CHAPTER

30

Down Syndrome

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OUTLINE

30.1 INTRODUCTION

Trisomy of human chromosome 21 (HSA21) is the genetic basis of Down syndrome (DS). DS is associated with a spectrum of developmental disabilities and physiological and health disturbances of varying penetrance. Despite the variability of DS-associated phenotypes, all individuals express some degree of intellectual disability. Triplication of a large number of genes on one human chromosome has made basic research into the molecular genetics and the cellular and neuropathological basis quite challenging. Yet advancing our understanding of DS pathophysiology as well as identifying new interventional strategies requires living animal and cellular models. Herein lies the challenge; how can one most accurately model a disease caused by trisomy of an entire

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human chromosome containing more than 400 individual genes? The best solution to date has been to duplicate large segments of syntenic regions of mouse chromosomes that carry subsets of genes located on HSA21. Alternatively, the insertion of segments of HSA21 into the mouse has also been employed to define specific genes that underlie aspects of the DS phenotype. Mouse models are, therefore, immensely valuable in deciphering genetic interactions of conserved human disease genes. But as the number of genes being studied grows, so does the risk of species-specific differences confounding the application of what can be learned in the mouse to the human disease. The recent advent of induced pluripotent stem cell (iPSC) technology offers the promise of human cellular models of DS that have full trisomy 21.

This chapter begins in Section 30.2 with a description of the DS genetic and clinical phenotypes, with an emphasis on neurological features. Section 30.3 details the experimental models of DS, with an emphasis on their utility and accuracy for translation to the human condition. Section 30.4 describes our current understanding of the neuroanatomical and functional correlates of the DS phenotype, with an emphasis on comparing research from experimental models with what is known about the human phenotype. These DS endophenotypes span both time (from embryonic neurodevelopment to adult aging) and scale (from molecular and cellular aspects up to local circuits and systems neuroscience). Section 30.5 outlines genotype–phenotype correlations in DS and the contribution of specific HSA21 genes as well as other genetic interactions with the DS endophenotypes. The chapter concludes with a discussion of directions for future research using iPSCs and consideration of potential therapeutic interventions.

30.2 DS MOLECULAR GENETICS AND CLINICAL PHENOTYPE

30.2.1 Trisomy of Human Chromosome 21 and the Molecular Genetics of DS

Euploid human cells contain 46 chromosomes (2N), including 22 pairs of autosomes and one pair of sex chromosomes (46,XX [female] and 46,XY [male]). Haploid human cells contain 23 chromosomes (N), which is characteristic of normal ovum and spermatozoa. Typical development is dependent upon the gene content of these chromosomes as well as chromosomal balance. Cells that do not contain an exact multiple of the haploid number of chromosomes are termed *aneuploid cells*. This abnormal chromosomal distribution is the most common and clinically significant type of human chromosome abnormality, occurring in 3–4% of all pregnancies (Lee and Summar, 2009). Human aneuploidies include monosomies (one copy of a particular chromosome) and polysomies (more than two copies of a particular chromosome). The majority of aneuploid conceptuses are spontaneously lost during the first trimester of pregnancy. Nondisjunction is the most common mechanism of aneuploidy. When nondisjunction occurs, during meiosis I or meiosis II, gametes are created that either contain an extra chromosome or lack a copy of a chromosome. During conception, these abnormal cells combine with haploid gametes and result in monosomic or trisomic zygotes (Figure 30.1). Nondisjunction occurring later during mitosis results in a mosaic cell line. In addition to nondisjunction, chromosomal rearrangement such as translocation, partial duplication, and ring chromosome formation can result in aneuploidy.

Trisomy 21 is the quintessential example of aneuploidy in humans and results in the clinical phenotype of DS. This mechanism is responsible for the most common genetic cause of intellectual disability, occurring in 1 in 833 live births and making DS an excellent model for studying the relationship of genetics to neural function (http://www.cdc.gov/features/dsdownsyndrome). Individuals with DS have variations in neurodevelopment and neurodegeneration as well as disorders involving the central nervous system and other systems of the body. To further explore the complex relationship between aneuploidy, human development, and the clinical phenotype of DS, many researchers from diverse disciplines, including biologists, educators, physicians, and psychologists, have investigated pieces of the puzzle. A comprehensive review of all of these areas is beyond the scope of this text. The focus of this discussion is the influence of molecular genetics on the neurological phenotype of DS.

To elucidate the origins of the phenotypic features, scientists have approached aneuploidy and DS with the assumption that if a gene is present in three copies, the expression of that gene will be increased. The gene dosage hypothesis states that the increased expression of multiple trisomic genes directly leads to the features of DS (Antonarakis et al., 2004; Korbel et al., 2009). The amplified developmental instability hypothesis states that the phenotype is not directly due to specific genes on chromosome 21 but rather to a change in genetic balance and regulation (Patterson and Costa, 2005). Evidence of globally increased expression of genes on chromosome 21 in human fetal material has been documented by measuring mRNA levels (Mao et al., 2003). These same transcriptome studies failed to document the increased expression of genes not found on chromosome 21 in the same tissues. Proteomic studies have documented that mRNA from genes mapped to chromosome 21 translates into increased protein production in transgenic mice as well as in human tissues (Gulesserian et al., 2001; Tan et al., 1973; Wang et al.,

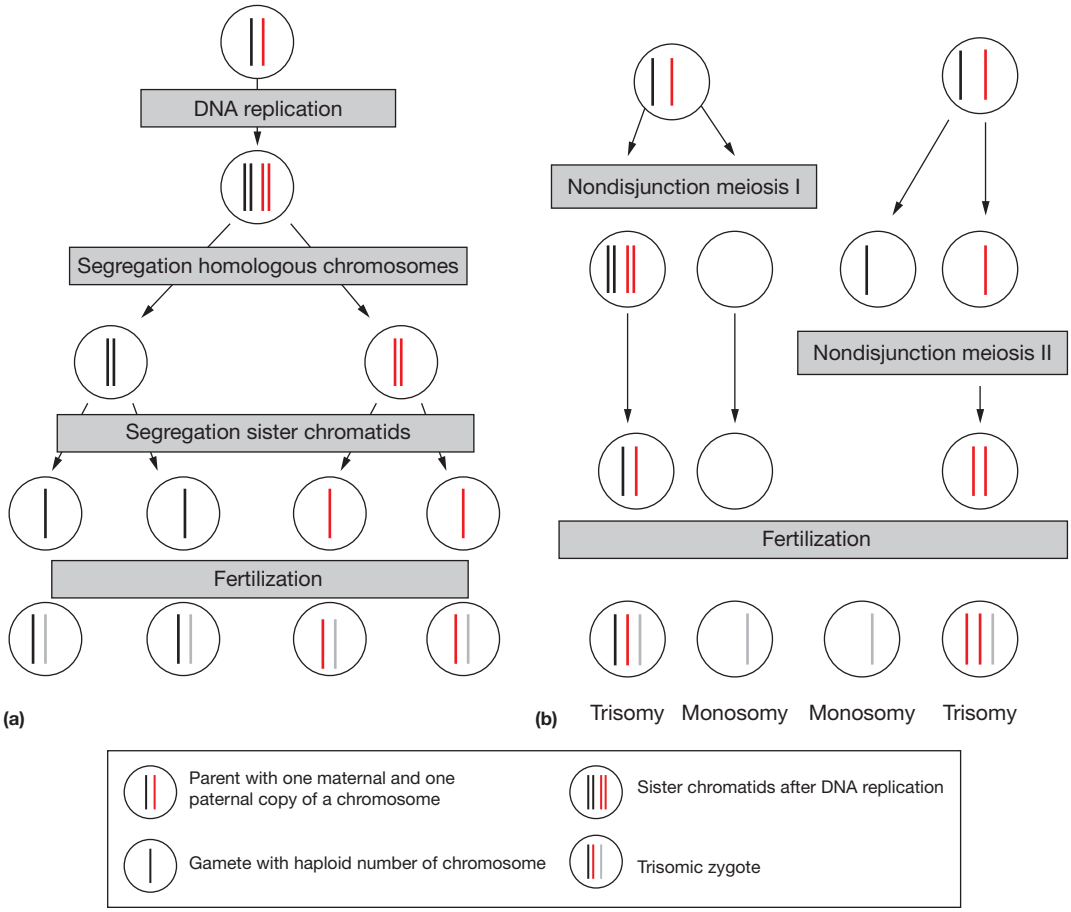

FIGURE 30.1 Meiotic nondisjunction. (a) Normal meiosis results in gametes with a haploid number of chromosomes. When fertilized with other normal gametes, a normal diploid state is reestablished. (b) In meiotic nondisjunction, two chromosomes migrate to the same daughter cell resulting in gametes with a diploid (or null) number of chromosomes. When fertilized with other normal gametes, abnormal trisomic or monosomic states are established. (a, b) Symbol key is provided in the box at the bottom of the figure.

1998). Recently, posttranscriptional regulators, including miRNAs, have been found to be overexpressed in DS brain and heart tissue specimens, resulting in a decreased expression of target genes, which very likely contributes to the DS phenotype (Kuhn et al., 2008).

Not only gene dosage, a factor in the phenotype of DS, but also gene content plays a crucial role. In 2000, through the collaborative work of many investigators, the complete DNA sequence of human chromosome 21 was published. This landmark work showed that human chromosome 21 is a relatively gene-poor chromosome, with 225 genes embedded in 33.8 Mb of genomic DNA compared with the 545 genes embedded in 33.4 MB of chromosome 22 (Hattori et al., 2000). With new sequencing technology, the number of genes on the human chromosome is now thought to be between 300 and 500 (http://www.ensembl.org). This finding of comparatively few genes on chromosome 21 offers a possible explanation of why trisomy 21 is compatible with postnatal survival and longevity whereas trisomy of HSA13, HSA15, and HSA22 are not. Finally, allelic variation of chromosome 21, epigenetic factors, mosaic status, and environmental effects must be taken into consideration when studying the correlations between the genotype and phenotype of DS. There are some aspects of the phenotype of trisomy 21 that appear consistently in every individual with DS (i.e., facial appearance, intellectual disability, and generalized hypotonia). However, each of these common phenotypic features exhibits a great deal of variability in expression from one individual to another (e.g., intellectual disability ranges from mild to moderate cognitive impairment). Clearly, more work is needed to fully understand all the factors involved in these variations.

