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Modeling a model: Mouse genetics, 22q11.2 Deletion Syndrome, and disorders of cortical circuit development

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ABSTRACT

Understanding the developmental etiology of autistic spectrum disorders, attention deficit/hyperactivity disorder and schizophrenia remains a major challenge for establishing new diagnostic and therapeutic approaches to these common, difficult-to-treat diseases that compromise neural circuits in the cerebral cortex. One aspect of this challenge is the breadth and overlap of ASD, ADHD, and SCZ deficits; another is the complexity of mutations associated with each, and a third is the difficulty of analyzing disrupted development in at-risk or affected human fetuses. The identification of distinct genetic syndromes that include behavioral deficits similar to those in ASD, ADHC and SCZ provides a critical starting point for meeting this challenge. We summarize clinical and behavioral impairments in children and adults with one such genetic syndrome, the 22q11.2 Deletion Syndrome, routinely called 22q11DS, caused by microdeletions of between 1.5 and 3.0 MB on human chromosome 22. Among many syndromic features, including cardiovascular and craniofacial anomalies, 22q11DS patients have a high incidence of brain structural, functional, and behavioral deficits that reflect cerebral cortical dysfunction and fall within the spectrum that defines ASD, ADHD, and SCZ. We show that developmental pathogenesis underlying this apparent genetic "model" syndrome in patients can be defined and analyzed mechanistically using genomically accurate mouse models of the deletion that causes 22q11DS. We conclude that "modeling a model", in this case 22q11DS as a model for idiopathic ASD, ADHD and SCZ, as well as other behavioral disorders like anxiety frequently seen in 22q11DS patients, in genetically engineered mice provides a foundation for understanding the causes and improving diagnosis and therapy for these disorders of cortical circuit development.

Contents

Abbreviations: ASD, autism spectrum disorder; ADHD, attention deficit disorder; CGE, caudal ganglionic eminence; CN, cranial nerve; CNV, copy number variant; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; hChr, human chromosome; LCR, low copy repeat; LGE, lateral ganglionic eminence; MB, megabase; MGE, medial ganglionic eminence; mFAC, medial frontal anterior cortex; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAHR, non-allelic homologous recombination; OFC, orbital frontal cortex; PH, periventricular heterotopias; PMG, polymicrogyria; SCZ, schizophrenia; SD, segmental duplication; SVZ, subventricular zone; VZ, ventricular zone.

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1. Disorders of cortical circuit development: finding a model

The inescapable causal relationship between disrupted developmental mechanisms and the pathology of human developmental disorders has proven difficult to evaluate rigorously in patients, especially for disorders of cortical circuit development like autism spectrum disorder (Geschwind and Levitt, 2007) (ASD), attention deficit/hyperactivity disorder (Shaw et al., 2010) (ADHD) and schizophrenia (SCZ; Insel, 2010). This difficulty reflects the timing of developmental pathogenesis, which occurs during embryonic and fetal life when observation is difficult, compounded by delayed clinical presentation and diagnosis of many of these disorders, which can occur fairly long after birth—from two to five years of age for ASD (Lord et al., 2006) to as late as the middle twenties for SCZ (Lewis and Lieberman, 2000). Thus, in human patients, associating developmental pathogenesis with post-natal pathology is likely to remain a daunting if not impossible task, even though the frequency of developmental disorders—particularly disorders of cortical circuit development that compromise brain function and behavior for much if not all of a lifetime—has increased significantly over the past two decades. We will argue that the most efficient and valuable solution to this challenge is identification of distinct human syndromes with a single genetic cause that includes ASD, ADHD and/or SCZ in its clinical spectrum, combined with use of valid animal models—preferably genetic—in which pre- and perinatal developmental changes can be rigorously analyzed and associated with later brain circuit and behavioral pathology. This integrative, iterative approach between human disease pathology and basic mechanistic biology in genetic animal models is likely to result in optimal progress for new therapeutic approaches (Delorme et al., 2013).

The assessment of key pathogenic mechanisms in disorders of cortical circuit development has been complicated by difficulties in genetic analysis in human patients. While many intriguing single candidate genes have been identified (for review see: Giusti-Rodriguez and Sullivan, 2013; Hoischen et al., 2014; Jeste and Geschwind, 2014), mutations in these genes do not necessarily predict that an individual will have a particular disorder of cortical circuit development. Assessing the mechanistic significance of these candidate human mutations—many of which are polymorphic over short DNA regions and can lead to amino acid or splice variant changes—can prove difficult if orthologous sequences are missing or highly divergent in available genetic model organisms. Thus, many current studies of candidate genes in animal models are based upon analysis of full null phenotypes rather than those caused by the complete range of disease-associated alleles. For example, deletions and mutations in *NEUREXIN1* have been associated with ASD in human genetic studies, and mouse null mutants for *neurexin1* have phenotypes that can be interpreted as parallel to key ASD phenotypes (Etherton et al., 2009; Grayton et al., 2013). Additional progress has been made with mouse models of single gene X-linked or parental imprinted disorders: Fragile X Syndrome (Pfeiffer et al., 2010; Ronesi et al., 2012), Rett's Syndrome (Garg et al., 2013; Shahbazian et al., 2002a,b) and Angelman/Prader-Willi Syndrome (Wallace et al., 2012). Distinctions between these single gene mouse models, most of which are null mutants, and male versus female human patients with mutations or polymorphisms complicate interpretation.

ASD, ADHD, and SCZ have also been robustly associated with aneuploid changes in the genome, now referred to generally as copy number variations or CNVs (Elia et al., 2012; Glessner et al., 2009; Stefansson et al., 2008). CNVs, as a cause for disease, are distinguished from mutation because quantitative changes in gene dosage—at least 150% for duplications, at least 50% for deletions—rather than a loss or modification of gene function are likely responsible for disease pathology. Several distinct syndromes that include behavioral changes seen also in disorders of cortical connectivity, including Down and Kleinfelter Syndromes (Chapman and Hesketh, 2000; Geschwind et al., 2000), are due to aneuploidy—the most extreme type of CNV that reflects partial or complete duplication of an entire chromosome. The large number of genes duplicated in these "extreme CNV" disorders leads to distinct pathology each syndrome that diverges from deficits associated with ASD, ADHD, and SCZ. Moreover, animal models of such CNV disorders are rare—historically limited to mouse models of Down Syndrome/Trisomy 21(Cox, 1983) (Haydar and Reeves, 2012; Reeves et al., 1995). They are further complicated by genomic/chromosomal divergence between humans versus standard model species. The dearth of additional CNV models likely reflects the difficulty of engineering targeted multi-gene versus single gene disruption using recombination-based approaches. Thus, if one wishes to assess the developmental origins of disorders of cortical connectivity based upon the clear association of these disorders with aneuploidy or CNVs, one must choose a single CNV of tractable size, conserved between humans and model species, and consistently associated with ASD, ADHD, or SCZ. The relevant deletion or duplication must then be amenable to chromosomal engineering in mouse or other genetically manipulable species to establish a starting point for studying developmental mechanisms of disrupted cortical connectivity.

Heterozygous microdeletion at human chromosome 22q11.2—referred to as 22q11.2 Deletion Syndrome, or 22q11DS—has

emerged in patients as a consistent genetic lesion with among the most substantial genetic association with ASD, ADHD, SCZ and other presumed disorders of cortical circuit development (Antshel et al., 2007; Bassett et al., 2005; Gothelf et al., 2004; Niklasson et al., 2009). This syndrome is fairly frequent, with an estimated occurrence in approximately 1/3000–1/4000 live births (McDonald-McGinn and Sullivan, 2011; Robin and Shprintzen, 2005). The genetics of 22q11DS, and the close homology between human Chromosome 22 and portions of mouse chromosome 16 permits fairly precise modeling of the causal CNV using targeted mutagenesis in the mouse (Lindsay et al., 1999; Merscher et al., 2001). A relatively limited set of core clinical phenotypes associated with 22q11DS in humans (Fig. 1, and see below) suggest distinct endpoints for developmental processes that can be evaluated in animal models to define mechanistic disruption due to diminished dosage of 22q11 genes during embryogenesis and early post-natal life. The introduction of murine models facilitates analysis of early embryonic developmental pathogenesis and its relationship to 22q11DS pathology (Fig. 1) that otherwise would not be possible. Thus far, this approach has been informative for the developmental mechanisms that lead to cardiovascular malformations as well as craniofacial disruptions and their consequences—both are key clinical features of 22q11DS. We will summarize that work, and then focus on the current status of parallel analyses of developmental disruptions in the peripheral and central nervous system that lead to additional 22q11DS pathology, especially the relationship of disrupted cerebral cortical development to the ultimate neural circuit and behavioral disruptions that characterize ASD, ADHD and SCZ.

2. Syndromes and spectrums: core features and variability in 22q11DS

22q11DS, like most developmental disorders, has a set of common features traditionally recognized as the clinical "core" of the syndrome, and several other features that are seen more variably in subsets of patients. Together, these features define a phenotypic spectrum of 22q11DS (Fig. 1). The core syndromic features include conotruncal cardio-vascular malformations, often focused on derivatives of the fourth pharyngeal arch artery (Botto et al., 2003; Ryan et al., 1997); characteristic craniofacial malformations including low set ears, high forehead, flattened nasal bridge, and velopharyngeal insufficiency/cleft palate (Ryan et al., 1997); hypotrophic or absent thymus and diminished parathyroid glands leading to hypocalcaemia (Choi et al., 2005; Cuneo et al., 1997), and a significantly enhanced risk of ASD, ADHD, SCZ, as well as anxiety disorder and language learning disabilities (Antshel et al., 2007; Bassett et al., 2005; Gothelf et al., 2004; Niklasson et al., 2009). These core physical or behavioral features can be mild to severe; however, there is general consensus that all 22q11DS patients have some subset of these core phenotypes (Robin and Shprintzen, 2005; Schneider et al., 2014). In many 22q11DS patients, some or all of these core phenotypes can be sub-clinical and not require therapeutic intervention; indeed there are even a small number of "occult" 22q11 deleted individuals who do not come to clinical attention until they pass the deletion on to an offspring who has more substantial core phenotypes that require clinical attention (Bassett and Chow, 1999; Shprintzen et al., 2005). Each of the core 22q11DS features is thought to reflect disrupted developmental mechanisms. Genetic modifiers that enhance or suppress flexible, regulatory developmental processes targeted by 22q11 deletion may underlie the variability seen between patients for core features of the syndrome. Environmental factors including pre-natal maternal health and toxic exposures most likely further modulate pathogenic developmental mechanisms in 22q11DS. There is, however, little clear clinical evidence for these hypotheses (Maynard et al., 2013).

Beyond these core features, several additional anomalies have been associated with 22q11DS in recent studies of a small

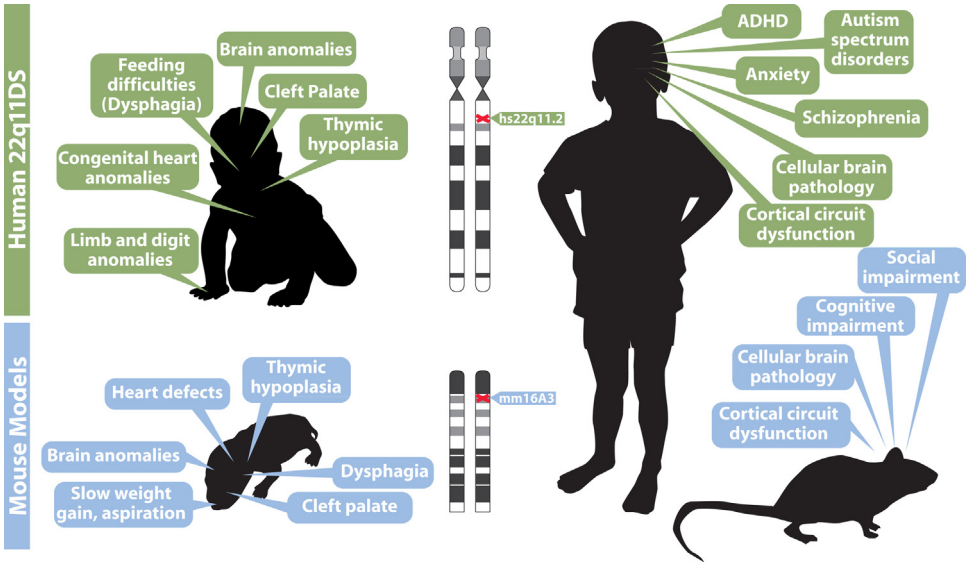

Fig. 1. 22q11.2 Deletion Syndrome (22q11DS) provides a model for disorders of cortical circuit development that can be analyzed mechanistically in genetically engineered mice. In this and all other figures, human data is indicated beneath green header boxes, and mouse data is provided beneath blue header boxes. Key clinical features of the syndrome in infants (top left) and in adolescents (top right) are summarized. The clinical features in infants are consistent with disrupted developmental/morphogenetic processes during embryonic/fetal life; those in adolescents are focused on disorders of cortical circuit development. We note that adolescents and adults with 22q11DS face a broad range of additional clinical challenges, some related to the early morphogenetic issues. Others that are seen variably across the population of individuals with the disease may reflect additional vulnerabilities that arise in maturity. Phenotypes in genetically engineered mouse models at birth (lower left) and in adulthood (lower right) are potentially parallel to the key clinical features of infants and children with 22q11DS. Thus, if these phenotypic features in mouse models are truly comparable to the clinical features of 22q11DS, it may be possible to model 22q11DS, which itself is a model genetic syndrome for understanding disorders of cortical connectivity, in genetically engineered mice. This modeling of a "model" syndrome can give insight into developmental, cellular and molecular mechanisms that cannot be easily gained working solely with human patients. This developmental/mechanistic insight is likely to be key for developing new diagnostic and therapeutic approaches for 22q11DS and more broadly for disorders of cortical circuit development including autism and schizophrenia.

number of fetuses with 22q11 deletions (Besseau-Ayasse et al., 2014; Noel et al., 2014) as well as in 22q11DS patients after birth; albeit at lower frequency than the "core" clinical phenotypes (Cheung et al., 2014; Guo et al., 2011b; Herman et al., 2012; Schneider et al., 2014). The anomalies recognized in fetuses, some of which may contribute to pre-natal demise, include regional dysmorphology of the developing forebrain including arhinencephaly—apparent absence of the olfactory bulbs and related forebrain regions (Noel et al., 2014). Those seen post-natally in patients, which can be clinically challenging for individual patients, include malformations of the hands and feet (Ming et al., 1997), short stature and skeletal malformations (Ming et al., 1997); sensory-neural hearing loss detected during early life (Dyce et al., 2002; Zarchi et al., 2011); oculo-motor disturbances (Sobin et al., 2006); and perinatal feeding and swallowing difficulties that are likely related to velo-pharyngeal insufficiency seen in 22q11DS (Eicher et al., 2000; Rommel et al., 2008). The variable frequency of these 22q11DS-associated anomalies suggests that they reflect developmental mechanisms that are even more sensitive to genetic, environmental, toxic, and modifying mechanisms. There is no evidence that any of these variable features are correlated with the severity of core features of 22q11DS, including disorders of cortical connectivity (Gerdes et al., 2001; McDonald-McGinn et al., 2001). More importantly, the breadth of 22q11DS anomalies indicates that 22q11 deletion and diminished gene dosage disrupt a substantial set of susceptible developmental mechanisms subject to complex modulation with few obligate endpoints.

While this spectrum of anomalies may seem idiosyncratic to 22q11DS, it is important to note that so called "non-syndromic" or "idiopathic" ASD, ADHD, or SCZ as well as other disorders of cortical circuit development (like intellectual disability) are often accompanied by clinically significant somatic maladies, including cardiovascular, craniofacial (Prasad et al., 2015), immune, gastrointestinal, and musculo-skeletal complications (Andreassen et al., 2013; Guy et al., 1983; Severance et al., 2014) that appear similar to those in 22q11DS, although they may differ in etiology and severity. Thus, the value—and challenge—offered by studying complex genetic/developmental syndromes like 22q11DS as a "model" of disorders of cortical circuit development is the potential for insight into shared developmental mechanisms that compromise the brain and other organ systems. Parallel understanding of disruptions of other somatic developmental processes may enhance insights into aberrant differentiation of cortical neurons and circuits. The growing list of rare developmental/genetic syndromes that include features of ASD, ADHD, and SCZ among their phenotypic spectrum indicates that developmental disruption is an essential contributor to the pathogenesis of these behavioral disorders (Amir et al., 1999; Luo et al., 2012; McLennan et al., 2011; Steffenburg et al., 1996). Even so, key disruptions of developmental processes that result in ASD, ADHD, and SCZ in these syndromes remain obscure. Thus, well-characterized genetic syndromes emerge as highly informative models for understanding the pathogenesis of disorders of cortical circuit development. We will now review data that establish 22q11DS as a paradigmatic genetic syndrome that offers potential insight into the pathology of ASD, ADHD, SCZ and other related disorders. The challenges of studying development in human patients, however, underscores the need to "model the model" to maximize the insight into development pathogenesis disorders of cortical circuit development by analyzing the consequences of 22q11 deletion in animals with parallel genetic lesions. Thus, we will synthesize insight into the disease phenotypes associated with 22q11DS and the underlying developmental mechanisms that can only be identified by assessment of genetically valid animal models of the disorder.

3. Genomic mechanisms of 22q11.2 deletion

The causal relationship between 22q11.2 deletion and the spectrum of cardiac, craniofacial, immune and behavioral disorders recognized clinically as DiGeorge Syndrome (Kirkpatrick and DiGeorge, 1968) became clear in the late 1980s and early 1990s, when the typical and minimal critical deleted regions of hChr22q11.2 were identified in DiGeorge Syndrome patients (Cannizzaro and Emanuel, 1985; Driscoll et al., 1992; Halford et al., 1993; Kelly et al., 1993; Fig. 2). Subsequent efforts in the 1990s defined the features of the hChr 22q11.2 chromosomal region that explain the susceptibility to genomic rearrangement and deletion that leads to 22q11DS. This work not only identified the genomic insult that underlies clinical features of 22q11DS, but also provided a detailed understanding of the gene architecture in the region, thus facilitating strategies to model 22q11DS in other species with a high degree of genetic accuracy.

