes dendritic spine formation (Irie and Yamaguchi, 2002; Tada and Sheng, 2006; Wegner et al., 2008) by regulating the polymerization of the actin cytoskeleton into filopodia (Nobes and Hall, 1995). Cdc42 is activated by Collybistin/ARHGEF9 (Reid et al., 1999; Reddy-Alla et al., 2010), which has recently been identified as a candidate blood biomarker in psychosis (Kurian et al., 2011). RhoA (Ras homologous member A) also belongs to the RhoGTPase family and regulates the destabilization of the actin cytoskeleton (Hill et al., 2006). The activation of RhoA leads to a reduction in the number of dendritic branches and the density of dendritic spines (Nakayama et al., 2000; Hill et al., 2006).

EXPRESSION OF microRNAs IN IDIOPATHIC SCHIZOPHRENIA

Post-mortem studies of human brain tissue have revealed alterations in microRNA expression in patients with schizophrenia. This research is reviewed elsewhere (Beveridge and Cairns, 2012). Briefly, numerous microRNAs have been implicated in the disorder across multiple studies, including 16 microRNAs with increased and 11 microRNAs with decreased expression (Beveridge and Cairns, 2012). Of particular interest in the context of the present review is the study by Moreau et al. (2011). This reported a significant overlap between microRNAs dysregulated in human post-mortem brain tissue and microRNAs previously found to be altered in the PFC of a 22q11.2DS mouse model (Stark et al., 2008; Moreau et al., 2011). This finding supports the hypothesis that findings in 22q11.2DS might be of relevance to idiopathic schizophrenia (Brzustowicz and Bassett, 2012).

GWAS OF IDIOPATHIC SCHIZOPHRENIA

The involvement of microRNA-dependent dysregulation in schizophrenia is supported by the results of the large GWAS of schizophrenia performed by the Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium (2011). In total 17,836 patients and 33,859 controls were investigated. A single-nucleotide polymorphism (SNP) in an intron of *MIR137* was the second strongest finding (odds ratio = 1.12). Four other loci with genome-wide significance in this study contained predicted targets of *MIR137* (*TCF4*, *CACNA1C*, *CSMD1*, *C10orf26*). All four genes have recently been validated as *miR-137* targets (Kwon et al., 2013).

The miRanda database lists 5,487 genes as targets of *miR-137* (John et al., 2004). Interestingly, *ZNF804A* is listed as a validated target (Kim et al., 2012a). This gene has shown strong association with schizophrenia in previous studies (O'Donovan et al., 2008; Williams et al., 2011). Other promising targets include the ubiquitin ligase Mind bomb one (Mib1; Smrt et al., 2010) which plays an important role in neurogenesis and neurodevelopment (Itoh et al., 2003; Choe et al., 2007; Ossipova et al., 2009).

Research in post-mortem brain samples suggests that the functional effect of the *miR-137* risk allele may result in a reduced *miR-137* expression (Guella et al., 2013). Further down-stream this may be responsible for the reduced white matter integrity, smaller hippocampi, and larger lateral ventricles observed in schizophrenia patients with the *miR-137* risk genotype (Lett et al., 2013).

CONCLUSION AND OUTLOOK

Strong evidence suggests that microRNA dysregulation is implicated in the development of schizophrenia in 22q11.2DS patients. This is consistent with the growing recognition of microRNAs as important regulators of gene expression. As microRNAs integrate different intracellular signals and regulate various signaling pathways (Johnston and Hobert, 2003; Choi et al., 2007), the dysregulation of specific microRNAs could lead to the heterogenous phenotype observed in 22q11.2DS.

As summarized above, emerging evidence from expression and genetic analyses suggests that the same microRNA-regulated pathways may also play a role in idiopathic schizophrenia. However, despite a number of systematic investigations of genes in the 22q11.2DS region and the ever increasing number of GWAS data sets (Karayiorgou et al., 2010; Sullivan et al., 2012), no genetic study to date has identified common variation in *DGCR8* or *MIR185* as a risk factor for schizophrenia. This may simply reflect a lack of common functional variants at these loci. This hypothesis is supported by a recent study of genetic regulation of microRNA expression (Gamazon et al., 2012). Gamazon et al. (2012) systematically investigated the relationship between microRNA expression levels (as quantitative traits) and common genetic variation. In this study, no SNP had significant *cis* effects on *miR-185* expression. A small number of SNPs have been reported to have significant *cis* effects on *DGCR8* expression in human monocytes (Zeller et al., 2010), and fibroblasts (Dimas et al., 2009). However, these associations might be tissue-specific, since a recent study of five different human post-mortem brain regions failed to identify any SNP with significant cis effects on *DGCR8* expression (Kim et al., 2012b).

A challenge for future research will be to identify and validate the target genes that are affected by microRNA dysregulation and their respective pathways in a more comprehensive manner (Drew et al., 2011). Such research will improve our understanding of how alterations in microRNA-regulated genetic networks contribute to the pathophysiology of both 22q11.2DS-related and idiopathic schizophrenia.

Idiopathic schizophrenia is a multifactorial disorder for which both genetic and environmental factors exert an impact on disease susceptibility (Sawa and Snyder, 2002). However, very few data are available concerning the influence of environmental factors on microRNA dysregulation. Recent studies in mice showed that environmental factors such as stress resulted in alterations of microRNA expression in the frontal cortex (Rinaldi et al., 2010). Future studies are therefore warranted to investigate the extent to which environmental factors are associated with microRNA dysregulation in schizophrenia.

Further research into the precise role of microRNAs in schizophrenia is important clinically, since modification of microRNA dysregulation would represent a novel therapeutic approach to this devastating and chronic disease. MicroRNAs are excellent candidates for therapy since they regulate multiple targets in various signaling pathways, thereby minimizing the risk of resistance development or compensatory mechanisms (Soriano et al., 2013). This view is supported by several recent studies and reviews, which have highlighted microRNAs as promising pharmacological targets in the treatment of complex diseases such as psychiatric disorders (Im and Kenny, 2012), cancer (Soriano et al., 2013), and diabetes (Mao et al., 2013).

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