30.2.2 Neurodevelopmental and Neurodegenerative Features of the DS Phenotype

Historically, DS has been the prototypical intellectual disability disorder in research as well as in societal portrayals and thus implies a nonspecific alteration in brain

development and pathology. However, DS is associated with distinct neuroanatomic and neuropathologic findings that in turn present with specific cognitive deficits. Postmortem observations (Crome et al., 1966; Davidson, 1928; Wisniewski et al., 1985) and volumetric magnetic resonance imaging (MRI) studies (Aylward et al., 1997b, 1999; Emerson et al., 1995; Pearlson et al., 1998; Raz et al., 1995) indicate that people with DS have reduced total brain volumes, most notably in the frontal and temporal areas as well as the cerebellum. Altered temporal volume, architecture, and function in DS (particularly of the hippocampal area) are considered to be responsible, in part, for the cognitive deficits associated with DS (Pennington et al., 2003). Disturbances in cerebellar volume and architecture are associated with the generalized hypotonia of DS as well as the inability to learn new skills (Daum and Ackermann, 1995; Konczak and Timmann, 2007). A similar finding of reduced hippocampal volume in children with DS suggests that these are neurodevelopmental findings rather than neurodegenerative findings of an aging brain (Pinter et al., 2001a). By contrast, people with DS have normal volumes of subcortical areas, including the lenticular nuclei and posterior parietal and occipital gray matter.

Interest in the neuropathology of DS existed long before the genetic etiology was delineated. Pathologic findings characteristic of those seen in dementia of the Alzheimer's type were described in the brains of individuals with DS long before the normal number of human chromosomes was even determined (Jervis, 1948; Struwe, 1929). It is now known that virtually all adults with DS who have come to autopsy have the hallmark neuropathology of Alzheimer disease (AD), with prominent β-amyloid plaques and neurofibrillary tangles (NFTs). Furthermore, decreased numbers of apical dendritic spines of pyramidal neurons in the hippocampus and cingulate gyrus were noted when comparing the brains of people with DS to those of normal controls (Becker et al., 1986; Takashima et al., 1994). Significantly reduced dendritic spines, increased β-amyloid plaques, and increased NFTss in DS are considered to be specific findings that are not seen in other types of intellectual disability (Suetsugu and Mehraein, 1980).

Like the gross anatomical and histological findings, the cognitive phenotype found in individuals with DS is specific (Silverman, 2007). Cognitive deficits in DS are not uniform across all domains. Particular deficits exist in learning, memory, and language that lead to difficulty with intellectual functioning. To further complicate this issue, a great deal of variability exists between individuals. People with DS have difficulty with verbal short-term memory and explicit (episodic or conscious) long-term memory (Lott and Dierssen, 2010; Silverman, 2007). The function of explicit memory has been linked to the hippocampus (Squire, 1992), which has been shown to function abnormally in DS (Pennington et al., 2003). Implicit memory – the ability to use previous experience to assist with the performance of a task without conscious awareness – is preserved in DS (Carlesimo et al., 1997). Prefrontal cortex function also affects explicit and working memory and has been shown to have deficits in DS (Nadel, 1999). This impairment seems to involve verbal information with sparing of visuospatial domains, offering a potential explanation of why people with DS learn better in an environment that includes visual materials in addition to verbal presentation (Frenkel and Bourdin, 2009; Lanfranchi et al., 2009). Morphology of grammar (internal structure of words) and syntax (how words are put together in phrases) are impaired in people with DS. The communication difficulties are specific to DS when compared to others with intellectual disabilities and mental age-matched controls. Communication is further complicated for people with DS because intelligibility is negatively affected by poor oral motor tone and anatomic factors of the mouth and pharynx (Abbeduto et al., 2001). New technologies, including functional imaging techniques such as functional MRI (fMRI) and spectroscopy, should allow for further studies of correlations between described cognitive and language deficits and brain function in humans with DS.

Longitudinal studies with adults with DS reveal the onset of cognitive decline (from baseline) in middle age similar to that seen in much older individuals without intellectual disability (Devenny et al., 1996, 2000). These observations along with the knowledge of the ubiquitous presence of amyloid plaques and NFTs in postmortem trisomy 21 specimens have led to many investigations into the risk of Alzheimer's type dementia in people with DS. Multiple studies of varying design have established that approximately 50–70% of adults with DS will develop dementia by age 60–70 years. Importantly, an alternative statement of these data is that some individuals with DS will survive dementia-free into old age (Devenny et al., 1996).

Understanding the genotype–phenotype relationship in DS may lead to a greater understanding of neurodevelopment and neurodegeneration through mechanisms involved in the gene dosage effect as well as gene balance and regulation. This has obvious application to the continued improvement of the lives of people with DS, but it may also lead to novel therapies for the general population that suffers from neurodevelopmental as well as neurodegenerative disorders of the central nervous system.

30.2.3 Other CNS Features of DS

As noted in Table 30.1, people with DS have increased risk for seizures, psychiatric disorders, and Alzheimer dementia. Alzheimer dementia was discussed in the

TABLE 30.1 Common medical comorbidities in children with Down syndrome

System	Finding
Ears, eyes, nose	Hearing loss (conductive and sensorineural), frequent and chronic otitis media, obstructive sleep apnea, glaucoma, cataracts (congenital and acquired), refractive errors, strabismus, nystagmus, amblyopia
Cardiovascular	Atrioventricular septal defect, ventricular septal defect, atrial septal defect, patent ductus arteriosus, tetralogy of Fallot, and persistent pulmonary hypertension; adolescents and young adults – mitral valve prolapse and aortic regurgitation
Endocrine	Diabetes mellitus, hypothyroidism, hyperthyroidism
Gastrointestinal	Constipation, celiac sprue (25%)
Hematological	Transient myeloproliferative disorder, leukemia
Neurological	Intellectual disability (mental retardation); hypotonia, seizures; psychiatric disorders, autism spectrum disorder
Orthopedic	Atlantooccipital instability, pes planus, subluxation of patella, developmental hip dysplasia
Dermatological	Hyperkeratosis, seborrhea, cutis marmorata, xerosis, folliculitis

previous section and will not be addressed here. Seizures have a bimodal distribution in DS with 40% of seizure disorders presenting in the first year of life and another 40% present in the third decade or later (Pueschel et al., 1991). Epilepsy in the very young can manifest as infantile spasms or generalized tonic clonic ('grand mal') seizures. Infantile spasms due to any etiology are associated with hypsarrhythmia, a specific electroencephalographic finding, and infants with DS and infantile spasms have more frequent diagnoses of an autism spectrum disorder later in life (Eisermann et al., 2003). Seizures presenting in adolescents and adults can be generalized tonic clonic or partial ('petit mal'). Both types of seizures are usually accompanied by some alteration of mental status that can be brief. This has led to missed diagnoses in people with DS as the seizures may be ascribed to a lack of focus or attention. Finally, age of seizure onset appears to be important in DS as adults older than 45 years are more likely to develop dementia, whereas early onset of seizures is not associated with dementia (Lott and Dierssen, 2010; Puri et al., 2001).

Behavioral and psychiatric disorders are more common in people with all intellectual disabilities when compared to the general population. However, people with DS score significantly lower on maladaptive behaviors when compared to people with other cognitive disabilities (Dykens and Kasari, 1997). Children with DS, for example, are frequently diagnosed with disruptive behaviors including attention deficit hyperactivity disorder, oppositional defiant disorder, or aggression (Myers and Pueschel, 1991). Less is known about behavioral and psychiatric problems in adolescents with DS. Preliminary data show that they may have fewer externalizing (disruptive) behaviors than their younger cohorts (Dykens et al., 2002). Adults with DS are more prone to depression when compared to the typical population and to others with intellectual disabilities (6–11% compared to 1–2%; Collacott et al., 1992). Historically, 'diagnostic overshadowing' has led to a failure to recognize co-occurrence of psychiatric illness in individuals with intellectual disability (Reiss et al., 1982). With improved recognition of these secondary disorders in this population, prompt treatment and eventually even more effective therapies may be discovered.

30.2.4 Non-CNS Features of DS

Some medical comorbidities occur more often in people with DS as compared to their typically developing peers, including congenital heart disease (100-fold increase; Ferencz et al., 1985), leukemia (30-fold; Hasle et al., 2000), and Alzheimer dementia (10-fold increase in DS; Zigman and Lott, 2007). Of the congenital heart lesions, the most common lesions are atrioventricular septal defects (45% of newborns with DS), ventricular septal defects (35%), atrial septal defects (8%), patent ductus arteriosus (7%), tetralogy of Fallot (4%), and others (1%) (Roizen and Patterson, 2003). Due to the prevalence of congenital heart disease in DS, the American Academy of Pediatrics recommends an echocardiogram and pediatric cardiology evaluation in every newborn with DS regardless of the presence of symptoms or physical findings (American Academy of Pediatrics and Committee on Genetics, 2011). Hearing loss (both conductive and sensorineural) and visual disturbances (glaucoma, cataracts, strabismus, myopia, astigmatism) occur with much more frequency in people with DS and can present in infancy through adulthood. For these reasons, vigilant screening of vision and hearing is recommended to prevent further deleterious effects on intellectual and adaptive functioning (American Academy of Pediatrics and Committee on Genetics, 2011; Roizen, 2002; Smith, 2001).

Advances in medical care have improved survival for people with DS (increasing from an average of 12 years in the 1940s to an average of 57.8 years for women and 61.1 years for men) (Bittles et al., 2007; Glasson et al., 2003). Despite this improved survival, there are many physical problems involving every organ system of the body that can affect people with DS. Additional studies are needed to better understand the impact of these

comorbidities on the intellectual and adaptive functioning of people with DS.