A defining characteristic of the region of hChr 22q11.2 deleted in DiGeorge/22q11.2 Deletion Syndrome (which we refer to as 22q11DS) is the presence of multiple fragments of repeated DNA known as segmental duplications (SDs), which are also known as low copy repeats in the 22q11DS literature (LCRs; Fig. 2) (Gotter et al., 2004; Shaikh et al., 2001, 2000, 2007; Torres-Juan et al., 2007). SDs have practically identical sequences that map to more than one region in the genome (Babcock et al., 2007). Due to the high degree of similarity between these regions, SDs are sites of non-allelic homologous recombination (NAHR) (Beckmann et al., 2007; Hurles and Lupiski, 2006). NAHR reflects errors in the normal process of meiotic recombination. Instead of crossovers occurring between homologous regions of chromosome pairs, non-homologous regions align (often along non-allelic, homologous SDs) and recombine, resulting in inappropriate splicing of chromosomal DNA. Deletion or duplication of segments of genes result from these NAHR-related recombination events, including the deletions and rare duplications associated with 22q11DS (Guo et al., 2011c). In 22q11DS, the typically deleted region contains four major SDs, referred to as LCR A-D. The most frequent deletion, in approximately 85% of DiGeorge Syndrome patients, is a recombination between LCR A on one hChr22 with LCR D on the other (Shaikh et al., 2001) resulting in a 3 MB "typical" deletion. Nevertheless, the full spectrum of 22q11DS phenotypes is also seen when the gene rich minimal critical deleted region of 1.5 MB between LCR A and LCR B is absent in heterozygozity, which occurs in approximately 10% of 22q11DS (Carlson et al., 1997). LCR-mediated deletion events could occur either within one chromosome (a "looping out" of the region between two LCRs), or across chromosomes (a non-homologous recombination yielding a matched pair of deleted/duplicated chromosomes). Analysis of deletions in individual spermatozoa suggests that 22q11.2 deletion events are only slightly more common (0.17%) than duplication events (0.12%), which indicates that the frequency of intrachromosomal recombination exceeds the frequency of interchromosomal events (Molina et al., 2011). The remaining clinically diagnosed cases of 22q11DS have a variety of atypical deletions, usually including segments of hChr22q11.2 between LCRs A and D (Shaikh et al., 2000). Nevertheless, the association of the minimal critical deleted region with the full phenotypic spectrum of 22q11DS has focused efforts to understand and model the disorder genetically on the 22q11.2 genes between LCR A and B.

The genes within the "minimal critical deleted region" are highly conserved in model organisms. This conservation became apparent as the human and mouse genome were mapped and sequenced in the late 1990s (Puech et al., 1997), and is particularly striking for the minimal deleted region between LCR A and B. In this region, there are only modest rearrangements from humans,

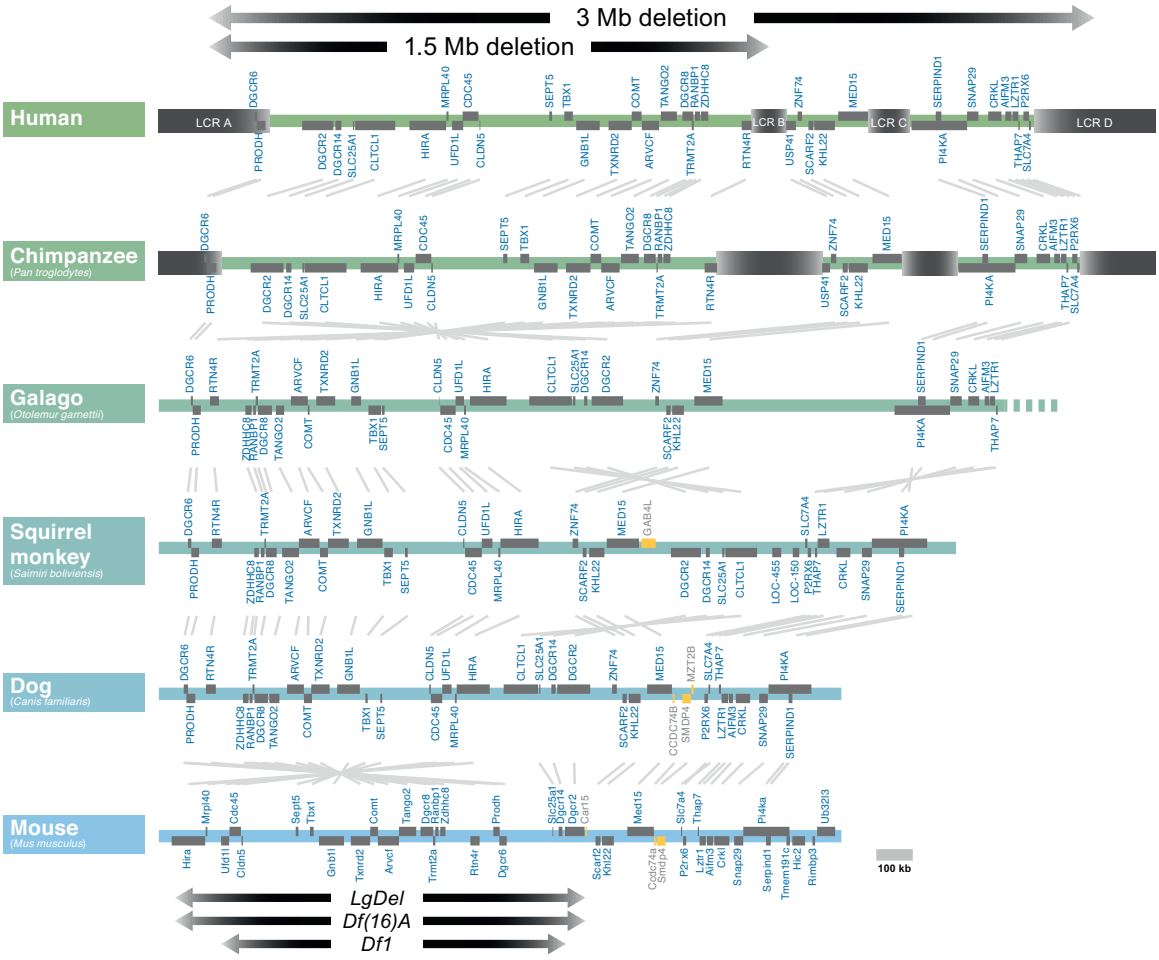

Fig. 2. The genomic organization of human 22q11.2 has been compared with that of orthologous regions in several mammalian species. The extent of the most common 22q11.2 deletions is noted (top). Low copy repeats (LCR) are indicated in beige. Open reading frames are indicated in gray, and non-conserved genes are indicated in yellow. Most deleted individuals (85%) carry deletions spanning approximately 3 Mb, while a subset (10%) carry deletions a shorter 1.5 Mb deletion. The low copy repeats (LCRs) that mediate the chromosomal deletion are evident in humans and chimpanzees, but are absent from the more distantly related primates (galago, squirrel monkey) and other mammals (Dog and mouse are shown here). In the Mouse, the minimal critical deleted region (1.5 MB deletion) has undergone a partial 3′ to 5′ inversion (left, near bottom). Key mouse models of the 1.5 MB minimal critical deletion, the *LgDel*, *Df*(16)*A*, and *Df*1 are indicated with arrows at bottom.

through non-human primates and rodents including the mouse (Fig. 2). The region remains highly conserved across a range of divergent non-mammalian vertebrate genomes including chicken, frog, and coelacanth (primitive, jawless fish) (Fernandez et al., 2014). The protein sequences of the individual genes within this region are also highly conserved, facilitating the study of the function of individual 22q11 proteins in multiple model organisms, including yeast (Johnson et al., 1995), worms (Gong et al., 1997), flies (Llevadot et al., 1998), frog (Tran et al., 2011), fish (Catalina-Rodriguez et al., 2012), and chick (Yamagishi et al., 2003) in addition to mice. Because of the high degree of conservation of the individual genes within the minimal critical deleted region, it is assumed that several are required for normal development and function. Thus, it is not surprising that of the 16 null alleles examined for the 28 murine orthologues of 22q11 genes in the minimal critical deleted region, 10 are homozygous embryonic lethal (Conrad et al., 2004; Lindsay et al., 1999; Merscher et al., 2001; Nitta et al., 2003; Paronett et al., 2014; Paylor et al., 2006; Roberts et al., 2002; Wang et al., 2007; Yoshida et al., 2001) (see below; see also Fig. 6). Our functional genomic analysis of the 32 genes in the human minimal critical deleted region shows that in both humans and mice, 22 of the genes from the minimal critical deleted region are expressed substantially in the developing or adult brain, as well as in a broad range of other tissues (Maynard et al., 2003). During early embryogenesis in the mouse, most of this subset of brain-expressed genes is also expressed in the heart and craniofacial primordia (branchial arches, maxillary and mandibular processes)—sites of presumed developmental pathogenesis leading to 22q11DS—(Maynard et al., 2002, 2003, 2013). Thus, based on the available comparative and functional genomic data, the chromosomal regions deleted in 22q11DS have clear orthologues in multiple species, and a substantial subset of the genes within the 22q11DS minimal critical deleted region are highly conserved and expressed in relevant tissues.

Studies using wild type model organisms—particularly the mouse—have been instructive for understanding the expression and function of individual 22q11.2 genes, and their potential contribution to 22q11DS phenotypes. Nevertheless, the essential pathogenesis of 22q11DS reflects heterozygous deletion of these genes. Thus, securing animal models that have genomic deletions parallel to those in 22q11DS is critical for mechanistic insight into the disorder. The potential value of analyzing developmental mechanisms in mouse models of 22q11 gene deletion was demonstrated in the late 1990s and early 2000s when two groups adapted the Cre-Lox approach, primarily used for manipulating the expression of single genes, to generate mouse models of the 1.5 MB minimal critical deletion. In particular, insertion of Lox-P elements ‘in-trans’ followed by screening for recombination events between

orthologous segments of chromosome 16 pairs in mice facilitated the generation of two mutant deleted lines, *Df1* (Lindsay et al., 1999) and *LgDel* (Merscher et al., 2001), which model the minimal 1.5 MB deletion of 22q11.2 with a high degree of accuracy. The introduction of these mouse lines facilitated assessment of the role of diminished dosage of 22q11 gene orthologues in developmental anomalies in the heart, face and brain.

4. From clinic to cage: 22q11DS cardiac phenotypes in mouse genetic models

Cautious comparisons of human disease features with parallel phenotypes in a genomically accurate animal model are key for assessing whether the model can be used to understand disease pathogenesis. Thus, a critical test of the relevance of mouse genomic models for 22q11 deletion is their capacity to reproduce—or at least approximate—diagnostic clinical features of 22q11DS. One of the most important clinical features of the syndrome—and one that often proved fatal prior to improvements in peri-natal cardiovascular surgery—is cardiovascular malformations that compromise primarily the arteries derived from the 3rd, 4th and 6th pharyngeal arches during development (Fig. 3). Based upon the nature of cardiac malformations in 22q11DS patients, it was assumed that these anomalies reflect disrupted morphogenesis of the pharyngeal arch arteries as they transform into the great vessels of the heart. Thus, a critical test of the relevance of the mouse models of 22q11 deletion (and thus diminished 22q11 gene dosage) is the presence of cardiac anomalies focused on the great vessels of the heart, and their possible developmental origin from dysmorphogenesis of the pharyngeal arches and their associated arteries.

Analysis of both *LgDel* and *Df1* models of 22q11 deletion showed aortic arch malformations in post-natal mice that were remarkably similar to those seen in 22q11DS patients (Lindsay et al., 1999; Merscher et al., 2001; Fig. 3). Moreover, analysis of *LgDel* and *Df1* embryos showed clearly that the mature dysmorphology was indeed prefigured by aberrant morphogenesis of the 4th pharyngeal arch arteries (and to a lesser extend to the 3rd and 6th) as predicted by the pathology seen in patients (Lindsay et al., 1999; Merscher et al., 2001). The developmental disruption in these animal models can be analyzed at the cellular and molecular level, and this analysis indicated that the neural crest and ectodermal components that constitute the pharyngeal arches were compromised by diminished expression of 22q11 genes. These disruptions apparently lead to dysregulation of cardinal signaling molecules required for patterning and growth in the developing embryo: Fgf (Frank et al., 2002; Vitelli et al., 2002b), Bmp (Bachiller et al., 2003), Shh (Maynard et al., 2013) and RA signaling (Braunstein et al., 2009; Guris et al., 2006; Maynard et al., 2013; Vermot et al., 2003) in either placodal ectoderm or adjacent neural crest derived mesenchyme or pharyngeal endoderm. These changes, and subsequent alterations in downstream signal transduction mechanisms, then lead to altered expression and activity of multiple downstream targets (Guo et al., 2011a; van Bueren et al., 2010). This mechanistic disruption of initial morphogenetic signaling in the pharyngeal arches is now thought to underlie the cardiovascular anomalies that are seen in 22q11DS patients.

The clear definition of morphogenetic phenotypes, as well as underlying cellular and apparent molecular mechanisms made it possible to analyze in more detail the contribution of individual genes in the minimal critical deleted and typically deleted regions to this apparent developmental pathogenic origin of a key 22q11DS clinical phenotype (Lindsay et al., 1999) (Guris et al., 2006). Further genetic modeling—using "nested" deletions of subsets of genes from the minimal critical deleted region, transgenic rescue of individual genes on the deleted background and then finally single gene deletions—suggested that one particular 22q11 gene, encoding the T-box transcription factor *Tbx1*, made a significant, and potentially singular, contribution to cardiovascular pathology in 22q11DS (Jerome and Papaioannou, 2001; Lindsay et al., 2001; Merscher et al., 2001). Full dosage of *Tbx1*, likely in combination with other genes from the 1.5 MB or 3 MB deleted regions (Guris et al., 2006) is a critical modulator of local morphogenetic signaling that results in appropriate development of the great vessels of the heart.

Our work (Maynard et al., 2013) has shown that normal 22q11 gene dosage, including but not limited to *Tbx1*, establishes a "dynamic range" for key signals that regulate pharyngeal arch artery and aortic arch morphogenesis (Fig. 3), particularly signaling via RA and Shh. Thus, when an apparently "benign" change in level of either RA or Shh signaling is introduced during development—either by maternal exposure or genetic mutation—there is no detectable consequence for wild type (undeleted) embryos, but significant enhancement of pharyngeal arch dysmorphogenesis for *LgDel* littermate embryos (Fig. 3). The effects in *Tbx1*$^{+/-}$ embryos are less severe than in *LgDel* embryos, suggesting that *Tbx1* acts in concert with other 22q11 genes to establish quantitative sensitivity and optimal morphogenetic outcome for a range of RA or Shh activity encountered during cardiovascular development. These data offer potential insight into sources of phenotypic variation seen in 22q11DS patients. 22q11 deletion, combined with otherwise benign polymorphic alleles in key morphogenetic signaling pathways/downstream effectors, or environmental exposure at levels beneath standard thresholds for teratogenicity, yield a spectrum of phenotypic severity in 22q11DS. Clearly, for clinically relevant 22q11DS cardiovascular phenotypes—and potentially other key disease features—mouse genetic models provide opportunities to rigorously define developmental mechanisms that lead to disease pathology as well as offering a new framework for understanding the substantial individual variability seen in patients with the syndrome. The remarkable comparison between essential clinically significant cardiovascular anomalies in 22q11DS patients and those in *LgDel*, *Df1* and *Tbx1*$^{+/-}$ mouse mutants establishes the utility of mouse genetic models for understanding underlying developmental pathogenesis.

