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A new Down syndrome rat model races forward

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Abstract

Animal models of Down syndrome (DS) provide an essential resource for understanding genetic, cellular, and molecular contributions to traits associated with Trisomy 21 (Ts21). Recent genetic enhancements in the development of DS models, including the new TcHSA21rat model, have potential to transform our understanding of and potential therapies for Ts21.

Keywords

trisomy; animal models; gene dosage; neurodevelopment; gene expression

Down syndrome (DS) results from three copies of genes on human chromosome 21 (HSA21) and is manifest by a subset of ~80 clinically defined phenotypes. An extra copy of HSA21 in every cell in most individuals with Trisomy 21 (Ts21) has been considered an intractable disorder, but the use of DS animal models has led to clinical trials to improve cognitive, behavioral, and other traits in individuals with DS. Although rodent models cannot exactly replicate human disease, DS animal models are tools for understanding the relationship between the triplicated genes of human chromosome 21 (HSA21), mechanisms that are altered with this extra gene dosage, and associated phenotypes [1]. For an organism to effectively model any human disease, fulfilling the criteria of construct, face, and predictive validity is essential [2]. Construct validity entails a replication of the etiology between the human disorder and animal model (in the case of DS, three copies of genes on or orthologous to HSA21); face validity refers to how well the model resembles human traits (including behavioral, physiological, cellular, and molecular); and predictive validity refers to how knowledge obtained using the model can be used to accurately predict what will be found in humans with the disorder (discovery of new phenotypes, response to treatment).

Over 20 mouse models of DS have been developed to dissect the gene-phenotype relationship and understand molecular mechanisms of DS-associated traits [3]. DS mouse models have been used to predict human phenotypes and test potential therapies [3]. Construct validity of these models is hampered because orthologous HSA21 genes are found on three different mouse chromosomes. Ts65Dn, the most utilized DS model for the past

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30 years, has a freely segregating chromosome with ~50% of HSA21 orthologs in three copies and some triplicated non-orthologous genes. Newer segmental duplication models of DS do not have an extra chromosome, and not all DS-associated phenotypes are represented in each model. Theoretically, the HSA21 transchromosomic Tc1 mouse overcame problems with construct validity, yet further investigation showed extensive mosaicism (not all cells carried the transchromosome) and was later found to have deletions, duplications, and rearrangements that dampened enthusiasm for this model [4]. Recently Kazuki, Reeves, and colleagues introduced a new transchromosomic model of DS, TcMAC21 mice, overcoming problems of construct validity and mosaicism by attaching the human chromosome to a mouse centromere and introducing this chromosome into mouse cells [5]. TcMAC21 mice replicate many DS phenotypes including behavioral, craniofacial, and learning and memory abnormalities and are a promising resource for future study of DS.

Kazuki, Reeves, and colleagues have now created a transchromosomic DS model, the TcHSA21rat [6]. This new rat model was made using microcell-mediated chromosome transfer (MMCT), ultimately placing a HSA21 with a EGFP insertion (HSA21-EGFP) into rat embryonic stem cells. Trisomic rat offspring can be detected with a UV flashlight because of the EGFP on the transchromosome. Humans, rats, and mice share 95% genomic homology [7], with HSA21 homology found on two rat chromosome [1]. Rats are not just big mice; the most common ancestor of rats and mice occurred 15–20 million years ago. Rats are often preferred in behavioral, cardiovascular and toxicology studies [7]. Additionally, in the dendrites of hippocampal neurons, genetic expression between different strains of rats appeared much more similar (0.5% different) than in different mouse strains (40% different) [8, 9].

The TcHSA21rat model demonstrated excellent construct validity with only two deletions totaling 8.3 Mbp (16 protein coding genes) on the modified HSA21. Genes from the extra chromosome were expressed within an expected range, with a global imbalance of gene expression as reported in DS mouse models and humans with DS. Analysis of highly proliferative lymphatic cells in the blood showed that the extra GFP positive transchromosome was retained in 80% of the cells in 81% of the TcHSA21rat models at one month of age. The TcHSA21rat model showed face validity by altered cognitive and behavioral, brain (including cerebellar), and craniofacial phenotypes. Some rats also exhibited a cardiac phenotype reminiscent of those seen in individuals with DS, but at a lesser incidence. Unlike some DS mouse models, the TcHSA21rat model exhibited a smaller overall brain size, which could have important implications for understanding how brain development is disrupted by extra genetic material on HSA21. The predictive validity of the TcHSA21rat model was confirmed in the detailed cerebellar foliation deficits which are not found in mice. Given the foliation deficits and smaller overall brain, the TcHSA21rat model may better recapitulate some neurological parameters associated with DS.

The TcHSA21rat model offers great promise to better understand DS deficits, leading to improved translational therapies. There are many advantages of using rat models of disease (See Box 1). Due to ease of genetic manipulation, mice have been used in genetics research more often in the past 20 years. Improved genetic techniques in rats shows promise for additional rat models of disease [8]. Success of this exciting new TcHSA21rat DS model

will depend on testing additional hypotheses, which will be contingent on a wide distribution of the model. Additional experimentation should build upon knowledge ascertained from DS mouse models and will require careful notation, similar to the detailed hippocampal foliation in the current study, of distinct predictive phenotypes not heretofore seen in DS mouse models. New studies in awake-behaving animals would be more feasible, e.g., using large-scale neuronal recordings combined with dynamical systems computational analyses [10] that could help uncover altered neural population dynamics underlying cognitive deficits in DS. It will be important to monitor the potential mosaicism of TcHSA21rat model to assure adequate face validity for ongoing studies. The availability of additional genetic tools that can be applied to rat, the strong track record of neurobehavioral phenotypes, and more robust drug studies in rats lead to an optimistic future for the TcHSA21rat, possibly leading to treatments of DS-associated traits.

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Text Box 1:

Advantages of rat models of disease [8, 9]:

- Leading animal model for neuroscience research since the 1940s
- Neurobehavioral phenotypes first established in rats (and later converted to mice) may more closely resemble those found in humans
- More engaged in social behavior, less affected by distractors, less stressed by human contact, less prone to territorial and hierarchical behavior, and perform more stably in tests over time as compared to mice
- Cognitive processing aspects of rats lead to more consistent results from learning and memory tests, including the Morris water maze (a test frequently performed with DS animal models)
- Larger size more amenable to surgical manipulation, and tissue spatial resolution is increased when following disease pathology
- Cardiovascular system more like humans, increased potential for serial blood sampling, and higher frequency of drug studies performed as compared to mice