Just as secondary medical conditions can occur with increased frequency in DS, there are comorbidities that appear to be less common in DS than in the general population. For example, analysis of the causes of deaths between these groups revealed that mortality due to ischemic heart disease is less than one half and deaths due to solid tumors less than one tenth in DS patients compared to the general population (standardized mortality odds ratio of 0.42 and 0.07, respectively, for causes of death; Yang et al., 2002). Review of cancer registries has confirmed that people with DS have fewer solid tumors even though they have an increased risk of leukemia (Hasle et al., 2000). Two candidate genes from HSA21 have provided potential mechanisms for this 'protective factor' against solid tumors. The first gene is the Down syndrome candidate region 1 (DSCR1/RCAN1), which is a calcineurin inhibitor. DSCR1 is modestly overexpressed in transgenic mice, and this overexpression is sufficient to provide suppression of tumor growth by inhibiting angiogenesis by attenuation of calcineurin activity (Baek et al., 2009). Other mouse studies have implicated the upregulation of the oncogene Ets 2 as a possible factor in the prophylactic effect of trisomy 21 on solid tumor development (Sussan et al., 2008). Further studies need to be done to clarify this apparent advantage in cancer among people with DS and distinguish genetic from environmental differences. Potentially, novel therapeutic interventions for cancer in the general population could be designed by a better understanding of DS.

30.3 EXPERIMENTAL MODELS OF DS

30.3.1 Overview of DS Mouse Models

The need for animal models to study human development and disease has been recognized for millennia dating back to at least the time of Aristotle and Galen (Guerrini, 2003). The incredible pace of research during the last half century has allowed the creation of increasingly sophisticated and relevant animal models of many diseases. The mouse has become the favored model system given the well-defined anatomy and physiology of this species; completely sequenced genome; availability of robust quantitative assays of learning, memory, and anxiety; as well as a huge inventory of available tools including specific antibodies and genetic engineering to modify the mouse genome. This latter development continues to improve with refined and subtle manipulations now routine. However, modeling the complexity of a chromosomal human disease such as DS in the mouse has proven to be very difficult. This is due largely to evolutionary differences between mice and humans in the sequence, expression patterns, and function of many genes. Furthermore, HSA21 is not present in a direct orthologous fashion in mice as genetic material corresponding to that found on HSA21 is found mainly on mouse chromosomes 16 (Mmu16) but also on Mmu10 and Mmu17. Conversely, additional genes on Mmu16, Mmu10, and Mmu17 are not found on HSA21 and thus are likely not relevant to the study of DS. These evolutionary changes have made a 'simple' mouse model of DS very challenging. However, recent advances to allow complex genomic engineering have recently been achieved, leading to the recent creation of a mouse with trisomy of almost all the genetic information that is normally found on HSA21 (Yu et al., 2010). These models will likely be most informative when combined with single-gene knockouts to test whether three copies of specific genes contribute to the pathogenesis of DS and whether decreasing gene dosage can reverse the clinical features. Such findings would provide a clear rationale to selectively target identified pathways pharmacologically (Table 30.2).

30.3.2 DS Mouse Models with Mouse Additional Segments

Initial attempts to model DS reasoned that most HSA21 genes are found on a syntenic region of mouse chromosome 16. Animals with balanced chromosomal translocations were identified and then selectively bred to generate an Mmu16 trisomy mouse. These mice died *in utero*, likely because of cardiac and placental abnormalities (Miyabara et al., 1982). Additional relevant phenotypes include generalized edema and delayed development of the cerebral cortex. While these results strongly support that genes present on a syntenic region of HSA21 in the mouse are required for normal development, their lack of viability severely hampered further progress and determination of the relevance to DS. Furthermore, Mmu16 trisomy is unable to provide any information about the role of HSA21 orthologs found on Mmu10 and Mmu17. Finally, as Mmu16 contains multiple genes not found on HSA21, any results from these mice have to be interpreted with caution.

A major advance in DS research was the generation of a mouse with a balanced translocation of Mmu16 that corresponded closely to the syntenic region of HSA21 (Figure 30.2). Selective breeding of these animals allowed the generation of Ts65Dn mice that are trisomic for about 14 Mb of mouse DNA and contain the majority (at least 132) of the genes on HSA21 (Holtzman et al., 1996). Ts65Dn mice, however, have significant limitations including some mortality during early postnatal life and phenotypic variability. In addition, males are infertile, complicating the maintenance of this mouse

TABLE 30.2 Mouse models of DS

	Triplication	Abnormalities	Limitations	Reference
Mouse chromosome				
Mmu16	Entire Mmu16	Edema, abnormal cerebral cortex, heart defects, thymic hypoplasia	Lethal *in utero*, no Mmu10 and Mmu17 genes	Miyabara et al. (1982)
Ts65Dn	Partial Mmu16	Some perinatal death, cerebellar hypoplasia, cortical and hippocampal spine alterations, craniofacial dysmorphology	Perinatal death, no cardiac abnormalities, hyperactive, no Mmu10 and Mmu17 genes	Holtzman et al. (1996)
Ts1Cje	Partial Mmu16	Cerebellar hypoplasia, craniofacial dysmorphology, hippocampal spine alterations	No cardiac abnormalities, hypoactive, no Mmu10 and Mmu17 genes	Sago et al. (1998)
Ts1Rhr	Partial Mmu16	Increased size of mandible	Lack of CNS and cardiac phenotypes??	Olson et al. (2004)
Ms1Rhr	Deletion partial Mmu16	None	Lack of CNS phenotype	Olson et al. (2007)
Duplication of human chromosome				
Tc1	Extra copy of HSA21	Decreased density of cerebellar granule neurons, cardiac defects	Variable penetrance likely due to mosaicism	O'Doherty et al. (2005)
Chromosomal engineering				
Ts1Yah	Mmu17	Impaired working memory, enhanced spatial memory	No Mmu16 genes	Pereira et al. (2009)
Dp(10, 16, 17)	Mmu10, Mmu16, Mmu17	Impaired cognition, hippocampal-mediated deficits, hydrocephalus	Only initial characterization to date	Yu et al. (2010)

colony. While Ts65Dn mice exhibit no cardiac defects, over the years they have proven invaluable because of CNS and craniofacial abnormalities (Kurt et al., 2000; Roper et al., 2006b). The brain abnormalities include a small cerebellum with decreased numbers of granule neurons and Purkinje cells (Baxter et al., 2000). In addition, decreased spine density was seen on dendrites from hippocampal dentate granule neurons (Belichenko et al., 2004). The failure of Ts65Dn mice to more closely phenocopy DS should not be too surprising given the complexity of this syndrome and the lack of triplication of many additional orthologous genes that reside on Mmu10 and Mmu17. The Ts1Cje model (Figure 30.2) has also been used by many investigators and features a partial trisomy of Mmu16 though the region is smaller than in Ts65Dn containing approximately 85 orthologous genes (Sago et al., 1998). These mice have CNS abnormalities similar to those seen in Ts65Dn, including small cerebellums and abnormalities in the number of cerebellar granule cells, but not Purkinje neurons. Similar to Ts65Dn, decreased spine density with dendritic spine enlargement was seen in this model (Belichenko et al., 2007). Multiple histogenic and physiological processes have been examined in these mouse models, revealing important insights into a spectrum of DS-relevant phenotypes (see Sections 30.3.3 and 30.4 for more details).

While models with triplication of Mmu16 continue to provide important information about global DS phenotypes and preclinical testing, additional mouse models are clearly needed to more finely define genetic requirements for the pathogenesis of DS. Also, other models were needed to test the emerging hypothesis that trisomy of a 'critical region' of HSA21 (Down syndrome critical region, DSCR) is sufficient or required for the phenotypes seen in DS. This hypothesis was based on the identification of rare patients with DS that appeared to have trisomy of a relatively discrete region of HSA21. This hypothesis has been more rigorously tested in mice using Cre/LoxP technology to duplicate (Ts1Rhr) or delete (Ms1Rhr) an approximately 4-Mb region of Mmu16 containing the approximately 33 orthologous genes found in the DSCR (Olson et al., 2004). Interbreeding with wild-type mice then allows the production of animals with one or three copies of the mouse DSCR. A particularly elegant application of this technique was to breed Ms1Rhr mice to Ts65Dn or Ts1Cje mice. This allowed the generation of mice that were trisomic for genes within Ts65Dn or Ts1Cje but disomic within the DSCR. These Ms1Rhr/Ts65Dn mice did not reverse abnormalities of cranial morphology, and Ts1Rhr mice that were trisomic for just the DSCR also did not exhibit cranial abnormalities (Olson et al., 2004). CNS

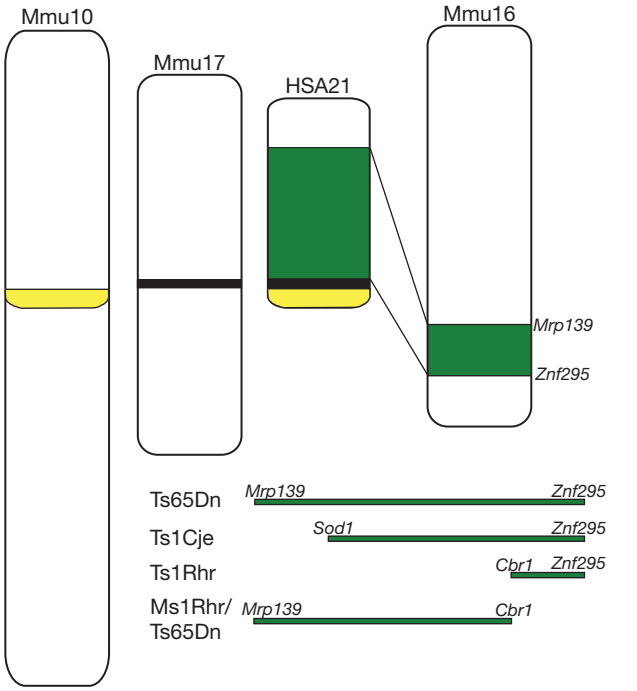

FIGURE 30.2 Schematic of human and mouse chromosomes relevant to DS and comparison of the most commonly used mouse models. The majority of HSA21 orthologous genes are located on Mmu16 but they can also be found on Mmu10 and Mmu17. The commonly used Ts65Dn, Ts1Cje, Ts1Rhr, and Ms1Rhr/T65Dn mouse models of DS feature triplication of variable segments of Mmu16 as shown. The Ts1Rhr region contains the 'Down syndrome critical region' (DSCR). The names of specific genes are listed to denote the approximate beginning and end of each Mmu16 segment.

manifestations have not been extensively studied though trisomy of the DSCR in Ts1Rhr mice was insufficient to produce abnormalities of spatial learning (Olson et al., 2007). However, removing the DSCR region with Ms1Rhr/Ts65Dn mice reversed hippocampal-dependent memory deficits. In addition, detailed analyses of Ts1Rhr mice revealed an increased size of dendritic spines and decreased spine density as seen in Ts65Dn or Ts1Cje mice (Belichenko et al., 2009a,b). These models demonstrate that despite its name, genes within the DSCR are not sufficient for the craniofacial abnormalities and some of the CNS manifestations seen in DS. This approach again underscores a complex interplay of genes in the DSCR with non-DSCR genes located on Mmu16 as well as Mmu10 and Mmu17. A further study of the DSCR was recently reported with overexpression of *RCAN1* (Dierssen et al., 2011). These mice have disruptions in visual–spatial learning similar to that seen in people with DS.