5. Dysphagia in 22q11DS humans and mice: compromising body and brain

It is not clear whether apparent conservation of morphogenetic mechanisms in the hearts of humans and mice as well as their disruption by diminished 22q11 gene dosage extends to the brains of humans and mice—especially since the most noted brain-related disease phenotypes in 22q11DS, ASD, ADHD and SCZ, reflect disruptions in complex human behavioral capacities whose murine equivalents—if they exist—are uncertain (Crawley, 2012). Thus, as a further assessment of the utility of 22q11DS mouse models for understanding 22q11DS neural dysfunction, we evaluated parallels for a likely more comparable nervous system-related 22q11DS disease feature: difficulties in feeding and swallowing. One key diagnostic feature associated with 22q11DS—prior to the identification of the causal genetic deletions—was a combination of craniofacial dysmorphology and related behavioral disruptions in feeding, swallowing, and speech production. This combined dysmorphology and behavioral difficulty, referred to as velo-pharyngeal insufficiency, was an essential component of the mnemonic for the syndrome prior to identifying the causal deletion: 22q11DS was often referred to as VCFS or Velo-Cardio-Facial Syndrome (Shprintzen et al., 1981). Initial characterization of this disease phenotype focused on the structure of the soft palate and associated tissues; less was known

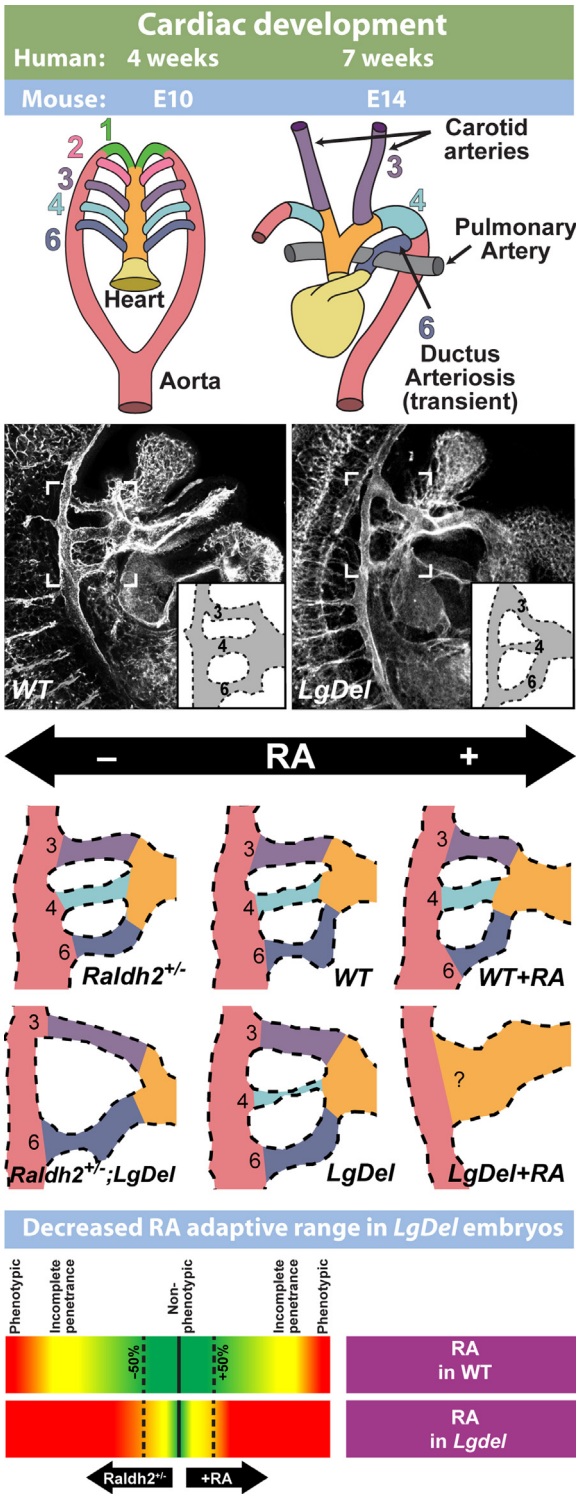

Fig. 3. The *LgDel* mouse models cardiovascular 22q11DS pathology and underlying developmental mechanisms. (Top): Simplified schematic of cardiac development, illustrating the remodeling of the branchial arch arteries to form the arteries of the aortic arch. (Top left) The cardiac vasculature arises from the arteries of the pharyngeal/branchial arches, 1–6. Each arch, except the fifth (which is only present as a transient structure, not shown here) has its own artery that connects the outflow of the heart tube (truncus arteriosis, yellow, and aortic sac, orange) to the aorta (red). (Top right) As heart development proceeds, the branchial arch arteries are remodeled to produce the aortic arch arteries. (Second row) Developing vasculature in wild-type control (WT) and *LgDel* embryos at E10.5, visualized by immunofluorescent staining for a vascular marker (PECAM). Brackets outline the region containing the 3rd, 4th, and 6th pharyngeal arch arteries. Most *LgDel* embryos have a constricted 4th arch artery (stenosis). A schematic version of the arch vasculature is provided as an inset for additional clarity. (Third row) Cardiac development in *LgDel* embryos is highly sensitive to even modest changes of embryonic retinoic acid (RA) signaling that are benign for wild type (WT) littermates. Center panels show WT and *LgDel* vasculature under normal conditions. A modest reduction in RA levels in the *Raldh2* heterozygote ($Raldh2^{+/-}$) does not cause detectable changes in aortic arch morphology by itself, but it severely disrupts arch development in a compound *LgDel*:$Raldh2^{+/-}$ embryo. Likewise, injection of low-levels of RA does not significantly impair arch development by itself, but causes catastrophic anomalies in *LgDel* embryos. (Bottom row): These results suggest that RA signaling is dysregulated in the *LgDel* embryo, and normal mechanisms that compensate for modest fluctuations in RA levels are impaired. Morphology schematics adapted from Larsen's Human Embryology, 4th edition (2009), Figs. 13–16. *LgDel* illustrations and schematic adapted from Maynard et al. (2013).

about its sensory innervation or motor control. Thus, a further test of the validity of the mouse models of 22q11DS is to determine whether these mice have any signs of the "V" or "F" disruptions and the neural correlates that may underlie feeding/swallowing disruption in the clinical syndrome.

Most 22q11DS patients have structural or functional oro-facial anomalies that require clinical attention (50–75%; Lay-Son et al., 2012; Ryan et al., 1997). The morphogenetic anomalies include an approximately 10–15% incidence of an overt cleft palate (Lay-Son et al., 2012; Ryan et al., 1997). The remaining deleted individuals have either a submucosal cleft palate (McDonald-McGinn et al., 1993), and/or a high arched palate (Lay-Son et al., 2012; Ryan et al., 1997). There also functional deficits; 75% of 22q11DS patients have velopharyngeal insufficiency (VPI), an inability of the muscles of the soft palate to properly elevate to close off the nose during speech and swallowing (Dyce et al., 2002). *LgDel* mice have palatal defects as well as other craniofacial anomalies. 28% of *LgDel* mouse embryos show a failure of the palatal shelves to fuse appropriately at E14.5 (Karpinski et al., 2014), which is an early indicator of cleft palate. While it is not yet clear precisely which 22q11.2 genes are responsible for these palatal anomalies, *Tbx1* has emerged as a likely contributor to this phenotype. Virtually all *Tbx1* null embryos have a cleft palate (Funato et al., 2012; Goudy et al., 2010; Jerome and Papaioannou, 2001; Liao et al., 2004), as well as additional inappropriate oral epithelial fusions (Funato et al., 2012). There is some evidence that *TBX1* polymorphisms may be associated with cleft palate beyond 22q11 deletion (Paranaiba et al., 2013). Nevertheless, in the context of 22q11 deletion in mouse models, *Tbx1* by itself is not likely the singular cause of cleft palate. Heterozygous *Tbx1* mice do not have any palatal phenotypes (Jerome and Papaioannou, 2001; Liao et al., 2004). In 22q11DS patients, it does not appear likely that the subset of deleted individuals with cleft palate have additional mutations in the remaining copy of *TBX1* (Herman et al., 2012). Furthermore, there is no correlation between cleft palate and cardiovascular defects in 22q11DS patients (Friedman et al., 2011), which would be expected if reduced *TBX1* were the primary cause of cleft palate in the syndrome. It is likely, therefore, that other 22q11.2 genes interact with *Tbx1* to mediate the cleft palate phenotype.

Oropharyngeal/palatal morphogenetic anomalies in 22q11DS patients as well as *LgDel* and other mouse models of the disorder raise the possibility that *LgDel* 22q11DS mouse might model another related, clinically critical feature of the syndrome. This feature defines an interface of peripheral dysmorphogenesis (in this case, craniofacial/velo-pharyngeal anomalies) and nervous system development: significant difficulties in feeding and swallowing that occur immediately after birth through early childhood referred to as perinatal or pediatric dysphagia (Darrow and Harley, 1998; Lefton-Greif, 2008; Rommel et al., 2008). At least 30% of 22q11DS patients have multiple signs of dysphagia in the perinatal period (Eicher et al., 2000) and this is likely reflected in lower rates of growth and weight gain in children with 22q11DS from birth onward (Tarquinio et al., 2012) (Fig. 4). These difficulties

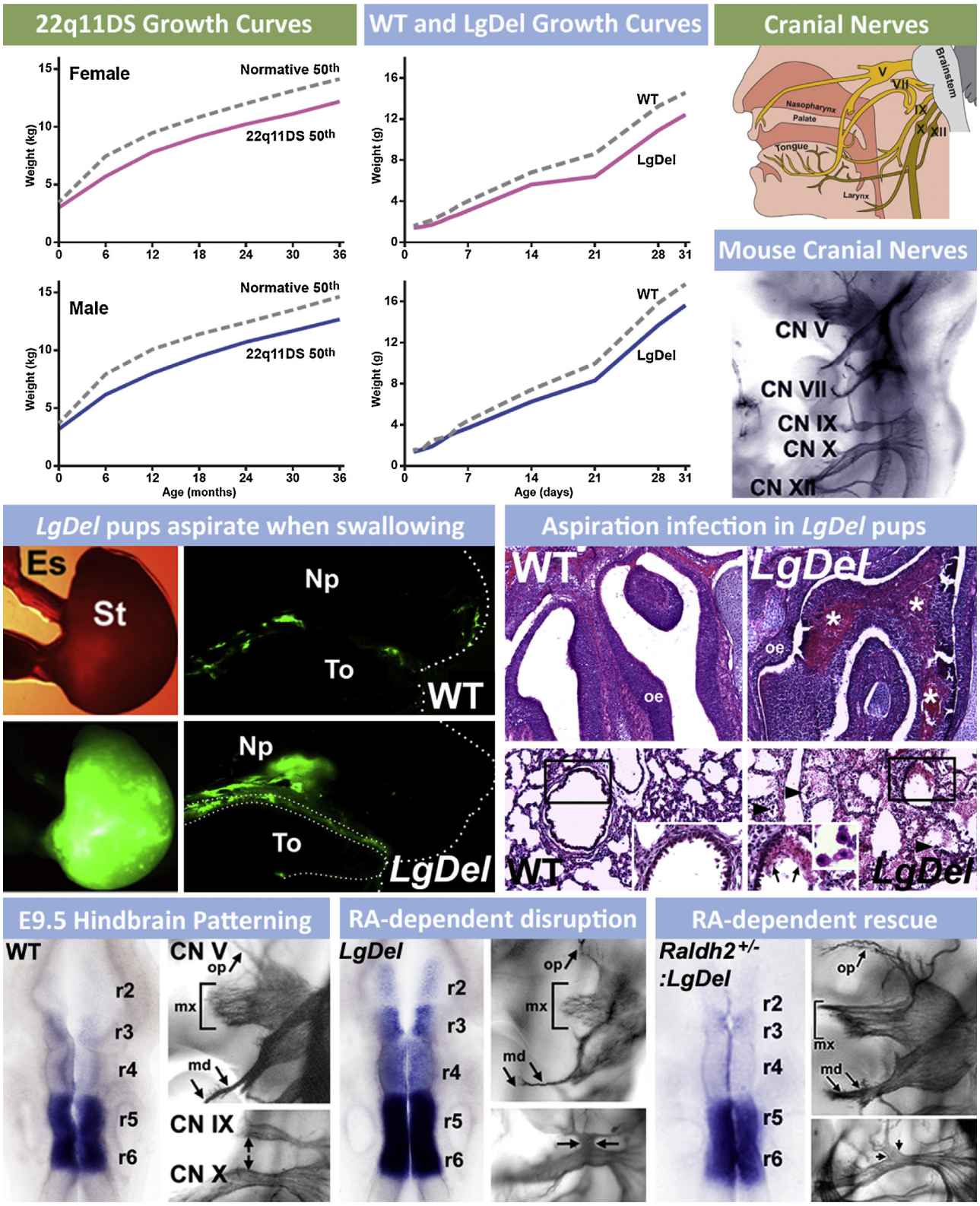

Fig. 4. The consequences of pediatric dysphagia—feeding and swallowing difficulties during early life—in 22q11DS are also seen in mouse models of 22q11 deletion. (Upper left) Growth curves for male and female 22q11DS patients from birth through 3 years of age show that birth weights are comparable to typically developing infants/toddlers, and then diverge so that 22q11DS children weigh less (data re-graphed from Tarquinio et al., 2012). Some of this lack of normal weight gain is attributed to feeding/swallowing difficulties. (Upper middle) Growth curves for female and male *LgDel* mice as well as wild type (WT) littermate controls from birth through 30 days of age. Similar to 22q11DS patients, birth weights for both female and male *LgDel* and WT littermate pups are equal. The weights, however, diverge shortly after birth, with a similar deficit in weight gain seen for *LgDel* pups as is seen in 22q11DS children. (Top right) Cranial nerves in humans that are critical for feeding and swallowing. These include the trigeminal (V), facial (VII), glossopharyngeal (IX), vagus (X) and hypoglossal (XII) nerves. Coordinated activity of sensory and motor divisions of these nerves (and the related peripheral ganglia and brainstem motor nuclei) insures optimal feeding and swallowing. In the panel below, these cranial nerves are visualized clearly in the developing mouse embryo at E10.5 using whole embryo immuno-staining. (Middle left) *LgDel* pups aspirate when swallowing milk during nursing. We developed the equivalent of the "barium swallow" test used in human infants and children to monitor the distribution of milk once ingested in WT and *LgDel* pups at post-natal day (P) 7. P7 WT pups swallow milk so

with food ingestion and swallowing often result in further clinical complications including aspiration-related nasal/sinus and respiratory infections. Thus, we asked whether the *LgDel* mouse had any signs of feeding/swallowing difficulties that parallel those seen in 22q11DS patients. The perinatal growth curves of 22q11DS patients (Fig. 4) indicate failure to gain weight, even though infants begin at approximately the same weight as typically developing control infants (Tarquinio et al., 2012). We found a similar deficit in weight gain in *LgDel* mice; both males and females begin at the same weight as wild type littermates controls, but fail to gain weight, and are ultimately smaller by weight (Karpinski et al., 2014; Fig. 4). This raised the possibility that these mice, similar to 22q11DS patients, might be aspirating milk into the naso-pharynx and lungs resulting in irritation and infection that compromises overall health and growth. We evaluated aspiration by examining sections through the naso-pharynx, the murine equivalent of the Eustachian tubes and lungs. We found protein inclusions in these structures that were composed primarily of murine milk proteins, often infiltrated by leukocytes and other immune cells (Fig. 4). Further histological examination, especially in the lungs, showed that many of the *LgDel* pups have the equivalent of aspiration-related pneumonia—a common complication related to perinatal dysphagia (Darrow and Harley, 1998; Lefton-Greif, 2008; Rommel et al., 2008).

The high frequency of dysphagia-associated phenotypes raised the possibility that one might use the *LgDel* 22q11DS mouse model to gain insight into the developmental pathogenesis of dysphagia, parallel to the use of this and other 22q11DS models to define the relationship between cardiovascular malformations and disrupted pharyngeal arch artery development due to 22q11 deletion. We first asked whether patterning of the brain region that provides neural crest cells for craniofacial structures as well as generating the cranial motor and sensory nerve innervation critical for feeding and swallowing—the rhombencephalon or hindbrain (Cordes, 2001; Guthrie, 2007)—was disrupted by 22q11 deletion. In the *LgDel* mouse, but not *Tbx1* embryos, we found that the anterior regions of the developing hindbrain—especially rhombomeres 1 through 3 of the seven repeated segments that define the brainstem—were dysmorphic at early stages. We then assessed expression of critical genes, and found that expression levels of multiple genes associated with signaling via RA, which is known to promote posterior versus anterior identity in the hindbrain (Dupe and Lumsden, 2001; Glover et al., 2006; Marshall et al., 1992; Niederreither et al., 2000) were increased, suggesting that RA signaling might be aberrant. Finally, *in situ* hybridization for *Cyp26b1*, a key RA-regulated gene that defines anterior versus posterior rhombomere boundaries, showed enhanced, ectopic expression, consistent with anomalous "posteriorization" of the hindbrain in *LgDel*, but not $Tbx1^{+/-}$ embryos (Fig. 4).

We then assessed the consequences of this early hindbrain patterning change for the initial differentiation of the cranial ganglia and sensory/motor nerves that are key for feeding and swallowing control. We found that Cranial Nerve V and CN IX/X were disrupted in the *LgDel* (Fig. 4). CN V is derived from anterior rhombomeres (r1–r3) while CN V IX/X come from more posterior regions (r6, r7). Further genetic analysis, motivated by reports of a similar CN IX/X phenotype in *Tbx1* homozygous mice (Vitelli et al., 2002a), showed that the CN IX/X anomaly reflects primarily diminished dosage of *Tbx1* in the *LgDel*, and is apparently independent of changes in RA signaling (Karpinski et al., 2014). In contrast, the CN V phenotype was specific to the *LgDel*. This suggested that the CN V anomalies in *LgDel* might be sensitive to changes in RA signaling levels in the anterior hindbrain during early development. We found that in *LgDel* embryos, the CN V phenotype, and RA-related patterning changes in anterior rhombomeres that prefigure anomalous CN V morphogenesis, could be rescued with a mutation that lowers RA signaling by approximately 25% (Fig. 4). These experiments define a new relationship between early RA-dependent mechanisms of anterior-posterior hindbrain patterning, cranial nerve differentiation, craniofacial morphogenesis and dysphagia in 22q11DS. It seems likely that the craniofacial as well as feeding and swallowing anomalies reflect altered mechanisms of early hindbrain patterning. Once again, the value of genetically valid animal models for 22q11DS is clear: only with these models (*LgDel*, $Tbx1^{+/-}$) can one define essential contributions of brain patterning, and altered development of cranial nerve circuits that control feeding and swallowing. Using these models (*LgDel*, $Tbx1^{+/-}$ $Raldh2^{+/-}$ rescue of *LgDel*) it should be possible to develop therapeutic interventions to correct key deficits that result from 22q11 deletion, and cause a clinical complication—dysphagia—associated more broadly with neurodevelopmental disorders, including several disorders of cortical circuit development.

6. 22q11DS: a paradigmatic disorder of cortical circuit development?