A similar technique of chromosomal engineering was used to make Ts1Yah mice that are trisomic for the syntenic region of Mmu17 including 12 orthologous genes found on HSA21 (Pereira et al., 2009). These mice have learning and behavioral abnormalities but enhanced spatial learning, which is typically a hippocampal-dependent process. These somewhat contradictory results firmly support the need for animal models that have genetic alterations of genes outside of Mmu16 and further underscore the complexity inherent to DS.

The most exciting recent advance using chromosomal engineering was the creation of a mouse model that is trisomic for essentially all the relevant portions of Mmu16, Mmu10, and Mmu17 that correspond to HSA21 (Yu et al., 2010). These Dp(10)1Yey/+, Dp(16)1Yey/+, and Dp(17)1Yey/+ mice (Dp(10, 16, 17)) exhibit impaired hippocampal-dependent learning and hippocampal long-term potentiation (LTP). In addition, a few Dp(10, 16, 17) mice had aqueductal stenosis and hydrocephalus. No potential abnormalities of the cerebral cortex or craniofacial or cardiac defects relevant to DS have been reported to date.

30.3.3 Transchromosomic DS Mouse Model Using Human DNA

While the new Dp(10, 16, 17) mouse described previously is very promising, alterations in DS may require increased expression of *human* genes and/or functional changes in *human* proteins. To address this possibility, mice have been generated using microcell-mediated chromosomal transfer (Shinohara et al., 2001). These Tc1 animals contain an approximately 42-Mb portion of HSA21 (O'Doherty et al., 2005). However, these animals are limited as a DS model because of loss of the human chromosome in a variable fashion in different organs and tissues. This mosaicism may be broadly similar to that seen in people with DS but significantly hampers the use of Tc1 mice for biomedical research.

30.3.4 Nonmouse Models of DS

While mouse models have dominated the field of DS research, additional models have been developed in *Drosophila*, *Caenorhabditis elegans*, and even yeast by modifying orthologous genes found within HSA21 (Guipponi et al., 2000; Moldrich, 2007; Tejedor et al., 1995). As discussed below, these additional model systems have allowed the testing of individual genes relevant to DS and the study of conserved gene expression and protein function (Chang and Min, 2005; Raich et al., 2003; Yu et al., 2009). *Drosophila* has been a particularly valuable and experimentally tractable system. For example, overexpression of any of the three HSA21 orthologs *dap160* (*ITSN1*), *synj* (*SYNJ1*), and *nla* (*DSCR1*) produced abnormalities in brain synaptic connections, but overexpression of all three genes impaired synaptic vesicle recycling and motor function (Chang and Min, 2009). Such 'simpler' model systems can complement existing

TABLE 30.3 Nonmouse models of DS

Organism	Gene alteration	Abnormalities	Limitations	Reference
Drosophila melanogaster	Overexpression of *dap160* or *synj* or *nla1*	Reduced recycling of neurotransmitter vesicles	Divergent evolution, lack of interactions with other DS-related genes	Chang and Min (2009)
Drosophila melanogaster	Overexpression of *dap160* and *synj* and *nla1*	Reduced recycling of neurotransmitter vesicles and impaired locomotion	Divergent evolution, studies limited to three overexpressed genes	Chang and Min (2009)
Drosophila melanogaster	Loss of *Dscam* exon 19	Impaired neural development and axonogenesis	Divergent evolution, unable to study interactions with other DS-related genes, unclear relevance to DS	Yu et al. (2009)
Caenorhabditis elegans	Overexpression of *mbk-1* (*DYRK1A*)	Impaired odortaxis	Divergent evolution, unable to study interactions with other DS-related genes	Raich et al. (2003)
Homo sapiens	iPSC with trisomy 21	None reported	*In vitro* studies only	Park et al. (2008)

mouse models and test single and multiple gene function and interaction within the developing brain. Furthermore, these additional model systems may be well positioned to identify and test new therapies to ameliorate various brain phenotypes relevant to DS (Table 30.3).

30.3.5 Human Cellular Models of DS: Stem Cells and Patient-Specific Models of Disease

Mouse models of DS described above were generated with the express intent of identifying biological pathways altered by the trisomy of genes found on HSA21. As described above, these models include Ts65Dn, Ts1Cje, Ts1Rhr, Ms1Rhr, Tc1, Ts1Yah, and Dp(10, 16, 17). They have all contributed to our knowledge in defining genomic regions required for subsets of DS phenotypes including craniofacial and age-related neurodegeneration, cardiovascular phenotypes, learning and memory deficits, cerebellar hypoplasia, and partial penetrance neonatal lethality. These models may have served best by reaffirming the complexity of DS and the ongoing challenges in modeling a 'simple' trisomic disease. In addition, these mouse models have focused attention on a subset of HSA21 genes (e.g., *DSCR1*, *DYRK1A*, *APP*, and *SOD1*) and biological pathways (nuclear factor of activated T cells (NFAT) activation, Hedgehog signaling, and microtubule-based intracellular transport) that appear to play an important role in the generation of these phenotypes in the mouse models (see Section 30.4). The existing mouse models and other model organisms as described earlier suffer from limitations that are important to consider when applying research findings to DS. First, most of the models are trisomic for only a subset (one or more) of the homologous genes on HSA21 and as such fail to account for the impact of these other genes in the processes and phenotypes being studied. The generation of the Tc1 model carrying an almost intact HSA21 largely overcame this problem. However, as described above, the mosaic loss of HSA21 from a significant portion of cells in these animals complicates the interpretation of the phenotypes in this model. Second, regulatory control of exogenous human genes may differ from that of their endogenous mouse counterparts; thus, the degree of overexpression of trisomic genes may not accurately model the expression of these genes in patients. Indeed, the lack of DS-like anatomical and morphological phenotypes in the Tc1 model may be due to differences in expression of human genes in the mouse. Third, genetic interactions with genes not found on HSA21 may show species-specific differences; thus, pathways identified in the mouse may play a stronger or weaker role in the human condition. Finally, there are several discrepancies between the mouse models and human patients including differences in skeletal modifications, absence of comparable gastrointestinal abnormalities, failure to observe cortical lamination defects, and hypoplasia of the cerebrum in the mouse models (Delabar et al., 2006). The recent creation of Dp(10, 16, 17) mice may circumvent many of these concerns though it remains possible that human genes and proteins have different pathological roles leading to the phenotypes seen in people with DS. Much more extensive evaluations of Dp(10, 16, 17) mice will be required to see if they will become the preeminent animal model for DS. Despite these shortcomings, trisomy mouse models are currently the best available research tool for studying the molecular pathophysiology of DS in a whole animal. However, a human-based neuronal/glial model of DS would address many of the caveats discussed here, facilitate the translation of research findings between human and animal research, and speed the discovery and testing of therapeutic targets.

At the end of 2007, three independent laboratories, headed by Shinya Yamanaka (Kyoto University), George Daley (Harvard Medical School), and James Thomson

(University of Wisconsin–Madison), generated pluripotent stem cells from adult human dermal cells with the developmental potential seemingly equivalent to that of human embryonic stem cells (Park et al., 2008; Takahashi et al., 2007; Yu et al., 2007). These iPSCs were found to be competent to generate all three major cell type lineages and resemble embryonic stem cells in their pluripotency and other important characteristics. Human iPSCs can be differentiated into embryoid bodies as has been done with human embryonic stem cells (Takahashi et al., 2007; Yu et al., 2007). Neural progenitor cells can be harvested from embryoid bodies and cultured prior to differentiation into neurons and glia (Yeo et al., 2007, 2008). The ability to generate iPSCs from human patients is anticipated to open up a new frontier of research into human disease. The study of the pathogenesis of DS represents an almost ideal application of this technology given the challenges of modeling trisomy of HSA21 in other model systems, as discussed earlier. Furthermore, the ability to differentiate neurons and glia from DS iPSCs offers a chance to examine in detail changes in both the development and maintenance of neural function caused by trisomy HSA21 in the context of human cells. Finally, the relative ease to expand, maintain, culture, and differentiate iPSCs will enable this resource to be utilized by a broader range of research laboratories around the world, expanding both the scope and depth of DS research being pursued. To date, there has been a single report of iPSCs being generated from trisomy 21 fibroblasts (Park et al., 2008). This is an important 'proof of principle' and establishes that trisomy of HSA21 does not prevent the reprogramming process required to make iPSCs and that this exciting new technology can be effectively applied to the study of DS.

30.4 NEUROLOGICAL AND FUNCTIONAL CORRELATES OF THE DS PHENOTYPE

Research efforts to better understand the cellular and functional basis of the DS phenotype have followed a two-pronged strategy. The first strategy is to characterize and define the neurological, functional, and neuroanatomical correlates of the DS genotype in human patients. This enables understanding of the specific neurological phenotypes associated with DS. The second strategy seeks to refine this knowledge by a detailed study of the molecular, cellular, and functional correlates of the DS genotype using experimental model systems. Under this approach, researchers have sought to understand the pathophysiological basis of the DS phenotype by characterizing and identifying the myriad observable differences between DS and control groups and developing a hierarchy of potential cause–effect relationships between biomarkers of the disease and the behavioral, cognitive, and neurological challenges facing patients. Thus, phenotypes in DS animal and cellular models are consistently compared and contrasted to the clinical phenotypes of the DS patient. This approach seeks to increase scientific confidence in the accuracy of DS model systems to recapitulate the pathophysiology of trisomy HSA21. Here, we examine known DS model phenotypes and their possible relationships with known DS phenotypes. Studies on phenotypic correlates of the DS genotype fall under two broad categories: (1) studies examining the influence of specific trisomic genes to particular DS phenotypes and (2) studies using models with multiple trisomic genes (from several genes up to near-complete representation of HSA21 genes) to better understand the cellular, behavioral, and functional correlates of the DS genotype.

30.4.1 Behavioral, Motor, and Cognitive Alterations

Mouse models of DS have been carefully examined for cognitive, motor, and behavioral deficits consistent with the intellectual disability, motor, and behavioral features associated with DS. The specific nature of the DS phenotype has been extensively characterized as well as compared and contrasted with other developmental disorders. The intellectual quotient of individuals with DS averages about 50 (Contestabile et al., 2010; Vicari, 2004; Vicari et al., 2000, 2005). However, mental retardation is insufficient to explain the specific pattern of neuronal functional domains affected in DS. For example, despite similar or even less severe mental retardation, the distinctive characteristics of children with DS, compared to children with other developmental and intellectual disabilities, have been recognized as advantageous for their rearing and social integration (Corrice and Glidden, 2009). Individuals with DS exhibit a decreased risk for maladaptive behaviors, psychopathology, or emotional disturbance compared to others having a similar degree of mental retardation (Dykens, 2007). However, DS individuals carry a tenfold larger risk for a comorbid diagnosis of autism than the general population (Molloy et al., 2009). Despite this, social interactions and repetitive movements are not considered a part of the core DS phenotype (Corrice and Glidden, 2009; Dykens, 2007; Molloy et al., 2009; Zigler and Hodapp, 1991). Instead, speech and language difficulties, along with learning and memory deficits, are the principal phenotypic features of DS (Contestabile et al., 2010). In addition, individuals with DS show elevated gaze fixation and decreased scanning for novel stimuli in the environment, as well as subdued emotional responsiveness (Zigler and Hodapp, 1991). Also, significant delays

in the development of cognitive and neurological milestones are reported for DS (Nadel, 2003). Hippocampal and prefrontal cortical dysfunction appears to be at the core of these deficits (Nadel, 2003). Declines in both short- and long-term memory as well as in memory consolidation have been reported, with deficits in both visual–spatial as well as verbal memory. Finally, a large portion of patients with DS exhibit a progressive cognitive decline with aging and the pathological features of AD.

Several recent reviews summarize the behavioral phenotypes of DS mouse models (Contestabile et al., 2010; Rachidi and Lopes, 2007). Common behavioral abnormalities in these models include decreased fear conditioning, decreased novel object recognition and long-term memory, decreased spatial learning and memory, hypoactivity and decreased exploratory behavior, and delayed acquisition of sensorimotor skills. These behavioral phenotypes are consistent with the human DS phenotype and arguably validate these models for mechanistic study and detailed characterization. By far the most widely used and extensively characterized of these models is the Ts65Dn segmental trisomy mouse model (Figure 30.2). Characterization of these mice revealed a significant developmental delay in acquisition of sensorimotor behaviors (Holtzman et al., 1996). Of particular note was a delay in the pattern of ultrasonic vocalizations, possibly similar to the delay in speech seen in human DS children (Holtzman et al., 1996). The newest and most complete mouse segmental trisomic DS genetic model, Dp(10, 16, 17), exhibits deficits in hippocampal-dependent learning and memory by the Morris water maze test, in which trisomic animals spent significantly less time searching for a hidden platform in the target quadrant as well as the contextual fear conditioning test (Yu et al., 2010). Analysis of the HSA21 'transchromosomic' mouse model, Tc1, also revealed spatial learning and memory deficits by Morris water maze and novel object memory deficits (Morice et al., 2008; O'Doherty et al., 2005). However, while defects in short-term spatial and novel object memory were detected, long-term memory appeared to be intact. This is in contrast to the Ts65Dn model, which exhibits deficits in long-term memory of novel objects (Fernandez and Garner, 2008), or the Ts1Cje model, which has normal performance in short- and long-term novel object memory tests (Fernandez and Garner, 2007). The basis for these discrepancies in DS mouse models is unresolved. Possible explanations include (1) the inclusion of different partially overlapping sets of HSA21 gene or related genes in the various models, (2) difficulties in modeling the influence of human trisomy in a rodent model, and (3) environmental factors or experimental differences that may influence mouse behavior experiments.

Genetic dissection of DS mouse phenotypes, to attribute specific HSA21 genes or chromosomal regions to the DS phenotype, has received considerable attention in the field. Approaches to asking questions on the role of genes specific to the DS phenotype take advantage of various mouse models with partially overlapping sets of triplicated genes, for example, the analysis of novel object memory in the Ts65Dn and Ts1Cje lines mentioned earlier (Fernandez and Garner, 2007), as the Ts65Dn line contains additional genetic material homologous to HSA21 not found in the Ts1Cje line. Comparison of partially overlapping segmental trisomic mouse models can provide insight into the genetic basis of the DS behavioral phenotypes. For example, the work of Epstein and colleagues with the Ts65Dn, Ts1Cje, and Ms1Ts65 lines examined correlations between motor activity and learning and memory by Morris water maze between the *App* to *Sod1*, *Sod1* to *Mx11*, and *App* to *Mx1* genetic intervals (Sago et al., 2000). However, complexities and differences in phenotypic penetrance have made clear genotype–phenotype correlations challenging. This complexity is further exemplified by work on a segmental trisomic model (Ts1Yah) that contains genes found in the subtelomeric region of HSA21 (*Abcg1* to *U2af1*) from Mmu17 and genes that are excluded from the widely used Ts65Dn, Ts1Cje, and Ms1Ts65 mice, which include only HSA21 homologous genes found on Mmu16 (Pereira et al., 2009). The Ts1Yah line exhibits deficits in novel object recognition, but improvements above control lines for spatial memory (Pereira et al., 2009). This work again revealed additional complexity in the combinatorial genotype–phenotype correlations that could contribute to the overall DS phenotype.

A complementary approach to genetic dissection of HSA21 genes and their contribution to the DS phenotype is to perform detailed phenotypic characterization in single-locus genetic models. For example, a BAC transgenic model of the *Abcg1* locus found no alterations in behavioral tests for anxiety or working memory (Parkinson et al., 2009). While these results suggest that the *Abcg1* locus does not contribute to the cognitive deficits in DS, caution must be taken in drawing this conclusion, given that the potential influence of other HSA21 loci cannot be ruled out. A *Dyrk1a* BAC transgenic model, in contrast, exhibited profound learning and memory deficits on the Morris water maze test (Ahn et al., 2006). While these results strongly suggest that *Dyrk1a* contributes to learning and memory deficits in DS, caution must also be taken concerning this conclusion as its relative contribution in the context of full trisomy HSA21 is unknown. Another example is the *Sim2* transgenic lines that display anxiety-related behaviors similar to those found in segmental trisomy models that include *Sim2* such as Ts65Dn (Chrast et al., 2000). In addition to overexpression models, genetic knockout of

HSA21 homologous genes may also inform us about the role of genes in the DS phenotype. For example, the *RCAN1* null mouse exhibits deficits in spatial learning and memory as well as contextual learning (Hoeffer et al., 2007). The phenotype is similar to lines with elevated calcineurin activity. Closer study revealed the *RCAN1* null mouse has elevated activity in this pathway (Hoeffer et al., 2007). Functional analysis of HSA21 genes can provide mechanistic insight into the neural pathways underlying behavioral phenotypes.

30.4.2 Neurogenesis

DS is associated with reduced brain size (~80% of typically developing humans) from very early in development (~5-month fetuses) through adulthood (Pinter et al., 2001b; Schmidt-Sidor et al., 1990; Winter et al., 2000). Both hypocellularity and hypoplasia likely contribute to this phenotype (Contestabile et al., 2010). Several regions of the brain are affected including the neocortex (entorhinal, frontal, prefrontal, and temporal cortices), hippocampus, amygdala, cerebellum, hypothalamus, and brainstem (Aylward et al., 1997a, 1999; Contestabile et al., 2010; Kesslak et al., 1994; Pine et al., 1997; Raz et al., 1995; Sylvester, 1983; Teipel and Hampel, 2006; Teipel et al., 2003, 2004). Several studies converge upon particularly substantial decreases in brain volume for the hippocampus and temporal lobe. Indeed, behavioral- and neural activity-based animal studies have focused upon phenotypic abnormalities of the hippocampus in part for this reason. Neurogenesis defects, reductions in the numbers of neurons generated in development, are likely to substantially contribute to reduced brain size in DS and have been observed in both DS fetuses and children (Contestabile et al., 2010; Guidi et al., 2008; Larsen et al., 2008; Wisniewski, 1990; Wisniewski et al., 1984). Schmidt-Sidor and colleagues examined brains of fetuses of 15–22 weeks gestational age and from birth to 60 months of age and reported that initial defects occur sometime between 22 weeks of age and birth (Schmidt-Sidor et al., 1990). Thus neurogenesis defects likely represent the earliest neurological phenotypic evidence of the DS genotype. Indeed, some of the earliest descriptions of neurological phenotypes in mouse models of DS (e.g., trisomy Mmu16) are reports of neurogenesis defects in these models (Haydar et al., 1996; Sweeney et al., 1989).

Detailed characterization and mechanistic studies in animal models of DS, such as the Ts65Dn and Ts1Cje, have confirmed defects in cell proliferation and neurogenesis (Chakrabarti et al., 2007; Contestabile et al., 2009a,b; Moldrich et al., 2009). In agreement with rodent models, a human neuroprogenitor model of DS revealed that despite similar initial production of neurons, progenitors with trisomy HSA21 produced fewer neurons when cultured for over 10 weeks (Bhattacharyya et al., 2009). Examination of granule cell precursors from the Ts65Dn mouse revealed that prolonged G1 and G2 phases of the cell cycle contributed to decreased proliferation (Contestabile et al., 2009a). Examination of cortical and hippocampal neuroprogenitors in the Ts65Dn model also revealed evidence of a longer cell cycle contributing to reduced neurogenesis (Chakrabarti et al., 2007; Contestabile et al., 2007). Furthermore, reductions in neurogenesis in the Ts65Dn mouse model are associated with decreased synaptogenesis in the first postnatal week (Chakrabarti et al., 2007). Multiple neuronal cell types are potentially influenced by alterations in neurogenesis and neurodevelopment, including the serotonergic, noradrenergic, GABAergic, and cholinergic neurons (Bar-Peled et al., 1996; Dierssen et al., 1997; Fiedler et al., 1994; Granholm et al., 2000; Kleschevnikov et al., 2004; Whittle et al., 2007). Finally, the neurogenesis defect may not occur only in development, as the Ts1Cje line exhibits a reduction in adult neurogenesis with a concomitant rise in production of astrocytes (Hewitt et al., 2010).