Parallels between 22q11DS cardiac and craniofacial anomalies, as well as clinical complications like dysphagia and mechanistically defined developmental phenotypes in mouse models of 22q11 deletion raise an essential question: can developmental pathogenesis of disorders of cortical circuit development including ASD, ADHD and SCZ, associated with 22q11DS, also be defined using mutant mice that approximate key genomic lesions in 22q11DS? The first essential step in such an enterprise is to establish fundamental "endpoint" pathologies in the cerebral cortex of 22q11DS patients and their behavioral consequences. This information can then be used to generate hypotheses and guide experiments in animal models, similar to how endpoint cardiovascular dysmorphology in 22q11DS patients has guided analysis of disrupted heart development in 22q11DS model mice. To make this essential step, one must define, as well as one can, critical "endpoint" pathologies in ASD, ADHD, and SCZ. Then one must determine whether similar anomalies are seen in 22q11DS patients with clinical diagnoses of these disorders. The common disruptions of cortical structure and function that emerge from this comparison should provide a framework for considering how animal models of 22q11 deletion can be used to define specific mechanisms that underlie disorders of cortical circuit development in 22q11DS.

that the bolus is seen in the stomach (St), with only remnants of fluorescent milk adhering to the tongue (To) after ingesting milk labeled with fluorescent microspheres via a feeding pipette. In contrast, *LgDel* pups aspirate into the nasal pharynx (NP). (Middle right) Aspiration results in protein inclusions (consisting of murine milk protein, data not shown) infiltrated with leukocytes, in the olfactory turbinates/nasal sinuses and lungs. (Lower left) Normal patterning of the hindbrain and constituent rhombomeres (r2–6), demonstrated here by expression of the RA regulated gene Cyp26b1, is key for the normal cranial nerve (CN) development. For CN V this includes a highly branched ophthalmic division (op), a robust maxillary division with multiple axon fascicles (mx) and a bifurcating mandibular branch (md). (Lower middle) In the *LgDel* retinoic acid (RA) dependent patterning is disrupted so that RA-sensitive genes, including Cyp26b1, expand in the hindbrain. CN V and IX/X development is disrupted in parallel. Lower right: Genetically lowering RA signaling by crossing in one null allele of Raldh2, the key RA synthetic gene for RA signaling in the hindbrain, "rescues" the disrupted patterning in anterior rhombomeres, demonstrated by Cyp26b1 expression, and also the anterior CN V phenotype. Murine images and data are adapted from Karpinski et al. (2014).

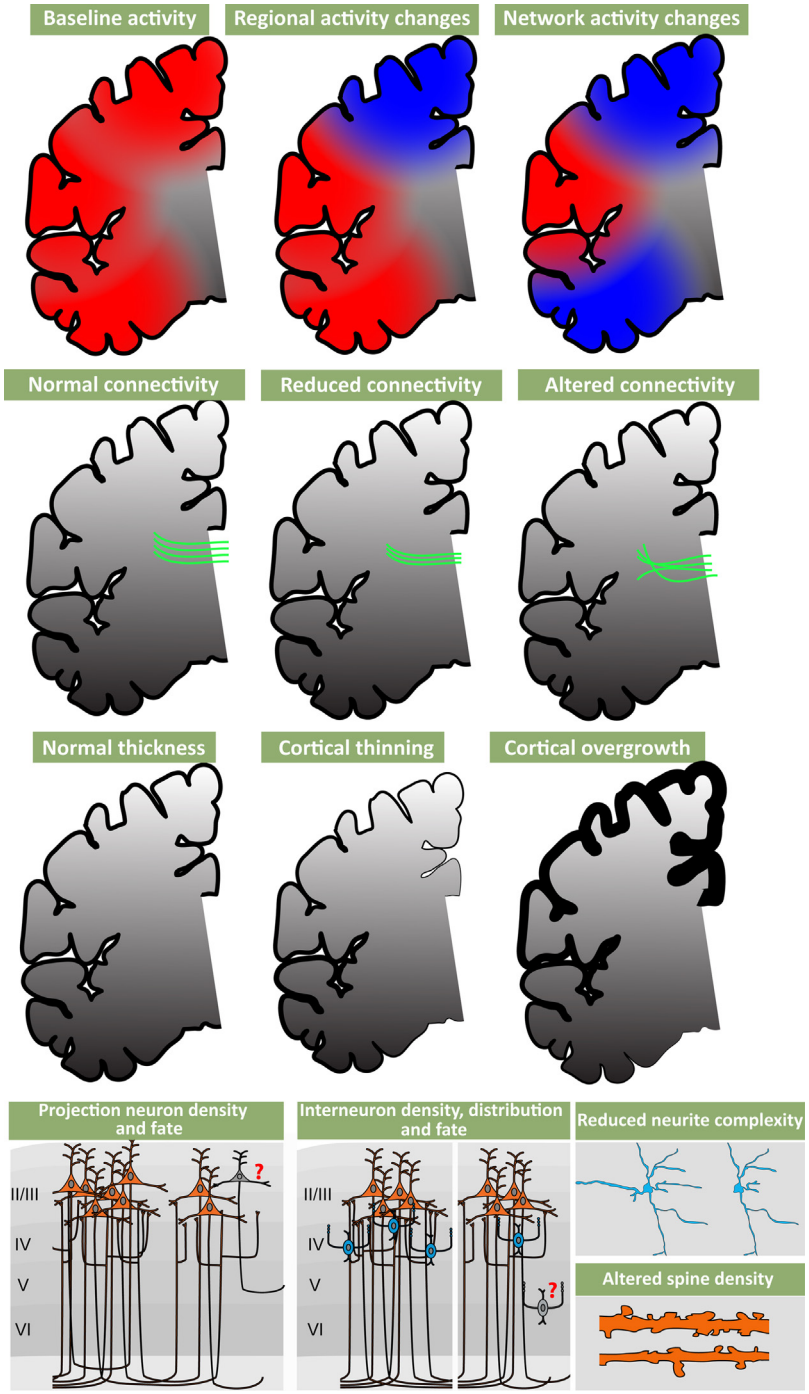

Fig. 5. Altered cortical Activity, disrupted axonal projections and neuronal changes are associated with disorders of cortical connectivity. (Top row) Functional magnetic imaging (FMRI) and other non-invasive physiological assessments in ASD, ADHD, and SCZ patients show localized and/or network related changes in cortical activity, especially in association regions. (Upper middle row) Diffusion tensor imaging (DTI) studies indicate that white matter tracts can be reduced in their density and topographical projections. (Lower middle row) MRI studies have shown both reduced cortex, particularly in schizophrenia, and thickened cortex, particularly in autism. (Bottom row) Activity and connectivity changes in patients may reflect reduced projection neuron density, location and inappropriate projection neuron cell fate (left). Density, distribution and cell fate of interneurons can also accompany these changes (middle). Associated with these changes to projection neurons and interneurons are altered neurite complexity and dendritic spine density (right).

6.1. The cortical pathology of disorders of cortical circuit development

The cerebral cortex is thought to be the primary target for pathogenesis in ASD, ADHD and SCZ (Fig. 5). Indeed, these disorders are also referred to as disorders of cortical circuitry (Geschwind and Levitt, 2007; Insel, 2010), and they are all thought to have a developmental origin. Thus, they are most accurately referred to as disorders of cortical circuit development. The key "endpoint" changes that support a common developmental origin for ASD, ADHD, SCZ and other related behavioral disorders are currently defined by integrating post-mortem cellular pathological, structural and functional imaging observations with genetic analyses in adolescent or adult patients. These observations—though highly variable—indicate subtle changes in overall cortical cellular architecture that are not likely explained by neurodegenerative changes. The literature that presents these data from ASD,

ADHD and SCZ patients is quite extensive. We will provide a very simplified summary of key points as a framework for considering in more detail how the cortex is altered in 22q11DS patients, and whether such alterations are consistent with those seen in "non-syndromic" (i.e. without a genetic or clinical diagnosis of an identified syndrome like 22q11DS) ASD, ADHD or SCZ patients. This information can then guide formulation and testing of hypotheses about disrupted cortical circuit development in mouse models of 22q11 deletion.

6.1.1. Cellular neuropathology

Cytological analysis of post-mortem samples, primarily in SCZ and to a lesser extent ASD, indicates that reduced gray matter and white matter thickness (Selemon et al., 2002) primarily due to diminished neuropil rather than extensive cell loss (Casanova et al., 2008; Selemon et al., 1998) is the most consistent cortical pathology. This change is accompanied by altered expression levels of projection neuron markers (Parikshak et al., 2013; Stoner et al., 2014) as well as key markers for cortical interneuron identity (Benes, 2000; Lewis et al., 2005). Apparently, projection neurons, especially (but not exclusively) in upper cortical layers (layers 2/3) are diminished in their degree of dendritic differentiation (Selemon et al., 1998). The limited evidence available from studies of small post-mortem samples from SCZ patients using variants of the Golgi method to visualize subsets of cortical cells suggests a decline in dendritic spines (Glantz and Lewis, 2000). In ASD, there are reports of increased dendritic spine frequency in some regions (Hutsler and Zhang, 2010) and a decrease in others (Raymond et al., 1996). There is more definitive data from SCZ versus ASD samples for changes in cortical GABAergic interneurons. The distribution and differentiation state of the basket cell subset of fast-spiking cortical interneurons is likely altered in SCZ (Lewis et al., 2012). The key post-mortem changes, particularly in the parvalbumin-expressing subset of GABAergic interneurons, appear to be most robust in frontal and cingulate association cortices (Beasley et al., 2002; Hashimoto et al., 2003; Volk et al., 2012); however, other regions have not yet been extensively analyzed. There is a great deal of additional speculation about the role of altered inhibitory interneurons and networks in ASD (Chu and Anderson, 2015; Marin, 2012; Rubenstein and Merzenich, 2003). Nevertheless, there is only one preliminary report, based upon observations in post-mortem material of two ASD subjects, that shows a decline in frequency of parvalbumin, presumed basket cell, GABAergic interneurons (Zikopoulos and Barbas, 2013). The conclusions that can be reached from neuropathological observation of post-mortem material are clearly limited due to small samples, technical challenges, and the difficulty of inferring developmental pathogenesis based upon a pathological endpoint in adult material. Nevertheless, cytological changes in cortical projection and interneurons in SCZ and ASD suggest that major neuronal elements that define cortical circuits—projection neurons and interneurons—are compromised in these, and related, disorders.

6.1.2. Structural MRI imaging

Magnetic resonance structural imaging (MRI) in living patients is generally consistent with observations of cellular pathology from studies of SCZ and ASD. Thus, gray matter and white matter volume, measured using structural MRI approaches, are diminished in ASD and SCZ patients (Fig. 5), as well as those with ADHD (McAlonan et al., 2005; Okugawa et al., 2007; Seidman et al., 2011; Silk et al., 2009); however, there is some indication that there may also be some increases in gray matter volume in ASD patients (Bonilha et al., 2008; Hazlett et al., 2006; McAlonan et al., 2005). There are also modest alterations in gyral/sulcal patterns (Nakamura et al., 2007; Nordahl et al., 2007; Watanabe et al., 2014). Finally, diffusion tensor-based analysis of MRI data (DTI) indicates that major cortico-cortical fiber tracts are disrupted in the brains of individuals with ASD, ADHD, and SCZ (Ashtari et al., 2005; Conturo et al., 2008; Phillips et al., 2011; Silk et al., 2009). These changes, similar to cellular pathological changes, are seen most robustly in association cortical areas. Thus, live structural imaging in ASD, ADHD and SCZ further supports the conclusion that these disorders are likely to compromise cortical circuitry and the behaviors that rely critically upon fully functional cortical circuits and connections.

6.1.3. Functional imaging

Extensive functional imaging assessments—far too numerous to review in detail—show that patterns of cortical activation in patients with ASD, ADHD and SCZ, elicited by cognitive, language, and social behavioral tasks, diverge from those in control subjects (Barch and Csernansky, 2007; Just et al., 2004; Loo et al., 2009). Once again, the cortical regions that are most compromised include association areas, particularly frontal association cortices (Baker et al., 2014; Bush, 2011; Mueller et al., 2013a; Tomasi and Volkow, 2012). In parallel, assessment of the "default mode network" or "resting state network", a set of apparently interconnected association cortical regions, based upon fMRI correlation, that are active in patients who are not asked to perform any specific task (Buckner et al., 2008; Raichle et al., 2001) (Horn et al., 2014) indicates that these regions are differentially active in ASD, ADHD and SCZ patients. The nature of these changes and their association with behavioral pathology is quite diverse, and beyond the scope of this summary. Nevertheless, these and other functional imaging observations identify association cortices, their circuits, inter-connections, and functions, as the primary (albeit large) target for functional pathology in ASD, ADHD, and SCZ.

7. Parallel cortical pathology in 22q11DS

These cytological, structural and functional studies, in broadly defined "non-syndromic" ASD, ADHD and SCZ patients (i.e. those without a specific genetic or clinical diagnosis of an identified developmental syndrome like 22q11DS) suggest that the cytology, circuitry and function of association cortices should be disrupted in 22q11DS patients, in register with the high frequency of ASD (Niklasson et al., 2009), ADHD (Niklasson et al., 2009; Tang et al., 2014) and SCZ (Bassett et al., 2005; Murphy et al., 1999; Pulver et al., 1994) in these individuals. Thus, establishing which, if any, of these deficits can be detected in 22q11DS patients is a necessary step to determine whether 22q11DS is truly representative of the pathology and pathogenesis of disorders of cortical circuit development and thus a genetically defined "model" of these diseases.

There have been few post-mortem pathological analyses of brains from 22q11DS patients. Nevertheless, the available observations are consistent with apparent changes in cortical circuit elements reported for ASD, ADHD and SCZ (Table 1). Analysis of perinatal autopsy material from one 22q11DS infant revealed reduced immunoreactivity for the pan neuronal marker, NeuN, in superficial layers of the cortex (layers 2/3) and white matter abnormalities including an absent anterior commissure (Sarnat and Flores-Sarnat, 2013). One additional study of material from three adult 22q11DS patients, all of whom were diagnosed with SCZ (Kiehl et al., 2009), found bilateral periventricular nodular heterotopias (PH)—ectopic accumulations of neurons and glia thought to reflect disrupted neuronal migration during embryonic development—in frontal cortical regions as well as ectopic neurons scattered throughout the frontal white matter (Kiehl et al., 2009). Though limited, these observations are consistent with the cellular cortical pathology reported for ASD, ADHD and SCZ: neuronal as well as cortical hypotrophy with some laminar selectivity focused

Table 1
Multiple imaging and post-mortem pathology studies have identified changes in the cortex from 22q11DS patients when compared to controls. These include cortical activity differences as measured by functional magnetic resonance imaging (fMRI), cortical thickness and volume measurements made using structural magnetic imaging (MRI), cortical white matter connectivity changes measured by diffusion tensor imaging (DTI), metabolic changes measured by magnetic resonance spectrometry (MRS), and tissue/cellular pathological observations from anatomical MRI scans and post-mortem studies.

Methodology	Study	References
Cortical activity Functional magnetic resonance imaging	Spatial working memory task, reduced neural activation in the intraparietal sulcus and superior frontal sulcus	Montojo et al. (2014)
	Weaker activity of frontal cortical areas during response inhibition tasks	Montojo (2015)
	Weaker connectivity and more diffuse connectivity pattern between default mode network nodes	Schreiner (2014)
	Abnormal response to faces with reduced activity in fusiform gyrus.	Andersson et al. (2008)
	Abnormal parietal cortical activation during response inhibition in patients.	Gothelf et al. (2007)
	Non spatial working memory tasks show reduced dorsolateral prefrontal cortex activation in 22q11DS youths compared to siblings	Kates et al. (2007)
Cortical connectivity Diffusion tensor imaging	Altered fractional anisotropy and axial diffusivity in multiple white matter structures. Particular defects associated with social cognition and psychotic symptoms	Jalbrzikowski et al. (2014)
	Cingulum bundle altered in 22q11DS youths, and correlates with prodromal measurements	Kates et al. (2015)
	Reduction in fibers connecting left fronto-temporal cortical regions in 22q11DS patients with and without psychotic symptoms	Ottet et al. (2013)
	Localized reduction in fractional anisotropy and axial diffusivity in WM underlying left parietal lobe of non-schizophrenic 22q11 individuals	Kikinis et al. (2012)
	Decreased fractional anisotropy in uncinate fasciculus and multiple white matter tracts decreased which correlate with executive function, IQ and working memory.	Radoeva et al. (2012)
	Decreased white matter in areas of frontal cortex between entire 22q11 subject group and controls	da Silva Alves et al. (2011)
	Severity of positive and negative schizophrenic diagnostic criteria correlate with decreased white matter in frontal and temporal areas.	
	Reduced white matter anisotropy in tracts connecting frontal and temporal lobes	Barnea-Goraly et al. (2003)
Cortical pathology Magnetic resonance imaging	Differential reduction of cortical thickness and surface area. Abnormalities in medial frontal areas associated with psychotic symptom severity.	Jalbrzikowski et al. (2013)
	Reduced gyrification along the cortical midline of children	Srivastava et al. (2012)
	Difference in the developmental trajectory of gyrification in particular cortical areas of children between 6 and 15 years	
	Gray matter reduction in frontal cortex and cingulate gyrus of non-psychotic children. Volumetric reductions correlate with poor neurocognition.	Shashi et al. (2010)
	Deviant trajectories of cortical thickness over time observed in patients versus control subjects	Schaer et al. (2009a)
	Within patient group, trajectory differences based on cognitive level and whether schizophrenia emerges	
	Altered midline cortical thickness and gyrification patterns in children	Bearden et al. (2009)
	Ventro-medial-occipital cortex and anterior cingulate cortex is reduced	
	Regionally specific cortical thinning. Superior parietal cortex and inferior frontal gyrus	Bearden et al. (2007)
	Reduced gyrification in frontal and parietal lobes	Schaer et al. (2006)
	Gender distinction in cortical thickness of dorsolateral prefrontal cortex between children/adolescents and control group	Kates et al. (2005)
Cortical metabolism Magnetic resonance spectroscopy	N-acetylaspartate (neuron specific metabolite) elevated in dorsolateral prefrontal cortex of 22q11DS kids versus controls, this level is maintained over time	Shashi et al. (2012)
	Reduced GABA levels associated with areas of altered cortical gyrification in 4 children compared to controls	Mori et al. (2011)
Cell neuropathology Post-mortem	Subtle cortical lamination defects, ectopic interstitial white matter neurons, 3 months old	Wu et al. (2014)
	Loss or failure to differentiate upper layer projection neurons in cortex from one perinatal individual	Sarnat and Flores-Sarnat (2013)
	Periventricular heterotopias, and ectopic neurons in the white matter. Four individual samples studied	Kiehl et al. (2009)
Synaptic/electrical defects IPSCs	No significant differences in electrical properties of IPSC derived glutamatergic neurons from one control and one schizophrenia patient with 22q11DS	Belinsky et al. (2014)

on layer 2/3, and local morphogenetic anomalies including PH. The role of presumed cortical projection neuron migratory anomalies like PH in ASD, ADHD and SCZ remains uncertain (for review see: Chu and Anderson, 2015; Marin, 2012; McManus and Golden, 2005). Nevertheless, disrupted migration is robustly associated with more severe developmental behavioral disorders, particularly intellectual disability (Liu, 2011), which is seen in some 22q11DS patients, either in isolation, or accompanying ASD, ADHD or SCZ related behavioral pathology (Jonas et al., 2014).