DYRK1A is a member of the dual-specificity tyrosine-regulated kinase family that maps to HSA21 21q22.2. The *Drosophila* homolog of *DYRK1A, minibrain* (*mnb*), is required for postembryonic neurogenesis. Loss of *mnb* causes reduced optic lobes and central brain likely caused at least in part by abnormal spacing of neuroprogenitors in the larval brain (Tejedor et al., 1995). This gene family shares homology with other kinases involved in regulation of cell division. The DYRK kinase family is so named because of its autophosphorylation of tyrosine residues in its YXY activation loop and serine/threonine phosphorylation of its protein substrates. The subsequent mapping to HSA21, findings of early neural expression in humans and rodents, and overexpression in DS brain and the Ts65Dn mouse model drew attention to this gene as a candidate for contributing to the neurogenesis and neurodevelopment phenotypes in DS patients (Guimerá et al., 1996; Guimera et al., 1999; Shindoh et al., 1996; Song et al., 1996). Decreased expression of the mouse homolog causes developmental delay and alteration in brain morphology (Fotaki et al., 2002). To more specifically examine the influence of this gene on neurogenesis in DS, D'Arcangelo and colleagues overexpressed mouse *Dyrk1A* in the cortex by *in utero* electroporation (Yabut et al., 2010). They report that overexpression promotes neuronal maturation while inhibiting proliferation of neural progenitors (Yabut et al., 2010). Minimal influence of cell fate was observed, suggesting that *Dyrk1A* acted predominantly by influencing production of neurons rather than alterations in the neurodevelopmental program itself. Furthermore, these phenotypes were dependent on kinase

activity and nuclear export and protein degradation of cyclin D1 (Yabut et al., 2010). In further support of a role of this gene in regulation of neurogenesis and brain size, patients with a loss of the *DYRK1A* gene present with microcephaly (Fujita et al., 2010; Moller et al., 2008).

Other genes likely also contribute to defects in neurogenesis and neurodevelopment. For example, the *Olig1* and *Olig2* genes contribute to an imbalance in excitatory and inhibitory neuronal systems (Chakrabarti et al., 2010). While many neuronal populations exhibit decreased numbers, examination of the Ts65Dn model revealed an increase in the parvalbumin and somatostatin subclasses of inhibitory neurons, with no change in the number of calretinin inhibitory neurons (Chakrabarti et al., 2010). Restoration of disomy to the *Olig1* and *Olig2* genes was found to rescue this phenotype. Other genes that may contribute include *TTC3*, which has been shown to inhibit neuronal differentiation in a cell culture model (Berto et al., 2007). *Sim2* plays a critical role in *Drosophila* neurogenesis (Chrast et al., 2000), and the HSA21 gene *Sim2* mouse homolog exhibits CNS-specific expression patterns consistent with a role in mammalian neurogenesis (Rachidi et al., 2005). Finally, altered responses to key neuronal proliferative signaling systems may also underlie alterations in neurogenesis. Cerebellar granule neuron precursors normally exhibit a strong mitogenic response to the morphogen Sonic hedgehog (SHH). Purified granule neuron precursors from the Ts65Dn model were found to have a significantly reduced proliferative response to SHH (Roper et al., 2006a). Interestingly, administration of a small molecule agonist of the SHH signaling pathway (Smoothed Agonist) was able to rescue the decreased proliferative phenotype of these cells (Roper et al., 2006a). In summary, a complex interplay of developmental signaling and altered expression of multiple HSA21 genes likely contributes to the DS neurogenesis phenotype.

30.4.3 Regional Connectivity and Development of Neural Circuits

One plausible explanation for the learning and memory deficits and other psychiatric and cognitive phenotypes associated with DS is a failure to set up the normal neural circuits and appropriate brain regional connectivity in development. Thus, in addition to alterations in the numbers and types of neurons generated during development (discussed earlier in Section 30.4.2), the establishment of abnormal brain circuitry during development is also hypothesized to contribute to the DS phenotype. However, less work has been done in this area relative to studies examining the contribution of alterations in neurogenesis and/or changes in neuronal activity at the cellular level. Indeed, reported alterations in brain morphology are often attributed to alterations in regional neurogenesis rather than changes in the neural circuits themselves (Contestabile et al., 2010; Rachidi and Lopes, 2007). MRI studies of people with DS indicate the potential of structural changes (e.g., disproportionate loss of volume in the cerebellum, hippocampus, and a subregion of the superior temporal gyrus and increased subcortical gray matter) to underlie DS cognitive and behavioral phenotypes (Frangou et al., 1997; Pinter et al., 2001a,b; Raz et al., 1995). A recent fMRI study of children with DS during a story-listening task revealed reduced activation of receptive language areas (superior and temporal gyri; Losin et al., 2009). Likewise, a magnetoencephalography study has suggested that cortical activation patterns during motor tasks and motor observational tasks are less coherent in the DS brain, showing broader activation patterns and reduced lateralization (Virji-Babul et al., 2010). Finally, changes in amino acid and monoamine neurotransmitters (e.g., serotonin, dopamine, and GABA) in the DS fetal brain also suggest defects in the development of neural circuits (Whittle et al., 2007). Despite evidence that alterations in brain structure and connectivity underlie mental retardation in DS and other developmental disorders, there is growing recognition that ameliorative therapy may still be possible (Dierssen and Ramakers, 2006).

As mentioned previously, a prominent feature of the DS phenotype is reduced brain size. Detailed three-dimensional quantification of brain morphology by high-resolution MRI in the Ts65Dn and Ts1Rhr models has examined the relative contribution of changes in brain volume and brain shape to this phenotype (Aldridge et al., 2007). Such analysis demonstrates severe reductions in cerebellar volume, with minimal volume loss in other brain regions (Aldridge et al., 2007), confirming early observations of reduced cerebellar volume in the Ts65Dn model as well as DS patients (Baxter et al., 2000; Scott et al., 1983). Interestingly, the Ts1Rhr model shows a subtle decrease in overall brain volume, with a relative sparing of the cerebellum (Aldridge et al., 2007). This suggests that genes triplicated only in the large segmental trisomic Ts65Dn model may be responsible for the reduced cerebellar volume phenotype. Furthermore, it is noteworthy that overall brain shape, measured using 29 independent morphological landmarks, is unchanged in the Ts65Dn model (Aldridge et al., 2007). One interpretation of these findings is that alterations in the cell number and perhaps degree of connectivity (see below) may be more important for the DS phenotype than dysmorphic or improper/aberrant neural connections across different brain regions.

Specific HSA21 genes have been implicated in the connectivity and neural circuitry phenotypes in DS. The triplicated *Dscam* gene functions in neuronal morphogenesis and connectivity by contributing to establishment of

diverse neural connectivity patterns in development (Gao, 2007; Schmucker, 2007; Yu et al., 2010). In addition, mosaic spacing, axonal targeting, and appropriate arborization of the neuronal pathways in the mouse and *Drosophila* brain require *Dscam* (Fuerst et al., 2008; Hattori et al., 2007; Hummel et al., 2003). Additional evidence for altered connectivity was acquired indirectly by measures of cellular transport between the hippocampal to forebrain circuit. That the circuit appears to be intact, and indeed more robust than wild type, suggests that this circuit is not functioning properly in Ts65Dn mice (Bearer et al., 2007). Lastly, alterations in the structural features on synapses likely contribute to the DS phenotype. Lucifer yellow injections into neurons of the hippocampus and cortex of the Ts65Dn model revealed enlarged dendritic spines and other changes in synaptic architecture (Belichenko et al., 2004). The *Dyrk1a* gene (trisomic in both Ts65Dn and Ts1Rhr models) has been strongly implicated in defects in both neuronal morphology and connectivity by altering synapse formation and dendritic architecture (Contestabile et al., 2010). Heterozygosity (loss of a single allele) of *Dyrk1a* in the mouse alters cortical circuitry by decreasing dendritic branching and spines (Benavides-Piccione et al., 2005), perhaps via alterations in cAMP-responsive element-binding protein or NFAT activity (Arron et al., 2006; Hammerle et al., 2003). Furthermore, alterations in the Notch signaling pathway due to increased Dyrk1a activity could contribute to alterations in neural developmental pathways in DS (Fernandez-Martinez et al., 2009). Additional evidence for alterations in neural circuitry comes from analysis of electrophysiological alterations in the hippocampus revealing increased connectivity despite reduced excitatory and inhibitory inputs (Hanson et al., 2007). An important question for potential therapeutic intervention is whether these and other changes in neuronal morphology can be altered once established. Evidence in favor of this view is emerging, based in part on improvements in cortical pyramidal cell dendritic and spine phenotypes associated with environmental enrichment in Ts65Dn models (Dierssen et al., 2003). Interestingly, such environmental enrichment-related alterations in brain structure correlate with amelioration of behavioral, cell signal transduction, and neurogenesis phenotypes in the Ts65Dn model (Baamonde et al., 2011; Chakrabarti et al., 2011; Martínez-Cué et al., 2005). These data add to a growing awareness that even neuronal structure-related phenotypes in DS may be amenable to clinical intervention (Dierssen and Ramakers, 2006).

30.4.4 Neuronal Dysfunction in DS

Alterations in neuronal function are diverse, as expected given the DS genotype. Our discussion of a key subset of altered cellular function is split into four broad categories below.

30.4.4.1 Plasticity and Synaptic Function

There is evidence for alterations in both excitatory and inhibitory circuits in DS. Loss of asymmetric synapses (predominantly excitatory), without changes in the number of symmetric synapses (predominantly inhibitory), in the cortex of the Ts65Dn model suggested that the excitatory circuits may be the first to be affected (Kurt et al., 2000). However, detailed examination revealed alterations in the size of symmetric synapses (Belichenko et al., 2009a,b). Furthermore, immunostaining for markers of inhibitory neural circuits revealed increased calretinin GABAergic synapses in the cortex of the Ts65Dn model (Pérez-Cremades et al., 2010). Modulatory circuits may also be affected, as suggested by the loss of striatal interneuron LTP in the Ts65Dn model (Di Filippo et al., 2010). Indeed, changes in synaptic plasticity have been observed throughout the brain including decreased LTP in the hippocampus (Hanson et al., 2007; Kleschevnikov et al., 2004; Siarey et al., 1997). LTP and LTD deficits have also been reported in the Ts1Cje DS mouse model (Siarey et al., 2005). Importantly, the most complete of the segmental trisomic mouse models, the Dp(10, 16, 17) mouse model, validated electrophysiological and corresponding behavioral deficits (Yu et al., 2010). Changes in a pair associative stimulation (PAS) paradigm confirmed these findings of LTP deficits in DS patients (Battaglia et al., 2008). Reduced activation of NMDA receptors, increased $GABA_B$ potassium currents, and elevated rates of mESPCs in the Ts65Dn model likely contribute to the changes in synaptic plasticity (Best et al., 2007, 2008; Kleschevnikov et al., 2004). Depressed hippocampal LTP was found to be suppressed by pharmacological interventions that increase inhibitory tone (Kleschevnikov et al., 2004). The GIRK2 potassium channel, encoded by an HSA21 gene, has also been implicated in changes in the balance of excitatory and inhibitory transmission in DS (Best et al., 2007; Harashima et al., 2006). Another HSA21 gene, *RCAN1*, regulates LTP via phosphatase signaling (Hoeffer et al., 2007). Additionally, LTP and LTD are altered in a *DYRK1A* BAC transgenic model overexpressing this single HSA21 gene (Ahn et al., 2006).

Careful expression analysis of functional components has revealed subtle defects in synaptic functional components in DS. Proteomic analysis of synaptosomal fractions in Ts65Dn mice suggested that the overall composition of synaptic proteins is similar to that in wild-type animals (Fernandez et al., 2009), though careful quantitative assessment of key components (e.g., NR2A, GAD65/67, VGAT, GluR2, Cdk5, neurotrophin-3, and $GABA_A$ receptor) has revealed subtle changes (Altafaj et al., 2008; Belichenko et al., 2009a,b; Pérez-Cremades et al., 2010; Pollonini et al., 2008). One contributing genetic factor is likely to be trisomic expression of *Dyrk1a,* which has been linked to changes in

NR2A expression and calcium transients (Altafaj et al., 2008). The HSA21 gene *SYNJ1* encoding Synaptojanin 1 is a key regulator of the phosphatidylinositol signaling and metabolism that is required for normal neuronal transmission (Voronov et al., 2008).

30.4.4.2 Genetic and Proteomic Dysregulation

The most obvious of the cellular changes expected in DS are gene expression differences due to the extra copy of all HSA21 genes. However, likely due to the complexities of gene regulation, not all HSA21 genes are overexpressed by the expected 1.5-fold (Ait Yahya-Graison et al., 2007; FitzPatrick et al., 2002; Mao et al., 2003, 2005). Indeed, these studies revealed genes on HSA21 whose expression was either unchanged from diploid, overexpressed beyond what is expected from the dose alone, or even downregulated (FitzPatrick, 2005; Rachidi and Lopes, 2008). Furthermore, genes located on other chromosomes also have been found to exhibit profound differences in expression. These results from human tissues have been corroborated across DS mouse models including the Ts1Cje and Ts65Dn (Amano et al., 2004; Hewitt et al., 2010; Kahlem et al., 2004; Moldrich et al., 2009; Wang et al., 2004).

Clearly, the magnitude of expression differences dictates the phenotype, and the temporal and physical pattern of expression contributes as well to the phenotypic consequences of DS. HSA21 gene and HSA21 gene homolog expression maps have been generated to identify tissues and brain regions where and when HSA21 genes are expressed and misexpressed in DS (Gitton et al., 2002; Kahlem et al., 2004; Reymond et al., 2002). The influence of trisomy HSA21 is further complicated by the finding that overexpression of the HSA21 homolog Dyrk1a is sufficient to elicit global changes in cortical gene splicing that are also seen in DS fetal brain samples (Toiber et al., 2010). Thus, even a single gene whose expression is altered by trisomy can influence gene expression throughout the genome. Finally, changes in gene expression do not consistently result in matching changes in protein levels. Thus recent analysis of the DS proteome will also be necessary to achieve an accurate model of the cellular consequences of the DS genotype (Delom et al., 2009; Patterson, 2009; Shin et al., 2006, 2007).

30.4.4.3 Dysregulation of Vital Cellular Processes

The transcriptome and proteome alterations in DS potentially lead to diverse dysregulation of vital cellular processes. For example, several HSA21 genes have been functionally linked to membrane and vesicular trafficking. The HSA21 homologous gene, *Itsn1*, plays a role in endocytic processing and vesicular trafficking (Yu et al., 2010). Misexpression of the HSA21 homolog of β-amyloid precursor protein (β-APP) contributes to alterations in nerve growth factor (NGF) transport (Salehi et al., 2006), while the *DSCR1/RCAN1* homologue regulates vesicle exocytosis (Keating, 2008). Other changes include alterations in the levels of myo-inositol in the brain, altered proteolytic processing of APP, and increased sensitivity to genotoxic stress (Beacher et al., 2005; Micali et al., 2010; Tansley et al., 2007).

30.4.5 Aging and Neurodegeneration

Neurodegeneration in DS is known to produce significant cognitive deficits and declines in patients afflicted with this illness. The pathogenesis of the disease is thought to be based on several major age-related processes: the formation of amyloid plaques, the degeneration of basal forebrain cholinergic neurons (BFCNs), and increased production of reactive oxygen species (ROS). Neurodegenerative mechanisms contribute to DS cognitive impairment given that early-onset AD occurs with an extremely high prevalence in these individuals (Contestabile et al., 2010). These neurodegenerative processes are known to have a strong genetic component, as several genes promote amyloidosis and respond to oxidative stress in the pathophysiology of DS. As the lifespan of DS individuals has increased significantly in recent years, obtaining greater understanding of pathways critical to the neuropathology of DS has been an active area of research that may yield future therapeutic targets to halt the progression of neurological symptoms.

30.4.5.1 DS and the Formation of Amyloid Plaques and NFTs

Individuals with DS present in the clinic with formations of amyloid plaques and progressive degeneration of BFCN (Casanova et al., 1985; Lockrow et al., 2009; Mufson et al., 2003). The presentations of senile plaques generally occur during middle age and are highly similar to that observed in the pathology of AD. The formation of these AD-type brain lesions occurs by the fourth decade of life, which is 20–30 years earlier in onset than patients suffering from AD (Iqbal and Grundke-Iqbal, 2010; Iqbal et al., 2010). These plaques are causally related to overexpression of β-APP whose gene is triplicated in DS (Contestabile et al., 2010). Full-length β-APP is proteolytically cleaved by β- and γ-secretase generating Aβ peptides, which then form plaques in the DS brain (Contestabile et al., 2010). Aβ lesions in the form of this 'preamyloid' appear by around 12 years of age (though they have been described in the DS neonatal brain as well) and are described as amorphous non-fibrillar aggregates with few dystrophic neurites (Contestabile et al., 2010; Giaccone et al., 1989; Kida et al., 1995; Lemere et al., 1996; Mann and Esiri, 1989; Motte and Williams, 1989; Wisniewski et al., 1994). These

preamyloid plaques progress to mature Aβ plaques that are associated with neuronal damage and generally appear during the third decade of life (Contestabile et al., 2010; Lemere et al., 1996; Wisniewski et al., 1994). Current research suggests that in addition to amyloidosis, overproduction of Aβ can trigger early cognitive impairment in dementia by modulating synaptic activity (Contestabile et al., 2010; Conti and Cattaneo, 2005; Gasparini and Dityatev, 2008). Aβ aggregates block LTP in excitatory synapses and enhance LTD by inhibiting glutamate receptors and downregulating *N*-methyl-D-aspartate receptors (NMDARs; Contestabile et al., 2010; Lambert et al., 1998; Li et al., 2009; Shankar et al., 2008; Townsend et al., 2006; Walsh et al., 2002; Wang et al., 2002).

In addition to Aβ, intraneuronal inclusions of hyperphosphorylated tau, a microtubule-stabilizing protein, develop in the proximal dendrites and cell bodies of neurons and within dystrophic neurites (Contestabile et al., 2010; Gasparini et al., 2007). Abnormal phosphorylation of tau causes the formation of NFTs, neuropil threads, and plaque dystrophic neurites associated with various neocortical tauopathies that cause dementia (Grundke-Iqbal et al., 1986a,b, 1988; Iqbal et al., 1986, 1989, 2009; Lee et al., 1991). In addition, Aβ and tau lesions are known to impact many brain regions in DS such as the prefrontal cortex, hippocampus, basal ganglia, thalamus, hypothalamus, and midbrain (Contestabile et al., 2010; Wisniewski et al., 1985). These lesions are believed to mediate the cognitive decline and dementia associated with DS.

The age-dependent DS phenotypes in the central nervous system are not restricted to cognitive processes but they also impact the visual system. DS patients present with distinctive early-onset cerulean cataracts, 'blue dot' cataracts that emerge at the equatorial periphery of the lens (Moncaster et al., 2010). The lenses of DS individuals have a characteristic pattern of supranuclear opacification accompanied by accumulation of Aβ, amyloid pathology, and fiber cell Aβ aggregates (Moncaster et al., 2010). Laboratory experiments have demonstrated that incubation of human lens protein in synthetic Aβ promoted light scattering, protein aggregation, and amyloid formation suggesting that the DS lens phenotype is a genetic cataract (Moncaster et al., 2010).