Altered cortical morphology in 22q11DS patients has been more thoroughly assessed in structural imaging studies (Table 1). Magnetic resonance imaging (MRI) of 22q11DS patients has confirmed anatomical changes including regional thinning of the cortex (see Table 1). Reduced gray matter volumes have been reported for several cortical areas; however, diminished volumes have been found consistently in the frontal gyrus and dorso-lateral prefrontal cortex (Kates et al., 2005; Schaer et al., 2006; Shashi et al., 2010). In addition, structural MRI imaging has confirmed PH seen in post-mortem material (van Kogelenberg et al., 2010) and has clearly associated polymicrogyria, especially peri-sylvian PMG, with 22q11DS (Bingham et al., 1998; Gerkes et al., 2010; Robin et al., 2006). Thus, MRI observations are consistent with altered neurogenesis as well as migration in the developing cortex of 22q11DS patients. Finally, additional anatomical anomalies are seen in subsets of 22q11DS patients, including agenesis of the corpus callosum and forebrain midline defects (Bearden et al., 2007; Kraynack et al., 1999; Lee et al., 2003a; van Amelsvoort et al., 2004). In one of these studies, the severity of gray matter reduction

predicted psychotic outcomes (Gothelf et al., 2011). These MRI observations are consistent with primary pathogenesis in the cortex of 22q11DS patients occurring during pre-natal development.

Cortical cytological and structural anomalies in 22q11DS patients are accompanied by changes in cortical activity (Table 1 and Fig. 5). Most functional changes are seen in association cortices, particularly the frontal cortices, and are detected during performance of complex cognitive tasks. There is reduced activity in medial frontal association cortical regions during a task that assesses working memory a key component of executive dysfunction (Montojo et al., 2014). Executive function, required for problem solving and task flexibility, is perturbed in all disorders of cortical circuit development (Kenworthy et al., 2009; Montojo et al., 2014; van Os and Kapur, 2009). This apparent divergence of association cortical function in 22q11DS patients is further supported by analysis of resting state network activity (Debbane et al., 2012). Magnetic resonance spectroscopy studies suggest that these changes may reflect disruptions of synaptic mechanisms, as is the case in ASD, ADHD and SCZ (Stone, 2009; Stone et al., 2009). In children with 22q11DS, there are apparently regionally decreased GABA levels at sites of cortical malformation (polymicrogyria) (Mori et al., 2011). This functional change may reflect altered interneuron number, placement or function. Thus, disruptions of cortical function in 22q11DS patients assessed using fMRI and MRS includes a representative array of deficits that are also robustly associated with non-syndromic ASD, ADHD and SCZ.

Cortical pathology in 22q11DS, though variable, is parallel to that seen in non-syndromic ASD, ADHD and SCZ patients. These commonalities define an endpoint to guide developmental analysis in 22q11DS animal models. The most obvious hypothesis is that diminished 22q11 gene dosage compromises association cortices, disrupting projection and interneuron integrity—selectively, but not exclusively—in layer 2/3 of these regions where most projection neurons that link association regions with one another are found. Using mouse models of 22q11 deletion, it should be possible to test this hypothesis and identify critical cortical developmental mechanisms that are compromised by 22q11 deletion throughout embryonic, fetal and early post-natal life. To accomplish this goal, one must assess where and when 22q11 genes act to compromise cortical development, and then to define specific cellular and molecular mechanisms that are disrupted by diminished 22q11 gene dosage. Once this foundational analysis is complete, then it should be possible to assess whether developmental disruptions actually lead to mature circuit anomalies, and if such circuit dysfunction is relevant for understanding behavioral changes seen in 22q11DS patients—and shared with individuals with ASD, ADHD, SCZ and other disorders of cortical circuit development.

8. Can 22q11 genes influence cortical circuit development?

Diminished dosage of 22q11 genes is likely to compromise cortical development if one, a few, or most of the deleted 22q11 genes are expressed in the developing cortex. Thus, to formulate and test hypotheses, it is first necessary to establish a thorough 22q11 gene expression profile throughout pre- and post-natal cortical development. We compared the general expression of 22q11 genes in developing human cortex to that of orthologous genes in the developing murine cortex as an initial test of the utility of studying how 22q11 deletion might cause developmental cortical circuit pathogenesis in mouse models. We evaluated the presence of mRNA for a subset of human 22q11 genes from the 1.5 MB minimal critical deleted region in samples of "normal" human fetal cortex. We selected this subset based upon their apparent enriched expression in the adult mouse brain (Maynard et al., 2003), or their presumed neural functions. We found that 9/12 of these genes were expressed at detectable levels in the developing human cortex (Maynard et al., 2003 and see Fig. 6). We then asked whether the same subset of genes was expressed in the mouse fetal cortex. These same 9 genes were expressed in murine fetal cortex at embryonic day 14 (Maynard et al., 2003); indeed, subsequent analysis in the developing cortex has established substantial expression of 20/28 orthologues of human 22q11.2 genes from the minimal critical deleted region in the E14.5 cortex. This expression analysis indicates that diminished dosage of any of these 20 genes might have a direct impact on genesis or differentiation of cortical neurons, depending upon the cellular localization of key genes.

To better assess the likely cellular sites of action of diminished 22q11 gene dosage, we localized, by *in situ* hybridization or immuno-staining, a subset of 22q11 candidate genes in the developing, early post-natal and adult mouse cortex. We focused on two key groups of genes: first, a set of five 22q11 genes implicated in cell cycle control (Maynard et al., 2003; Meechan et al., 2009), and second, a group of six 22q11 genes that are all localized to synaptic mitochondria (Maynard et al., 2008). Each of these 11/28 22q11 genes, or their protein products, is expressed in the developing or adult cerebral cortex. In some cases, 22q11 genes are selectively expressed in cortical progenitors in the ventricular zone (VZ) and subventricular zone (SVZ; *Ranpb1*, *Cdc45l*, *Trmt2a*, *Hira*), or in subsets of differentiating cortical neurons (*Sept5*, *Tango2*, *Mrpl40*) including apparent subplate cells (Fig. 6). Additional genes are more broadly expressed, apparently in all cortical neurons. These include mitochondrial genes *Prodh2*, *Txnrd2*, and *Zdhhc8* as well as the microRNA processing co-factor *Dgcr8* (also know as *Drosha*; Lee et al., 2003b). Thus, the available evidence indicates that several 22q11 genes expressed generally in the human and mouse cortices have cellular localization that could lead to specific phenotypes in developing cortical progenitors, their early neuronal progeny, or fully mature cortical neurons.

Finally, we asked whether 22q11 gene dosage in the cerebral cortex is actually diminished—either by the predicted 50% or some other value—as a result of 22q11 deletion. While this seems likely, there are examples of dosage compensation at both the transcriptional and translational level throughout the genome (Guidi et al., 2004; Takahashi et al., 2002) as well as imprinting that leads to additional diminished expression or effective null phenotypes (Albrecht et al., 1997). We assessed 22q11 gene expression in the developing and adult cerebral cortex in the *LgDel* mouse model of 22q11DS. In the mature cerebral cortex, we found that 9 22q11 genes that are expressed moderately to robustly in wild type cerebral cortex are indeed diminished by 50% in the *LgDel* cerebral cortex (*Dgcr2*, *Prodh2*, *Zdhhc8*, *Ranbp1*, *Tango2*, *Comt*, *Tbx1*, *Ufd1l*, and *Hira*; Fig. 6) (Meechan et al., 2006). We analyzed in detail the cellular expression pattern and distribution of one of these genes, *Prodh2*, in the mature cortex. Our assessment indicates that for at least this one 22q11 gene, expression is likely diminished by 50% on a per cell basis, rather than due to large-scale loss of expression in a particular cell class (Meechan et al., 2006). Our mRNA analysis in the developing cortex of a subset of 22q11 genes (*Ranpb1*, *Cdc45l*, *Trmt2a*, *Sept5*, and *Hira*) implicated in cell cycle regulation showed that each of these genes was diminished by the expected 50% (Meechan et al., 2009). Similarly, a microarray analysis of FACS sorted cortical interneurons from *LgDel* versus WT embryos showed that expression of all detectable 22q11 genes was diminished in this particular developing neuron class (unpublished observation). Surprisingly, there is little additional information on expression changes of 22q11 genes in additional mouse models or in human tissue samples. A recent analysis of a small subset of human 22q11 genes from the minimal critical deleted region in 22q11DS patients confirms 50% diminished expression in

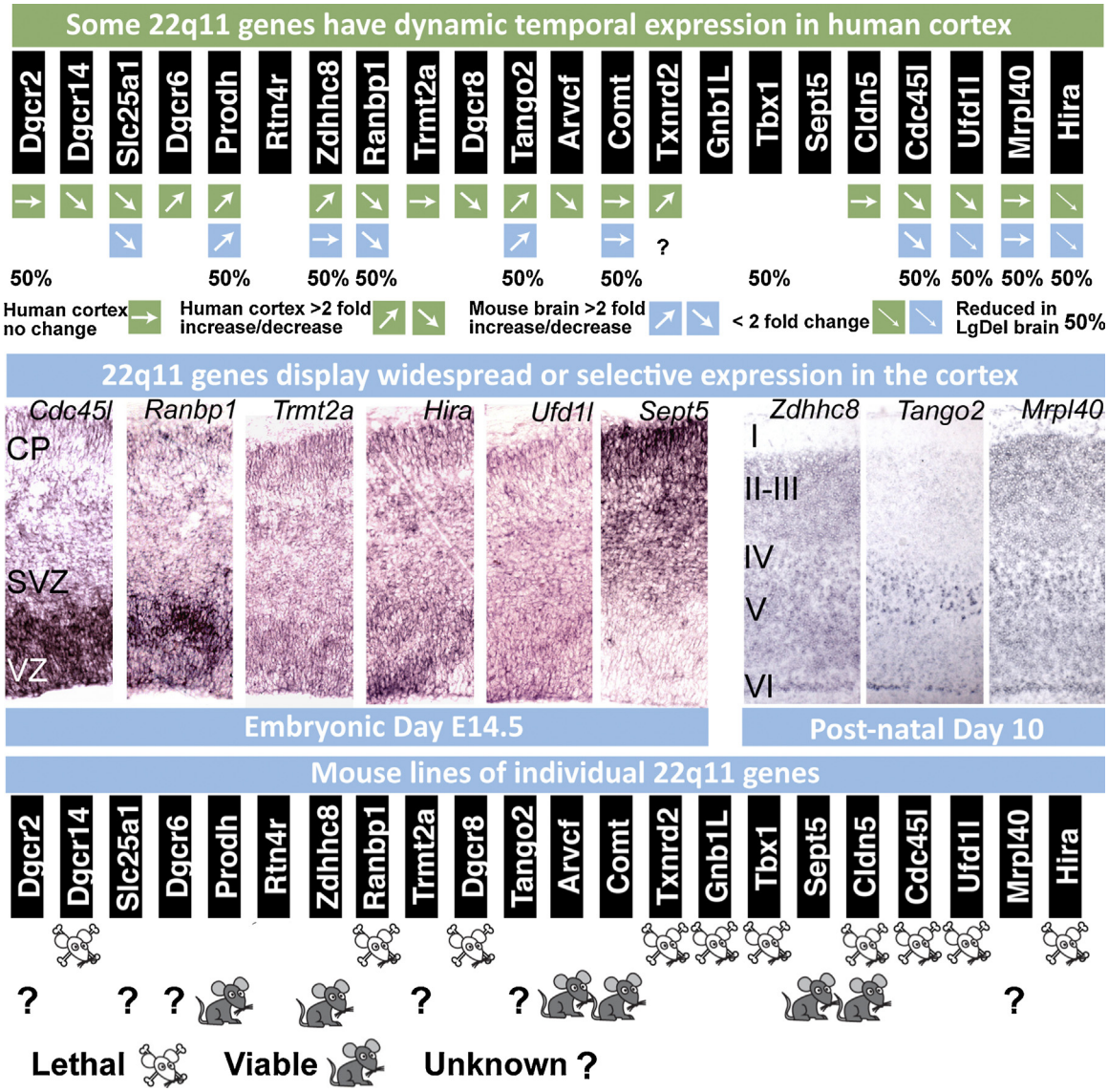

Fig. 6. Expression, localization and genetic analysis of individual 22q11 genes during development. (Top row) Dynamic expression of 22q11 genes from the minimal critical deleted region analyzed in 13 weeks post conception fetal human and adult human cortex as well as embryonic and post-natal mouse brain. In most cases, there is agreement between mouse and human in the direction of change of gene expression between fetal and adult cortex. Human gene expression levels were assessed from the brainspan database (brainspan.org) and averaged across ventrolateral prefrontal cortex, anterior cingulate cortex and dorsolateral prefrontal cortex at both time points. Gene expression levels in mouse brain between embryonic and post-natal time periods were assessed by qPCR and derived from data in Meechan et al. (2006, 2009) and Maynard et al. (2008). (Middle row) At left, *in situ* hybridization on E14.5 coronal brain sections indicate selectivity of 22q11 gene expression in the progenitor zones (the ventricular zone, VZ and subventricular zone, SVZ) as well as the location of newly generated neurons (the cortical plate, CP) in the cortex. *Cdc45l* and Ranbp1 are expressed most robustly in the progenitor zones that contain the apical and basal progenitor cells. Trmt2a, Hira and Ufd1l display a more ubiquitous expression pattern, while Sept5 is more robustly present in the cortical plate occupied by post-mitotic neurons. At right: In maturing post-natal cortex, Zdhhc8 and Mrpl40 displays widespread expression across all layers, while T10 shows robust and selective expression in layer 5 (modified from Maynard et al., 2008; Meechan et al., 2009). (Bottom row) Targeted inactivation of 22q11 genes in the mouse result in embryonic/perinatal lethality in 10 of the 16 loci that have been deleted thus far, indicating the importance of genes in this region for embryonic development and survival.

lymphocytes (Sellier et al., 2014). There are no data, however, measuring altered 22q11.2 gene expression in the cerebral cortex from any 22q11DS patient samples.

Together, the available data show that the cerebral cortex is a major site of 22q11 gene expression in the developing brain. The expression dynamics and patterns of the genes evaluated thus far, most of which are candidates for cortical phenotypes based upon their function (cell cycle or mitochondrial regulation) or SCZ vulnerability, indicate that several distinct cortical cell classes—progenitors, projection neurons, interneurons, and to a lesser extent glial cells—express 22q11 genes, and may be compromised by the 50% diminished expression that results from heterozygous deletion. Critically, in the mouse, most 22q11 genes are expressed in the developing, as well as in the adult, cerebral cortex, and their expression is locally diminished by 50%, consistent with dosage effects of 22q11 deletion. Thus, it is highly likely that the primary genetic lesion that results in 22q11DS leads to disorders of cortical circuitry by disrupting cortical circuit development due to diminished dosage of key genes. It is also possible that diminished 22q11 gene dosage in the adult brain compromises mechanisms for maintenance or function of cortical neurons and circuits.

9. Cortical neurogenesis is disrupted by 22q11 deletion

The expression of several 22q11 genes implicated in cell cycle regulation in the VZ and SVZ during cortical neurogenesis raised the possibility that 22q11 deletion might contribute to disorders of cortical connectivity by altering cortical neurogenesis, especially for projection neurons that are derived from cortical progenitors resident in the VZ and SVZ (Molnar and Clowry, 2012). Cortical progenitor populations in the VZ and SVZ are diverse. There are two broad classes: apical/radial glial progenitors which are apparently the multipotent slowly dividing stem cell of the cortex (Hevner, 2006; Kriegstein and Gotz, 2003), and basal progenitors which are thought to be transit amplifying, rapidly and terminally dividing precursors with a bias—but not absolute specificity—for producing layer 2/3 projection neurons (Kowalczyk et al., 2009; LaMonica et al., 2012; Noctor et al., 2007). In addition, there may be other progenitor classes, including the outer SVZ cell, (OSVZ; Fietz et al., 2010; Lui et al., 2011), which has properties similar to apical/radial glial progenitors. OSVZ cells are more frequent in primates (including humans) and carnivores, and they are believed to contribute to the expansion of the cortical mantle (Hansen et al., 2010). Their frequency in the mouse cortex and their distinct role in murine cortical development remain uncertain. The expression patterns of several 22q11 genes in the VZ/SVZ of developing mouse cortex, especially *Ranpb1*, *Trmt2a*, *Hira*, and *Cdc45l* (see Fig. 6 above), all implicated in the cell cycle (Guarguaglini et al., 1997; Moyer et al., 2006), suggest that diminished 22q11 gene dosage might compromise the proliferative and neurogenic capacity of VZ/SVZ precursors. Thus, we analyzed VZ/SVZ proliferation and projection neuron neurogenesis in the *LgDel* and several other genetic models of 22q11 deletion.

There are selective deficits in cortical precursor proliferation and projection neuron neurogenesis in the *LgDel* mouse. We found that proliferative activity, based upon assessment of VZ/SVZ cells in M-phase as well as S-phase, was substantially diminished for basal progenitors, but not for apical progenitors in the fetal *LgDel* cortex during the peak period of mouse cortical neurogenesis (E13.5-E14.5; Fig. 7; Meechan et al., 2009). We did not see similar changes in the cerebral cortex of fetal $Tbx1^{+/-}$ or $Prodh2^{-/-}$ mice, even though both genes have been suggested as candidate genes for 22q11DS behavioral phenotypes (Paterlini et al., 2005; Paylor et al., 2006). In *LgDel* mice, this cortical precursor proliferative deficit was sustained throughout the period of cortical neurogenesis. The consequence is consistent with the reported bias of basal progenitors to generate layer 2/3 versus 5/6 cortical projection neurons (Arnold et al., 2008; Sessa et al., 2008). Accordingly, layer 2/3 projection neuron frequency is diminished in the mature *LgDel* cortex, while that of layer 5/6 projection neurons was indistinguishable from WT (Fig. 7; Meechan et al., 2009). Additional analysis with layer-specific transcription factor markers that identify projection neurons, confirmed this observation (Fig. 7). We found these changes in frontal association cortical regions (areas 24/25 and 6 based upon the maps of Caviness (1975); see below). It remains to be determined whether this basal progenitor-related disruption of layer 2/3 projection neurogenesis is limited to these regions, or is seen in additional association as well as primary sensory and motor cortical regions. Together these results indicate that diminished 22q11 gene dosage—beyond candidate genes *Tbx1* and *Prodh2*—disrupts cortical projection neurogenesis. Clearly, this developmental disruption of layer 2/3 projection neurons, a key element in cortical circuitry thought compromised in ASD, ADHD, and SCZ, may contribute to the disruption of complex behaviors in 22q11DS. This observation provides one of the first clear indications that a genetic lesion robustly associated with ASD, ADHD and SCZ post-natally can selectively disrupt a major cellular mechanism that underlies appropriate genesis of cortical neurons and circuits during prenatal development.

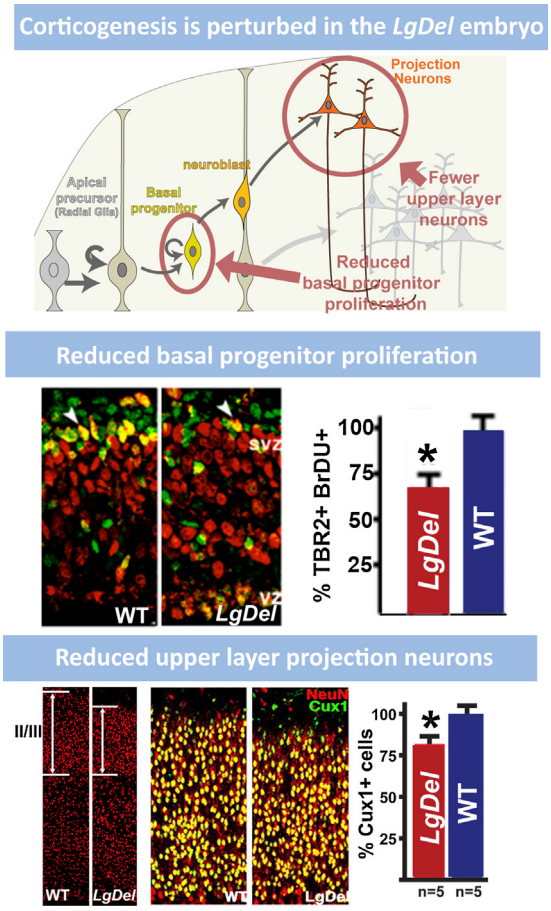

Fig. 7. Neuronal proliferation defects during development in the *LgDel* model prefigure changes to the mature cortex. (Top row) A schematic of cortical neurogenesis, migration, and projection neuron differentiation. Cortical neuroepithelial progenitors (far left) give rise to apical/radial glial progenitors, the committed stem cells of the cortex. Radial glia can directly generate neurons (and at later stages, astrocytes), or an intermediate/transit amplifying precursor called the basal progenitor. Basal progenitors give rise to projection neurons, with a bias toward generating layer 2/3 projection neurons. After terminal divisions, newly generated cortical neurons. (Middle row) Basal progenitor proliferation, but not apical progenitor proliferation in the embryonic *LgDel* cortex is disrupted. At left: labeling for the S-phase marker BrdU and the basal progenitor specific marker, Tbr2, show reduced co-labeling in the *LgDel* embryonic cortex. Arrowheads indicate double-labeled cells (modified from Meechan et al., 2009). At right: quantification of Tbr2-positive basal progenitors in S-phase based on BrdU labeling. There is a statistically significant, approximately 25% decrease in actively proliferating Tbr2-labeled basal progenitors. (Bottom row) Neuronal markers in post-natal *LgDel* cortex reveal reduced numbers in layer 2/3. At left: Immunofluorescent staining for the pan-neuronal marker, NeuN, displays reduced cell numbers in layer 2/3. At right: the layer 2/3 projection neuron marker, Cux1, is also reduced in *LgDel* cortex (modified from Meechan et al., 2009).

10. Cortical interneuron migration is disrupted by 22q11 deletion

Morphologically and biochemically diverse classes of GABAergic interneurons (Monyer and Markram, 2004), whose local connections establish appropriate inhibitory/excitatory balance in cortical circuits (Markram et al., 2004) are also thought to be altered in ASD, ADHD, and SCZ (Chattopadhyaya and Cristo, 2012; Inan et al., 2013; Lewis et al., 2005). The opportunities for disrupting the genesis, migration and differentiation of GABAergic interneurons are manifold: these neurons are generated in a

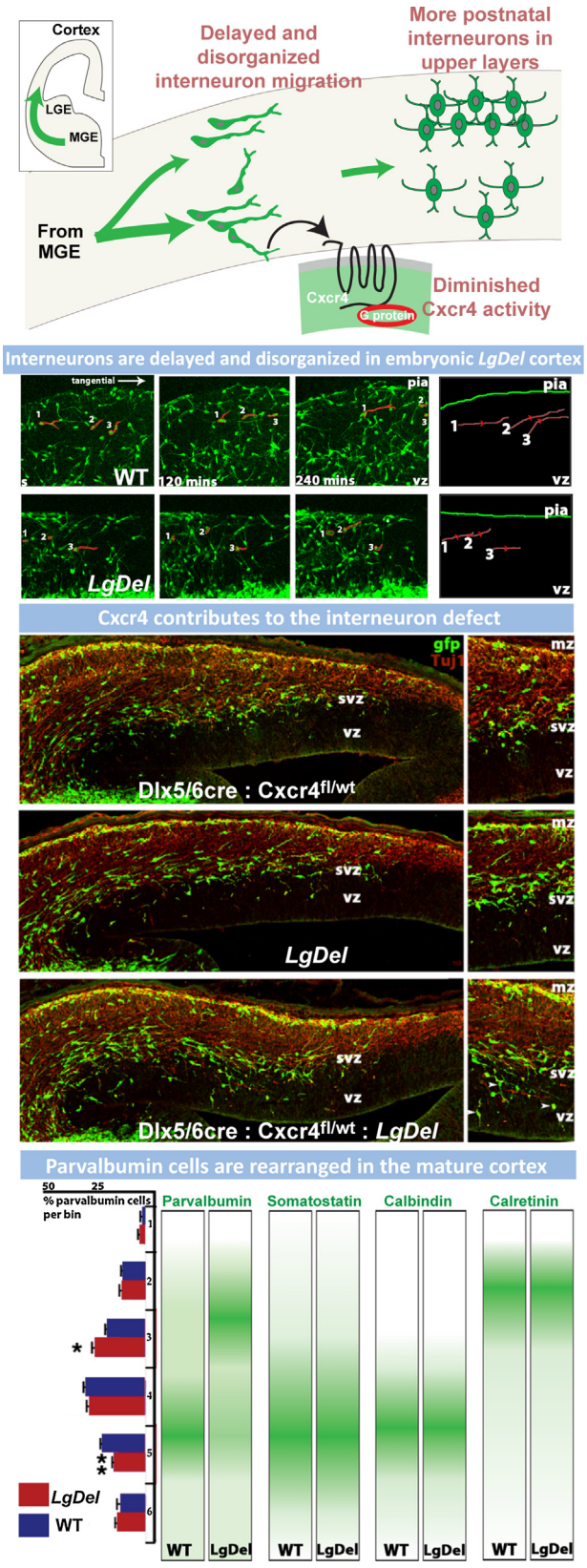

Fig. 8. Disrupted migration and placement of subsets of GABAergic interneurons reflects altered function of the Cxcr4 receptor caused by 22q11 deletion. (Top row) Schematic of interneuron migration from their site of neurogenesis in the medial ganglionic eminence (MGE) to the neocortical rudiment. The drawing indicates the migratory disruption seen for subsets of GABAergic interneurons in the *LgDel* fetus, as well as the final consequence for interneuron distribution in the *LgDel* adult cortex. (Upper middle row) Live imaging of migrating GABAergic interneurons, labeled with a *Dlx5/6:Cre:eGFP* transgene, as they enter the cortex at E14.5 shows that *LgDel* cells have diminished velocities as well altered trajectories. (Lower middle row) Top panel: heterozygous deletion of Cxcr4 in interneurons, using the *Dlx5/6:Cre:eGFP*, does not have a detectable effect on interneuron migration. Middle panel: In *LgDel* fetuses, migrating interneurons accumulate in the SVZ. Bottom panel: When 1 copy of *Cxcr4* is excised using the *Dlx5/6:Cre:eGFP*, the accumulation of migrating interneurons in the SVZ is enhanced specifically. (Bottom row) In mature *LgDel* cortex, laminar distribution of one specific interneuron sub-type, those expressing parvalbumin, is altered in layers 2/3 and 5/6. The distribution of several other subtypes of interneurons is not altered, as shown by the schematics. Images and data are from Meechan et al. (2012).

distinct region of the telencephalon, must migrate into the rudimentary cerebral cortex over a long distance, and once arrived, must traverse cortical laminae to establish appropriate positions and differentiate into a broad range of molecular and cytologically distinct subtypes. These multiple developmental vulnerabilities, and observations of diminished frequency or altered molecular identity of GABAergic interneurons in post-mortem material, especially from individuals with SCZ (Beasley and Reynolds, 1997; Beasley et al., 2002; Hashimoto et al., 2003; Volk et al., 2012), implicates these cells in the pathology of cortical circuit disorders. Nevertheless, the relationship between these apparent pathologic changes in post-mortem material and disrupted development remain unclear. We therefore used the *LgDel* mouse model of 22q11DS to determine whether disrupted GABAergic interneuron development occurs as a consequence of a genetic lesion associated with ASD, ADHD and SCZ.

Our expression analyses of 22q11 genes in WT embryos showed that several are expressed in the medial and caudal ganglionic eminences (MGE and CGE), the basal telencephalic source of most cortical interneurons (Fig. 6). A comparison of expression levels of a number of 22q11 genes from the MGE, CGE, lateral ganglionic eminence (LGE); the basal telencephalic source of olfactory bulb interneurons; (Tucker et al., 2008) versus the cortex at E14.5 indicates expression is moderately higher in the basal forebrain compared to cortex for *Dgcr8*, *Ufd1l*, *Txnrd2*, *Arvcf*, *Sept5*, *Ranbp1*, *Hira* and *Cdc45l* (unpublished microarray observations from) (Tucker et al., 2008). The expression patterns of 22q11 cell cycle-regulatory genes including *Ranbp1* and *Cdc45l* in the MGE/CGE equivalent of the cortical SVZ (Meechan et al., 2009) suggested that GABAergic precursor proliferation might be disrupted; however, this was not the case. We did not detect proliferative changes in basal or apical progenitors in the MGE (Meechan et al., 2012). Apparently, there are regional distinctions in consequences of diminished 22q11 gene dosage in the forebrain: deletion results in altered progenitor proliferation for dorsally derived cortical projection neurons, but does not seem to compromise progenitor proliferation for ventrally derived cortical interneurons. While cortical interneuron genesis was not altered by 22q11 deletion, the migration and final cortical placement of these neurons are modified. An initial analysis in histological sections suggested that, as a population, migrating interneurons in the E14.5 *LgDel* cortex did not advance as far into the cortical rudiment as their WT counterparts. Moreover, an assessment of the maturing *LgDel* cortex suggested that the parvalbumin-labeled subset of cortical GABAergic interneurons—the largest sub-population, primarily fast-spiking basket cells that synapse upon the somata and dendritic spines of cortical projection neurons (Freund and Katona, 2007; Kawaguchi and Kubota, 1997)—were distributed anomalously (Fig. 8; Meechan et al., 2009). The frequency of this class of interneuron was increased in layer 2/3 and diminished in layer 5/6. Together these observations suggested that interneuron migration might be selectively disrupted by 22q11 deletion.

We analyzed the dynamics of interneuron migration and the consequences of disruptions caused by 22q11 deletion using live imaging as well as detailed analysis of the placement of GABAergic

subclasses in the mature cortex. We found that the movement of GABAergic neuroblasts (visualized using a Dlx5/6:eGFP reporter) (Stenman et al., 2003) in living slices of the embryonic brain was aberrant. The velocity and trajectory of these cells was slowed and randomized as they entered the cerebral mantle (Fig. 8). Moreover, their radial traverses through the cortex to reach final positions were also altered. Additional experiments indicated interneurons motile capacity rather than the migratory environment in the developing cortex was altered. Accordingly, we asked whether there were specific molecular changes in these interneurons that might explain the migratory deficit and its consequences for interneuron placement. We sorted migratory *Dlx5/6*:GFP labeled GABAergic neurons from *LgDel* and WT developing cerebral cortex at E14.5—this allowed us to evaluate only the migrating neurons within the cortex rather than a much broader range of interneurons and precursors from the MGE or CGE. This approach allowed us to ask whether 22q11 deletion, via downstream transcriptional changes in a distinct cell type, specifically compromises distinct mechanisms for cell motility and migration in developing cortical interneurons.

Our subsequent transcriptional assessment of *LgDel* embryonic cortical interneurons using microarray analysis suggested reduced expression of several genes known to regulate interneuron migration once they have entered the developing cortex. In particular, the G protein-coupled cell surface receptor, *Cxcr4*, was reduced in expression. *Cxcr4* is not within the 22q11 deleted locus; instead it is found on mmChr1. The Cxcr4 protein is specifically found on the surface of interneurons migrating through the developing cortex and elicits a chemotactic response to the endogenously expressed ligand *Cxcl12* (Stumm et al., 2007, 2003). Moreover, *Cxcr4*$^{-/-}$ mice (which die in utero) have a developmental interneuron defect similar to that seen in *LgDel* embryos (Stumm et al., 2003). To clarify a functional role of *Cxcr4* in the *LgDel*, we assessed cortical interneuron migration phenotypes caused by selective inactivation of *Cxcr4* via Cre-mediated recombination in *Dlx5/6*-expressing interneurons in the context of 22q11 deletion. We found that diminishing expression of Cxcr4 by deleting one copy of the gene in *LgDel* but not WT interneurons, specifically increased the disrupted migration of interneurons seen in the *LgDel* cortex (Fig. 8). Apparently, 22q11 deletion acts as an effective loss-of-function *Cxcr4* mutation, which in the context of diminished dosage of 22q11 genes results in altered interneuron migration. Little is known about how signaling via Cxcr4 mediates migration and placement of nascent interneurons. We have shown that phosphorylation of the Cxcr4 receptor, which accompanies Cxcl12 ligand binding (Mueller et al., 2013b) is diminished in migratory *LgDel* GABAergic neurons. The consequences, however, of diminished Cxcr4 signaling for subsequent GABAergic interneuron cell motility or differentiation are unclear.

The developmental disruption of interneuron migration and that of cortical projection neuron genesis may be synergistically deleterious both during development and in the mature cortex. Basal progenitors provide secreted signals, including Cxcl12 the primary ligand for Cxcr4, to guide tangential interneuron migration through the cortical SVZ (Stumm et al., 2003; Wang et al., 2011). Accordingly, the deficit in basal progenitor proliferation in the developing *LgDel* cortex could contribute to the interneuron migration defect. Similarly, GABA generated by cortical interneurons is capable of modulating proliferation of cortical progenitor cells (LaMantia, 1995; LoTurco et al., 1995). In the *LgDel*, the Cxcr4-dependent surplus of GABAergic interneurons in the VZ/SVZ may aberrantly stimulate premature exit from the cell cycle or terminal division, thus reducing the overall number of proliferating basal progenitors. These hypotheses remain to be tested. Nevertheless, the available data suggest that disorganization in the cortical VZ/SVZ during development, due to disrupted migration of interneurons and diminished frequency of proliferative basal progenitors, can contribute to changes in key circuit elements, particularly in layer 2/3 in *LgDel* mice. This suggests a potential connection between developmental disruptions due to 22q11 deletion and pathology of disorders of cortical circuit development, especially SCZ. In SCZ patients, connections between layer 2/3 projection neurons and interneurons, especially in association cortical regions, are compromised (Beneyto et al., 2011; Glantz and Lewis, 2000; Pierri et al., 2001). Our results provide one plausible scenario of how this pathologic endpoint might be reached via a disruption of specific mechanisms of cortical circuit development: cortical neurogenesis via basal progenitors and Cxcr4-dependent interneuron migration. They also suggest that therapeutic interventions targeted to subsets of GABAergic interneurons—if warranted based upon functional studies of their contribution to behavioral pathology—may provide a potentially beneficial approach to ameliorating specific inhibitory/excitatory imbalances in patients with disorders of cortical circuit development.