30.4.5.2 Degeneration of BFCNs in DS

In addition to amyloid plaque formation, degeneration of BFCNs and decreased activity of choline acetyltransferase with increasing age has been observed in DS. One of the most significant symptoms associated with death of cholinergic neurons in DS patients is memory loss (Ginsberg et al., 2006; Lockrow et al., 2009). In addition, BFCNs are responsible for providing the majority of cholinergic innervations to the hippocampus and cortex and play a significant role in attention and cognition in both humans and mouse models (Lockrow et al., 2009; Perry et al., 1977; Whitehouse et al., 1982). In particular, DS-related cognitive declines and adult-onset degeneration of BFCNs are observed in Ts65Dn mice (Chen et al., 2008; Cooper et al., 2001; Granholm et al., 2000; Holtzman et al., 1996; Lockrow et al., 2009). These results are not unexpected, as there is a triplication of amyloid precursor protein (*App*) gene in the Ts65Dn mouse (Cataldo et al., 2003; Lockrow et al., 2009). *App* triplication in the Ts65Dn mouse also influences early endosomal processes, NGF trafficking, and loss of BFCNs (Lockrow et al., 2009; Salehi et al., 2006). Interestingly, these declines occur despite absence of amyloid plaques in the Ts65dn mouse model (Seo and Isacson, 2005).

30.4.5.3 ROS, Oxidative Stress, and Neurodegeneration in DS

Based on the close mirroring of the neuropathological findings between DS and AD, the role of mitochondria, specifically oxidative stress, has been highly implicated in the pathogenesis of DS. After development of a prooxidant state early in the progression of the disease, individuals suffering from DS demonstrate elevated levels of DNA damage and lipid peroxidation (Jovanovic et al., 1998; Lockrow et al., 2009; Pallardo et al., 2006). Furthermore, cortical neurons in DS individuals show elevation in ROS, which contributes to neuronal degeneration and induction of apoptosis (Busciglio and Yankner, 1995; Lockrow et al., 2009). Decreased levels of endogenous antioxidants such as α-tocopherol, an inhibitor of lipid peroxidation, have been demonstrated in patients with AD; however, no evidence for a protective effect has been reported for DS individuals (Azzi et al., 2003; Lockrow et al., 2009). ROS elevation does not determine the fate of cortical neurons, as administration of antioxidants such as vitamin E has been shown to be restorative (Behar and Colton, 2003; Lockrow et al., 2009; Schuchmann and Heinemann, 2000). This may provide a therapeutic window into improvement of learning and memory in DS patients.

30.4.5.4 Genetic Component of Neurodegeneration in DS

Genetics also plays a profound role in the development of plaques and NFTs. The protein dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) is a serine/threonine kinase that has activity both in neurodevelopment as well as in neurodegeneration (Contestabile et al., 2010). Upregulation of DYRK1A has been demonstrated in DS. This enhancement of expression may result in hyperphosphorylation of tau that further phosphorylates glycogen synthase-3β causing tau self-aggregation into NFTs (Contestabile et al., 2010; Liu et al., 2008). DS

does not solely associate with upregulation of DYRK1A, but its kinase activity is also enhanced, further promoting assembly of tau into filaments (Iqbal et al., 2009; Liu et al., 2008). Similarly, Down syndrome critical region 1 (*DSCR1*), a calcineurin inhibitor, is thought to play a role in DS given its important role regulating mitochondrial function and oxidative stress. *DSCR1* functions as a stress response element as it is upregulated in reaction to elevated hydrogen peroxide (Contestabile et al., 2010; Crawford et al., 1997; Lin et al., 2003). Despite this critical role in reducing oxidative damage to cells, chronic overexpression of *DSCR1* in the context of DS has a number of negative side effects consistent with an AD-type degenerative process (Contestabile et al., 2010). DSCR1 inhibits the Ca2+/calmodulin-dependent protein serine/threonine phosphatase calcineurin and regulates synaptic activity (Contestabile et al., 2010; Ermak et al., 2002; Fuentes et al., 2000; Kingsbury and Cunningham, 2000). DSCR1-mediated inhibition of calcineurin can lead to increased NMDAR mean open time and opening probability, which alters neuronal excitability in the brain (Contestabile et al., 2010; Lieberman and Mody, 1994). In addition to modulating synaptic excitability, calcineurin acts to dephosphorylate tau, and inhibition of this pathway leads to a pathological hyperphosphorylation of tau that correlates with cognitive impairment (Contestabile et al., 2010; Gong et al., 1996; Luo et al., 2008; Yu et al., 2006).

30.5 GENETIC MECHANISMS UNDERLYING DS

The prevailing model of the genetic mechanism underlying the DS phenotype is the 'gene dosage effect' model (Contestabile et al., 2010; Patterson, 2007; Rachidi and Lopes, 2007; Roper and Reeves, 2006; Salehi et al., 2007). This model suggests that individual genes along HSA21 each contribute to specific endophenotypes that culminate in the overall DS phenotype. This is likely an oversimplification, as it does not take into account genetic interactions among HSA21 genes. Thus, the emergent influence of interactions between multiple trisomic genes has also been proposed as a genetic mechanism in DS. However, this model can be viewed as just an elaboration of the 'gene dosage' model that accounts for genetic interaction effects. Indeed, strong evidence exists to support such a role of genetic interactions between HSA21 genes in the DS phenotype. For example, overexpression of homologs for three HSA21 genes (*ITSN1*, *SYNJ1*, and *DSCR1*) alters synaptic function in *Drosophila*, but restoring expression of just one ameliorates this phenotype (Chang and Min, 2009). Likewise, substantial evidence exists supporting a role for functional interactions between the HSA21 genes *DSCR1* and *DYRK1A* (de la Luna and Estivill, 2006). The concept of the DSCR has been put forward to support the hypothesis that a subset of genes on HSA21 contributes to many of the major DS traits (Contestabile et al., 2010; Patterson, 2009). Extensive phenotyping of mouse models that contain portions of the DSCR has elucidated genetic intervals that contribute to specific brain-related and other phenotypes (Belichenko et al., 2009a,b; Olson et al., 2007). In addition, case reports of patients with microdeletions and/or small segmental duplications have furthered the correlation of gene interval with specific DS endophenotypes; some recent notable examples are cited here (Eggermann et al., 2010; Fujita et al., 2010; Kondo et al., 2006; Lyle et al., 2009; Ronan et al., 2007; Sato et al., 2008). Lastly, nonspecific effects of the genetic imbalance caused by trisomy have the potential to modify global expression patterns to contribute to the DS phenotype (Contestabile et al., 2010; Patterson, 2007; Rachidi and Lopes, 2007; Roper and Reeves, 2006; Salehi et al., 2007). Together, these three genetic mechanisms are thought to underlie the complex genotype–phenotype correlations that exist in DS.

30.6 TRANSLATIONAL AND THERAPEUTIC STRATEGIES IN DS

As detailed above, owing to the strength of evidence that mouse models of DS display clinically relevant phenotypes, researchers have begun to explore pharmacological and other intervention strategies for therapeutic benefit. Therapeutic strategies range from very early phenotypes (e.g., decreased neurogenesis) to behavioral phenotypes (e.g., learning and memory deficits, anxiety) and neurodegenerative phenotypes (e.g., cognitive decline). For example, given the reduced levels of serotonin in the DS fetal brain, the selective serotonin reuptake inhibitor fluoxetine was tested for rescue of the reduced neurogenesis phenotype in the Ts65Dn model (Clark et al., 2006; Whittle et al., 2007). Indeed, 2- to 3-week treatment paradigms increased neurogenesis in the hippocampus, subventricular zone, cortex, and striatum (Bianchi et al., 2010; Clark et al., 2006). Fluoxetine treatment was also found to restore expression levels of the serotonin 1A receptor (5-HT1A) and brain-derived neurotrophic factor (BDNF) as well as to show improvement in a hippocampal-dependent memory task (Bianchi et al., 2010). The NMDA receptor uncompetitive antagonist memantine is FDA-approved for treatment of moderate to severe AD. Memantine was subsequently shown to rescue memory task deficits, reduced neuronal number in the hippocampus, and decreased vesicular glutamate transporter-1 (VGAT1) expression (Costa et al., 2008; Rueda et al., 2010). More recent studies in the Ts65Dn mouse model suggest therapeutic potential for $GABA_A$ receptor inverse agonists or β1-adrenergic

receptor agonists in amelioration of cognitive phenotypes (Braudeau et al., 2011; Faizi et al., 2011). In addition, nutritional manipulation has also shown therapeutic promise, for example, perinatal choline, vitamin E, or green tea extract supplementation (Guedj et al., 2009; Lockrow et al., 2009; Moon et al., 2010). Future studies aimed at counteracting the influence of trisomy HSA21 genes and dysregulated gene networks provide promise of therapeutic intervention.

30.7 SUMMARY

Trisomy of HSA21 perhaps yields a remarkably mild clinical phenotype in the face of the profound genetic insult expected from triplication of over 400 genes. The complexity of the genetics raises an incredible challenge to elucidate genotype–phenotype correlations across the constellation of endophenotypes and incomplete penetrance that contribute to the clinical presentation of this disorder. Experimental models of DS range in complexity, model organism, and genetic completeness. But without doubt, the mainstay of DS basic research has been mouse genetic models with trisomy of mouse chromosomal regions that are syntenic to HSA21 (e.g., Ts65Dn and Dp(10, 16, 17)). However, *Drosophila*, *C. elegans*, yeast, other model organisms and human cell lines also provide important tools in dissecting the function and interactions of HSA21 genes. The recent generation of DS iPSC lines yields the promise of human neuronal models of disease for mechanistic and translational studies. The major neurological phenotypes associated with DS include (1) behavioral, motor, psychiatric, and cognitive alteration; (2) deficient neurogenesis during development and perhaps in adulthood; (3) alterations in neural connectivity and synaptogenesis; (4) neuronal dysfunction including deficits in plasticity; and (5) neurodegenerative features similar to AD. Analysis of the genetic mechanisms underlying DS has revealed a prominent role for a subset of HSA21 genes. This provides hope that therapeutic targeting of specific functional deficits can ameliorate DS endophenotypes and provide clinical and behavioral benefits.

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Further Reading

http://www.cdc.gov/features/dsdownsyndrome. CDC Data of Statistics – Feature: Down Syndrome Cases at Birth Increased.

http://www.ensembl.org. Ensembl Genome Browser.