The association between Cxcr4 as a modulator of interneuron development in 22q11DS and broader pathological endpoints in SCZ (and perhaps ASD and ADHD where interneuron deficits have been proposed as pathologic endpoints) suggests that Cxcr4, Cxcl12 and other related signaling intermediates might serve as biomarkers for developmental disruption that establishes vulnerability for disorders of cortical connectivity. There are a few observations that lend preliminary support to this suggestion: human iESPCs from schizophrenic patients have reduced CXCR4 protein levels compared to control samples, and these cells also have altered motility (Brennand et al., 2015). Additionally, expression of CXCL12 is decreased in olfactory neurons from idiopathic cases with schizophrenia compared to normal controls (Toritsuka et al., 2013). If modified expression or activity of CXCR4/CXCL12 due to 22q11 deletion emerges as a key feature of neuronal molecular pathology more broadly in disorders of cortical circuitry including ASD, ADHD and SCZ, the expression of the receptor on lymphocytes, macrophages, and other peripheral circulating immune cells might facilitate further mechanistic or diagnostic assessment. Thus, analysis of developmental mechanisms only possible in animal models of 22q11 deletion provides potential insight into how cortical circuits may be altered in the disorders of cortical connectivity associated with 22q11DS, and potential diagnostic or therapeutic strategies.

11. One or many: how do 22q11 genes alter cortical development?

A significant challenge associated with CNV disorders is determining whether key syndromic phenotypes—like disrupted cardiovascular or cerebral cortical development—reflect the consequences of diminished dosage of one single gene in the deleted region (thus, true haploinsufficiency) or interactions between diminished dosage of multiple genes. Our data on general diminished dosage of multiple brain expressed mouse 22q11 gene orthologues (with only one instance of translational dosage compensation; (Meechan et al., 2006)) indicates that a substantial number of genes likely contribute to key phenotypes. Our analysis showing a lack of imprinting or parent of origin bias on any of the genes in the mouse equivalent of the 22q11.2 minimal critical deleted region (Maynard et al., 2006) amplifies the conclusion that 22q11 deletion pathology likely reflects dosage change. Genetic association studies in human patients and control subjects implicate several individual 22q11 genes, including *PRODH2*, *COMT*, *ZDHHC8*, and *ARVCF* in SCZ (Chen et al., 2005; Fan et al., 2002; Li et al., 2004; Liu et al., 2002b; Mas et al., 2009; Mukai et al., 2004; Sanders et al., 2005) and there are some indications of

independent association (single gene polymorphisms without deletion) of individual 22q11 genes with ASD (Chen et al., 2012). Nevertheless, the strongest genetic association between SCZ, ASD, or ADHD remains between these disorders and deletion across the 22q11 minimal or typically deleted region (Schneider et al., 2014). Thus, the available human genetic evidence supports potential contributions of individual genes to specific pathologic features in 22q11DS including disorders of cortical connectivity. Nevertheless, interactions between multiple deleted genes are likely to result in key syndromic features, including disorders of cortical circuit development. We will review in detail analysis of four candidate genes to further evaluate the role of individual candidate genes versus combined diminished dosage in 22q11DS disease features, and related phenotypes in mouse models of 22q11 deletion.

11.1. TBX1

The balance between one gene and many is supported by extensive analysis of one candidate gene in the minimally critically deleted region, *TBX1*, in cardiovascular and other phenotypes seen in 22q11DS patients. Elegant studies of 22q11DS-related developmental mechanisms in mouse models (Scambler, 2010), either in constitutive heterozygous or homozygous nulls or following conditional ablation of the gene in cardiovascular or craniofacial anlagen (Liao et al., 2004; Nowotschin et al., 2006; Papangeli and Scambler, 2013) suggest that the activity of *Tbx1*, particularly via interactions with Fgf and RA signaling pathways, makes a substantial—perhaps singular—contribution to the cardiovascular anomalies associated with 22q11DS (Braunstein et al., 2009; Guris et al., 2006; Vitelli et al., 2002b). There is less clear evidence in human patients, independent of 22q11 deletion, that *TBX1* gene variants alone (no frank mutations have been reported, polymorphic alleles have been identified) can cause cardiovascular anomalies (Griffin et al., 2010; Rauch et al., 2010). The contribution of this key 22q11 gene to 22q11DS neural phenotypes, especially those that may underlie disorders of cortical connectivity, is apparently not as significant as that seen for cardiovascular anomalies. *Tbx1* is not significantly expressed in the developing or adult mouse brain (Meechan et al., 2009). In *LgDel* versus $Tbx1^{+/-}$ mice there are clear distinctions between hindbrain and cranial nerve alterations associated with disrupted feeding and swallowing. *LgDel* mice have anterior as well as posterior hindbrain and CN patterning defects during embryogenesis as well as feeding and swallowing deficits during early post-natal life. In contrast, $Tbx1^{+/-}$ have neither the anterior hindbrain patterning changes nor trigeminal nerve developmental phenotypes, and their post-natal weight gain is comparable to WT (Karpinski et al., 2014). Thus the impact of *Tbx1* versus broader 22q11 deletion seems to distinguish between posterior peripheral branchial/pharyngeal phenotypes (*Tbx1*) and anterior central nervous system phenotypes (broader 22q11 deletion in the *LgDel*).

Diminished dosage of *TBX1* during heart development in 22q11DS patients could indirectly affect cortical development. Perturbed heart formation could affect blood supply to the brain during development resulting in aberrant cortical gyral patterns or lamination including local PMG or PH that have been reported in 22q11DS patients. There is some evidence that heart anomalies in 22q11DS patients can exacerbate disrupted cortical gyral patterns and cortical volume (Schaer et al., 2009b, 2010). Nevertheless, changes in cortical structure are present even in 22q11DS patients who do not have congenital heart disease (Schaer et al., 2010) This indicates that *TBX1* alone, via cardiovascular disruption or other effects, is unlikely to be a singular causal gene for the full scope of 22q11DS phenotypes, including disorders of cortical circuit development. Our analysis of cortical basal progenitor phenotypes included parallel analysis of $Tbx1^{+/-}$ mice; however, we did not detect the change in basal progenitor proliferation in E14.5 $Tbx1^{+/-}$ mice that we found in *LgDel* mice. The lack of significant, or at least consistent, cortical disruption in $Tbx1^{+/-}$ mice is underscored by variable reports of behavioral anomalies or their absence in $Tbx1^{+/-}$ mice (Long et al., 2006; Paylor et al., 2006). Together, these observations indicate that while *TBX1* may interact with other 22q11 genes to yield phenotypes beyond cardiovascular and craniofacial defects that it clearly regulates, it is not a singular contributor to CNS anomalies relevant for disorders of cortical connectivity associated with 22q11DS.

11.2. PRODH and DGCR8

We, and others, have assessed the role of additional genes in cortical development and function to determine whether their diminished dosage might significantly impact specific cortical developmental mechanisms also disrupted in the *LgDel* mouse. We did not detect the basal progenitor proliferative defect seen in *LgDel* mice in $Prodh2^{-/-}$ mice, even though *PRODH2* has been suggested as a candidate gene for disorders of cortical connectivity in human association studies (Li et al., 2004; Ota et al., 2014) as well as analyses in the mouse (Paterlini et al., 2005). In $Dgcr8^{+/-}$ mice, which have diminished dosage of the *Dgcr8* gene product Pasha, a key regulator of nuclear processing of miRNAs (Denli et al., 2004), hippocampal and cortical dendritic differentiation is compromised, and capacity for spatial learning altered. Some of these findings remain controversial (Earls et al., 2012). Nevertheless, the developmental causes—if any—of these *Dcgr8* related phenotypes are uncertain. *Dgcr8* is not expressed in cortical progenitors making it less likely that the disruptions seen in $Dgcr8^{+/-}$ mutants reflect changes in cortical neurogenesis. It is possible that diminished *Dgcr8* dosage, via its influence on microRNA processing, compromises additional genes and networks that regulate synapse development, maintenance and function (Xu et al., 2013). Additional analysis of developmental changes, as well as their cellular and functional consequences in *Dgcr8* loss of function mouse models will help resolve the role of 22q11 gene dosage dependent microRNA regulation and its consequences for disorders of cortical circuit development.

11.3. RANBP1

We focused on another candidate gene in the 22q11 minimal critical deleted region, *Ranpb1*, based upon associations with cortical circuit disorders, as well as its developmental expression profile and its apparent cellular functions. *RANBP1* is included in a subdomain of the 22q11.2 minimal critical deleted region that has been linked independently to SCZ and other disorders of cortical circuit development (Liu et al., 2002a). In the mouse, *Ranbp1* expression is selectively enhanced in apparent neural crest derived cells in the periphery as well as apparent ventricular precursors at E9.5 and E10.5 (Maynard et al., 2002). At late stages of cortical development, *Ranbp1* mRNA as well as protein is highly expressed in the ventricular zones of the cerebral cortex and other forebrain regions (Maynard et al., 2003; Meechan et al., 2009). Based upon a small number of cell biological studies in non-neuronal cell lines, *Ranpb1* is one of several proteins (including GTPases, importins and exportins) that define the Ran complex, a key regulator of nuclear/cytoplasmic transport (Kehlenbach et al., 1999). *Ranpb1* is thought to be critical for the removal of cargo from the Ran complex following nuclear export.

Based upon its selective expression in apparent neural precursors, and its role in an essential cellular function key for cell cycle progression and nuclear integrity during chromosome segregation (Guarguaglini et al., 1997; Tedeschi et al., 2007), we asked whether *Ranbp1* might regulate cortical precursor

proliferation, especially for basal progenitors. We generated a *Ranbp1* mutant mouse carrying a null allele created via a gene-trap strategy. This novel targeted mutant mouse line allowed us to assess the obligate functions of *Ranbp1* in the developing nervous system (Paronett et al., 2014). We found that *Ranbp1* loss of function (*Ranbp1*$^{-/-}$) disrupts multiple aspects of embryonic development, and is not consistent with post-natal survival. A second null allele of *Ranbp1* has also been reported; however, these mice were generated on a mixed background. On this mixed background, *Ranbp1* mutation apparently results in at least 75% prenatal lethality for homozygous embryos. The 25% of mutants that are born live are dramatically reduced in size and have gross behavioral defects. The males are infertile, and females are significantly less fertile (Nagai et al., 2011). In our targeted null mutation, which is maintained on a pure C57Bl6-N line and 100% prenatally lethal, we focused on the developmental defects in the *Ranpb1*$^{-/-}$ embryos, especially those in the developing cerebral cortex. At least 50% of the *Ranbp1*$^{-/-}$ embryos are exencephalic from E10.5 onward. Those that are not exencephalic are microcephalic, and the cerebral cortex in these embryos appears particularly diminished in size (Fig. 9).

We next asked whether microcephaly reflected accelerated cell loss or retarded neuron proliferation in *Ranbp1*$^{-/-}$ embryos. We found no evidence of enhanced cell death in the cerebral cortex of *Ranbp1*$^{-/-}$ embryos. Thus we asked whether cortical progenitors were proliferatively compromised, and whether laminar cohorts of cortical projection neurons were generated in altered proportions. We found that during early stages of cortical development—prior to the onset of substantial neurogenesis—rapidly dividing radial glial progenitors are significantly less proliferative (Fig. 9; Paronett et al., 2014). Subsequently, as neurogenesis progresses and large numbers of projection neurons are generated, we found that the subset of rapidly dividing transit amplifying cortical precursors, the basal progenitors, were significantly less proliferative (Fig. 9). The slowly dividing apical progenitor/radial glial population did not appear disrupted at these later stages. These proliferative deficits resulted in a cortical lamination phenotype that resembled that in the *LgDel* mouse, but is significantly more severe. Thus, the frequency of layer 2/3 projection neurons is dramatically decreased, while that of layer 5/6 projection neurons does not decline significantly. Together, these observations suggest that *Ranbp1* acts in rapidly dividing precursors in the developing cortex. At early ages, loss of *Ranbp1* function may limit the overall pool of cortical radial glial progenitors, which are dividing rapidly at this time (Kriegstein and Gotz, 2003), resulting in a proportionately smaller cerebral cortex in *Ranbp1*$^{-/-}$ mice. At later ages, the rapidly dividing basal progenitors, which preferentially (but not exclusively) generate layer 2/3 projection neurons (Arnold et al., 2008; Sessa et al., 2008), are compromised.

These observations establish *Ranpb1* as a likely contributor to disrupted cortical development that prefigures altered cortical structure and function following 22q11 deletion. The coincidence

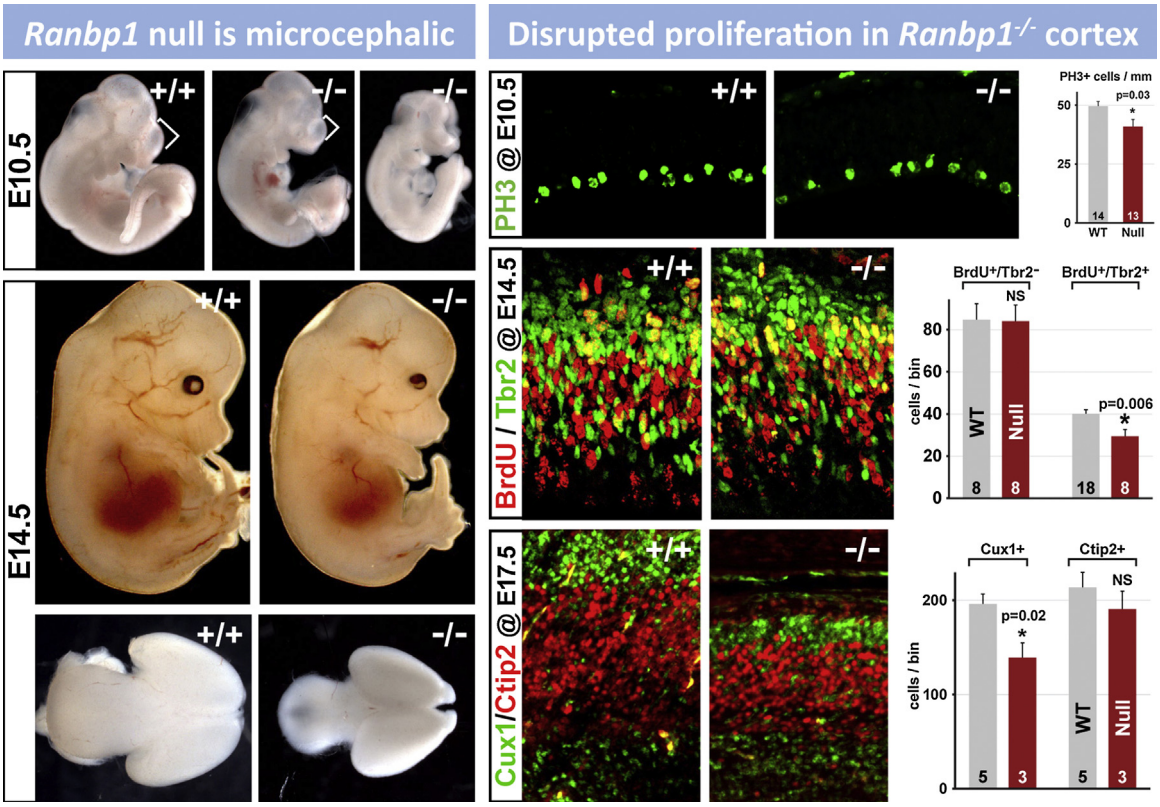

Fig. 9. *Ranbp1*, a 22q11 gene implicated in cell cycle control, is necessary for normal cortical development. (Top left) *Ranbp1*$^{-/-}$ embryos are dysmorphic at E10.5. Anomalies include a shortened telencephalic vesicle (bracket) and hypoplastic branchial arches. In addition, a subset of *Ranbp1*$^{-/-}$ embryos is exencephalic. (Bottom left) At E14.5 *Ranbp1*$^{-/-}$ embryos are visibly dysmorphic, including a smaller head and frequent eye defects. The brain, and particularly the cortex of *Ranbp1*$^{-/-}$ embryos is substantially smaller at E14.5, as shown in dorsal view. (Right) Cortical precursor proliferation and neurogenesis is disrupted in the *Ranbp1*$^{-/-}$ embryo. Proliferation of rapidly dividing neuroepithelial progenitors in the E10.5 *Ranbp1*$^{-/-}$ embryo is diminished, shown here using PH3 labeling of mitotically active precursors (top right). At later stages proliferation of rapidly dividing Tbr2+ basal progenitors in the E14.5 cortex is diminished, as evidenced by decreased numbers of Tbr2+/BrdU+ double-labeled cells (middle right). These proliferative defects prefigure an overall loss in cortical size, as well as a selective loss of layer 2/3 neurons (bottom right). This change is seen clearly in the E17.5 cortex. The frequency of layer 2/3 projection neurons (labeled with Cux1) is diminished; however, the frequency of layer 5/6 projection neurons (labeled with Ctip2) is not significantly changed.
Figure adapted from Paronett et al. (2014).

of developmental disruption by *Ranbp1* identified in mouse models, and its genetic association with vulnerability for SCZ (Liu et al., 2002a), independent of 22q11 deletion, further suggests that altered *RANBP1* function during development could contribute to the pathogenesis of disorders of cortical connectivity. We note that our analysis of cortical developmental phenotypes in heterozygous mutant *Ranbp1*$^{+/-}$ fetuses did not show significant changes in the proliferative capacity of basal progenitors. This indicates that *Ranbp1*, like many other 22q11 genes, is not likely to be simply haploinsufficient. Instead diminished dosage of *Ranbp1*, in concert with other 22q11 genes, may lead to disrupted mechanisms of cortical development seen in the *LgDel* mouse. If similar multi-genic, dosage-dependent mechanisms that include diminished *RANBP1* expression operate in 22q11DS patients during cortical development, they may result in altered cortical structure and behavioral deficits.

12. 22q11 deletion, disrupted cortical development, and behavior

Our observations show that the genesis and differentiation of cortical layer 2/3, especially in association cortical regions, is selectively compromised by diminished 22q11 gene dosage. These changes modify the mature organization of projection neurons and interneurons in layer 2/3, and may contribute to disrupted cortical connections, information processing, and behavior in 22q11DS. Developmental disruptions caused by 22q11 deletion result in phenotypes similar to adult pathological changes reported for the cerebral cortex in SCZ (Beasley and Reynolds, 1997; Beasley et al., 2002; Benes et al., 1991, 2001), and some preliminary assessments in ASD (Stoner et al., 2014; Zikopoulos and Barbas, 2013). In each instance, there is some laminar specificity, and layer 2/3 is either primarily compromised, or altered in parallel with layers 4, 5, and 6. It remains uncertain, however, whether the pathology seen generally in ASD and SCZ patients is due to primary developmental disruption or secondary degenerative changes. Furthermore, the key challenge that remains is to associate the developmental changes, behavioral changes and mature pathology as causally related in ASD, ADHD or SCZ. This challenge can be met using mouse models of 22q11 deletion in which analysis of development, mature anatomy and circuitry, and behavior can be integrated.

There is no doubt that 22q11 mouse models—those carrying the full deletion as well as several with either heterozygous or homozygous mutations in 22q11 genes—have significant behavioral deficits. 22q11DS mouse models recapitulate 'sensory gating' behavioral defects that are frequently observed in several disorders of cortical circuit development including SCZ (Braff et al., 1978; Hazlett et al., 2007). *LgDel* and other full deletion models (*Df1*, *Df(16)A*; Paylor et al., 2001; Stark et al., 2008) all have diminished pre-pulse inhibition (PPI), suggesting that normal sensory gating and its behavioral consequences are disrupted (Long et al., 2006). While informative, recent reports of aspiration-related inner ear infections (Fuchs et al., 2013; Karpinski et al., 2014) indicate that some of these changes in 22q11DS mouse models may be secondary to peripheral dysfunction.

It is also important to note that the specific relationship between PPI deficits and disrupted neural circuits remains uncertain. A recent study of PPI deficits in 22q11DS patients reported a modest, statistically insignificant trend toward altered gating compared to control subjects (McCabe et al., 2014). Nevertheless, it is difficult to discern how this behavioral deficit might ultimately relate to specific developmental disruptions that lead to disorders in cortical circuit development in 22q11DS. Single gene mutations—either heterozygous or homozygous—in a small number of individual 22q11 genes, *Tbx1*, *Comt*, *Sept5* and *Dgcr8*, might compromise behavior. Deficits have been reported for sensory/motor control (*Tbx1*; Long et al., 2006), social interactions (*Sept5*; Harper et al., 2012; Suzuki et al., 2009), anxiety/aggression (*Comt*; with added complexity of sex differences Gogos et al., 1998), and spatial memory (*Dgcr8*; Stark et al., 2008). Of this list, only the spatial memory deficits have been demonstrated in full 22q11 deletion models (*Df1* or *Df(16)A*; Paylor et al., 2001; Stark et al., 2008). These deficits have been variably correlated with changes in hippocampal synaptic plasticity, hippocampal/cortical oscillatory synchrony and dendritic spine differentiation in *Df(16)A* as well as *Dgcr8*$^{+/-}$ mice (Sigurdsson et al., 2010; Fenelon et al., 2013; Stark et al., 2008). In addition, cellular phenotypes in *Prodh*, *Zdhhc8* and *Dgcr8* mutant mice suggest these three genes—all of which have been independently linked to SCZ in human genetic association studies (Chen et al., 2012; Kempf et al., 2008; Zhou et al., 2013)—may have roles in synaptic function or maintenance (Jacquet et al., 2002; Mukai et al., 2004; Fenelon et al., 2011; Mukai et al., 2008; Stark et al., 2008). These studies have focused on deficits in mature mice, and thus do not address whether changes reflect developmental alterations versus disruption of mature function independent of developmental mechanisms. Furthermore, although informative, many of the behavioral assessments completed thus far lack specificity: the tasks cannot be easily associated with specific brain areas or circuits.

We sought to identify a behavioral task whose execution was associated with specific brain regions and connections, and for which deficits could be assessed in the context of potentially localized disruption of cortical circuitry. We also wanted to use a task that assessed a behavioral domain that was disrupted in 22q11DS patients, even though we fully recognize the substantial differences between behavioral capacities in mice versus humans. We selected a visual discrimination/reversal task (Fig. 10) that evaluates the murine equivalent of working memory and cognitive flexibility (Brigman et al., 2006; Brigman and Rothblat, 2008; Rutz and Rothblat, 2012). This task has the added feature of apparent cortical localization; distinct aspects rely upon the integrity of either the anterior cingulate/medial frontal anterior cortex (mFAC) (Brigman and Rothblat, 2008) or the orbitofrontal cortex in rodents (OFC; Bussey et al., 1997; Chudasama and Robbins, 2003). Thus, we could use this touch screen-based visual discrimination task to ask whether the *LgDel* mouse has cognitive deficits associated with particular cortical regions and circuits. We found that *LgDel* mice had a deficit in reversal learning, which relies upon the integrity of the mFAC (Brigman and Rothblat, 2008), rather than in cognitive flexibility, which relies on the OFC (Chudasama and Robbins, 2003). As a group, *LgDel* mice had significantly more learning errors during the reversal phase of the discrimination task (when the reward contingency was shifted to the previously unrewarded stimulus; Fig. 10). In addition, we noted an increased degree of variability in behavioral performance in the *LgDel* mice not seen in WT littermate controls (Fig. 10). We took advantage of this substantial variability to assess the relationship between phenotypes with developmental origins in distinct cortical regions—altered projection neuron frequency and interneuron placement—and behavioral performance. The degree of cognitive impairment in *LgDel* mice was significantly related to the diminished frequency of layer 2/3 projection neurons—but not interneurons—in mFAC (Fig. 10; Meechan et al., 2015). This relationship was not seen in another frontal association region, area 6 (Caviness, 1975), which includes motor association cortex. Apparently, diminished 22q11 gene dosage variably results in a genetic "lesion" of the mFAC that contributes to specific cognitive deficits similar to those seen with physical lesions to this cortical area.

Together, these observations in the *LgDel* and other 22q11DS mouse models confirm the utility of using animal models to understand the relationship between cortical circuit disruption, developmental changes, and behavioral consequences in disorders of

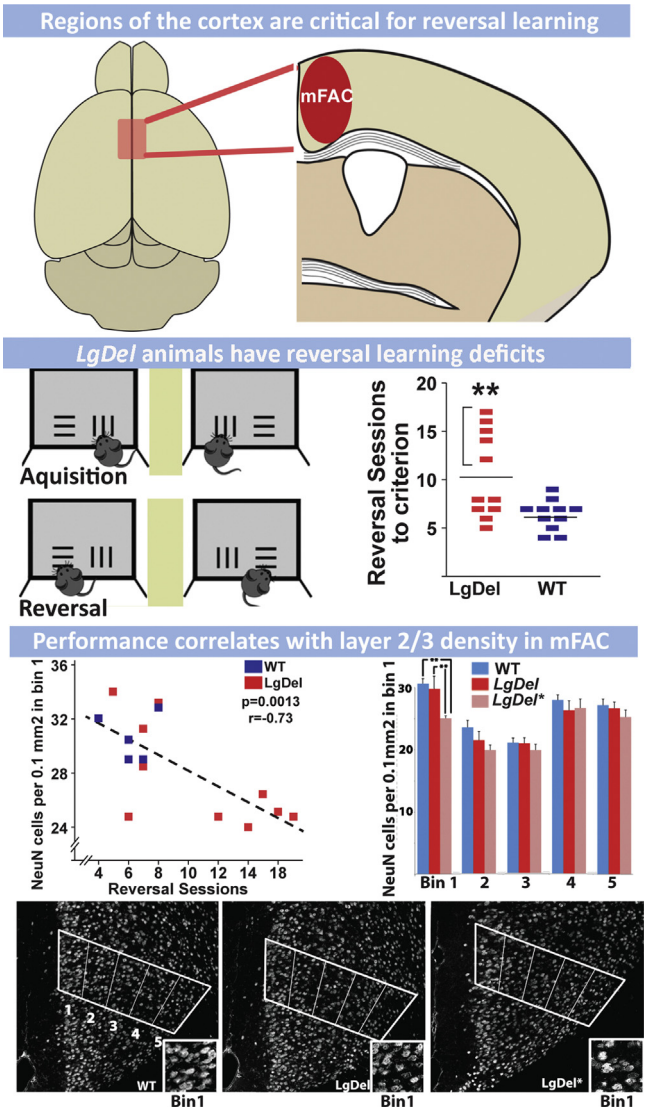

Fig. 10. Disruption of circuits in *LgDel* mice that engage the medial frontal association cortex (mFAC) is associated with cognitive deficits that rely on the integrity of mFAC. (Top row) Dorsal view of the mouse brain with the location of the mFAC highlighted in red. At right, the comparable area is indicated in a representation of coronal section of adult mouse cortex at mid-anterior levels (the level of the anterior commissure). (Middle row) At left, a touchscreen reversal task measures aspects of cognitive flexibility in WT as well as *LgDel* mice. During acquisition, the animals must correctly choose between horizontal or vertical bars to elicit a food reward. During the reversal phase, the reinforced stimulus is changed, and the animals have to learn that the previously reinforced contingency no longer elicits a food reward. At right: In *LgDel* mice, reversal learning takes significantly longer than in WT mice. There is, however, significant variability in performance in the *LgDel* animals that is not seen in WT. A subset of *LgDel* animals (indicated with a bracket) performs particularly poorly during the learning phase of the reversal task. (Bottom row) From the behaviorally tested animals, we observed that neuron density in upper layers of the mFAC (bin 1) correlated with reversal learning performance. A subset of *LgDel* animals had lower neuron density in bin 1 and performed particularly poorly during the task. At right, This 'behavioral subset' of *LgDel* animals is reported as its own group compared to normally performing *LgDel* animals and wild-type animals for NeuN density across 5 bins spanning all layers of the mFAC. There is a significant NeuN reduction in bin 1 for the behaviorally compromised *LgDel* animals. Tissue staining of the cortex of wild-type, normally performing, and poorly performing *LgDel* animals with an antibody for the neuronal marker, NeuN. Bin 1 density for neurons (upper layers) was notably reduced in the poorly performing *LgDel* animals.
Modified from Meechan et al. (2015).

cortical circuit development associated with 22q11DS. The substantial distinctions between mouse behavioral capacity and those in humans limit the comparisons that can be made between murine behavioral deficits and human cognitive pathology. The available data suggest that mouse models can be used to evaluate how specific aspects of cellular pathology lead to physiological and behavioral disruption, as illustrated by the analyses of *Dgcr8* and related models (Fenelon et al., 2011; Stark et al., 2008). Our work indicates how local regional distinctions in cortical developmental disruption can yield specific behavioral deficits (Meechan et al., 2015). Continued integrated analysis of behavioral, cellular, physiological and developmental changes should be able to answer questions that would remain unaddressed by studies of 22q11DS patients.

13. Models and hypotheses: 22q11DS disrupts association cortex circuit development

The increased incidence of developmental disorders (2014) and the ongoing challenges of managing these illnesses (Insel, 2010) underline an urgent need for new insight into diseases caused by disrupted cortical development and function. Human genetic analyses and non-invasive imaging approaches, integrated with careful behavioral and clinical assessment, has provided a strong foundation for understanding hereditary risk, neuropathology and behavioral consequences of ASD, ADHD and SCZ. These observations also indicate that disruption of circuit organization and function, focused on association cortical regions, likely caused by aberrant development, is shared across all of these disorders. To move forward from these foundational observations toward new opportunities for better diagnoses and therapies, there is clearly a need for new hypotheses of developmental pathogenesis, and new insight into pathological consequences that may actually identify targets for effective intervention. The available evidence, reviewed here, shows that 22q11DS has emerged as a paradigmatic genetic syndromic model of ASD, ADHD, and SCZ. Moreover, our work and that of several other groups shows that 22q11DS mouse models, either full deletions or single gene mutations, allow one to formulate and test mechanistic hypotheses about disrupted development and its consequences for circuit organization/function and behavior.

Our current data on developmental disruption, cellular, and behavioral consequences, combined with observations of apparent structural and functional anomalies in the cerebral cortex of 22q11DS patients suggest a new hypothesis for pathogenesis of disorders of cortical circuit development (Fig. 11). We suggest that these disorders arise, at least in 22q11DS, due to selective developmental changes that alter a network of connections made within and between association cortical areas, primarily via layer 2/3 projection neurons. The change in basal progenitor proliferation we found may reflect disrupted patterning that preferentially modifies anterior versus posterior cortical progenitors. This might lead to diminished proliferative capacity of basal progenitors in frontal association regions, which in the mouse at least, are key nodes for association cortical interconnectivity and higher order functions. Alternately, the expansion of the SVZ niche defined by basal progenitors in domains that generate association cortices may be differentially compromised by a general change in basal progenitor proliferative activity. If increased frequency of basal progenitors in these domains yields enhanced frequency of layer 2/3 projection neurons in mature association regions, then layer 2/3 neurogenesis, and subsequent cortico-cortical connections made by these cells, would be disproportionately compromised. Either mechanism could lead to "under-connectivity" proposed for ASD and other disorders of cortical circuit development (Casanova et al., 2002; Courchesne et al., 2001). Such changes could contribute to altered activity in resting state networks that is also common in ASD, ADHD, and SCZ (Kennedy et al., 2006; Whitfield-Gabrieli et al., 2009). This hypothesis would be untestable in human patients, but can be evaluated using 22q11DS mouse models.

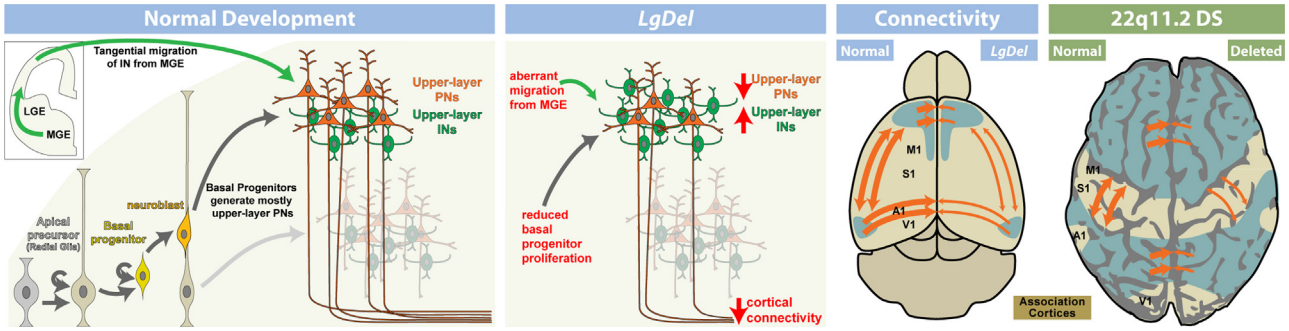

Fig. 11. A hypothesis of disrupted development that could underlie disorders of cortical circuit development associated with 22q11DS. (Left) A schematic of normal development indicating normal mechanisms of basal progenitor proliferation that insure appropriate numbers of layer 2/3 projection neurons as well as migratory mechanisms that mediate appropriate placement of key subsets of GABAergic interneurons. (Left middle) Changes in layer 2/3 projection neuron frequency lead to diminished cortico-cortical connectivity normally made by these neurons, while local alterations in excitatory/inhibitory balance due to disrupted migration and placement of GABAergic interneurons modifies local processing of information in layer 2/3. (Right middle) These changes lead to under-connectivity, especially between cortical association regions in the *LgDel* mouse. (Right) Similar changes may lead to underconnectivity in frontal, parietal and temporal association cortical regions in 22q11DS patients.

14. Modeling models: a translational foundation for understanding disorders of cortical circuit development

Disorders of cortical circuit development are likely to remain among the most costly and difficult to manage chronic diseases in the foreseeable future. While currently available treatments—both pharmacological and cognitive—offer some relief from symptoms (Lai et al., 2014; Miyamoto et al., 2012), there is a general lack of therapies that prevent symptoms, or correct key deficits. The variability seen among non-syndromic patients with ASD, ADHD, SCZ and related disorders of cortical circuit development argues strongly that efforts to study pathology and identify new therapeutic options will be complicated by "signal to noise" concerns (Haar et al., 2014). Accordingly, identifying model syndromes that provide a potentially more homogeneous population of subjects emerges as an absolute necessity to move the field forward. We have provided a summary of how 22q11DS, based upon its genetics and clinical manifestations in humans, provides a tractable and informative model syndrome to understand the pathology of the wider spectrum of disorders of cortical circuit development. We have summarized the current state of modeling this model in genetically modified mice to identify how a genetic lesion in mice that parallels that in 22q11DS disrupts critical processes in cortical development to alter circuit structure and function. As more genetic insights are gained into disorders of cortical circuit development, we suggest that this approach of "modeling the model" will continue to provide insight into the developmental pathogenesis of new model genetic syndromes—associated with either single gene mutations or CNVs—identified in humans whose developmental origins cannot be studied in humans. Furthermore, a thoroughly characterized catalog of animal models for genetic syndromes that yield ASD, ADHD, SCZ and other disorders of cortical circuit development will be an essential resource to develop new, targeted therapies that provide improved clinical management for patients with these disorders.

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