Down syndrome and the molecular pathogenesis resulting from trisomy of human chromosome 21

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Elizabeth Fisher and Victor Tybulewicz have worked collaboratively for many years on the Down syndrome mouse model project. Elizabeth Fisher’s background is in molecular genetics and mouse models, with an interest in aneuploidy. Victor Tybulewicz is an immunologist whose primary interest is in signal transduction from the antigen receptors of B and T cells. Victor was also one of the first people to manipulate mouse embryonic stem cells to create a knock out mouse. Together Fisher and Tybulewicz created the first mouse model to transmit an almost complete human chromosome through the germline (the Tc1 mouse) and they maintain their joint interest in the different facets of Down syndrome research afforded by the Tc1 mouse model, as well as their individual interests in immunology (Tybulewicz) and neurodegeneration (Fisher).

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Abstract

Chromosome copy number aberrations, aneuploidies, are common in the human population but generally lethal. However, trisomy of human chromosome 21 is compatible with life and people born with this form of aneuploidy manifest the features of Down syndrome, named after Langdon Down who was a 19th century British physician who first described a group of people with this disorder. Down syndrome includes learning and memory deficits in all cases, as well as many other features which vary in penetrance and expressivity in different people. While Down syndrome clearly has a genetic cause - the extra dose of genes on chromosome 21 - we do not know which genes are important for which aspects of the syndrome, which biochemical pathways are disrupted, or, generally how design therapies to ameliorate the effects of these disruptions. Recently, with new insights gained from studying mouse models of Down syndrome, specific genes and pathways are being shown to be involved in the pathogenesis of the disorder. This is opening the way for exciting new studies of potential therapeutics for aspects of Down syndrome, particularly the learning and memory deficits.

INTRODUCTION

Down Syndrome (DS) is the consequence of trisomy of human chromosome 21 (Hsa21) and is the most common genetic form of intellectual disability, occurring in approximately 1 in 700 live births[1]. DS is characterised by invariant features that are common to all affected individuals, including mild-to-moderate learning disabilities, craniofacial abnormalities and hypotonia[2,3]. In addition, at least 80 other variable phenotypes that affect only a proportion of DS individuals have been described, such as an early-onset of Alzheimer’s disease, atrioventricular septal heart defects, acute megakaryoblastic leukemia and a decrease in the incidence of some solid tumours[4-7]. Significant advances in medical treatment and social care have increased the average life span of people with DS to greater than 60 years[8]. The additional copy of Hsa21 results in elevated expression of many of the genes encoded on this chromosome, with varying expression levels in different tissues[9-11]. The increased dosage of Hsa21 genes, and the dosage imbalance between Hsa21 and non-Hsa21 genes has been proposed to cause the plethora of phenotypic alterations that characterize DS. The gene-rich distal part of Hsa21, identified as the ‘Down syndrome critical region’ (DSCR), was initially proposed to be sufficient to cause most of these DS phenotypes[12-14]. However, accumulating evidence points against a single DSCR[14,15]. Current data suggest that a number of ‘susceptibility regions’ located on Hsa21, which are modified by other loci on Hsa21 and elsewhere in the genome, increase the risk of developing specific DS associated phenotypes[14,15].

Mouse models of DS are instrumental in identifying which genes contribute to DS phenotypes, and unravelling the mechanisms by which these phenotypes arise[16-24]. Hsa21 is syntenic to three regions of the mouse genome. Most of the genes on Hsa21 have homologous genes on mouse chromosome 16 (Mmu16), but two smaller gene rich regions have synteny on Mmu10 and Mmu17 (Fig. 1). The majority of mouse models used for DS research are either trisomic for large regions of Mmu16, 10, 17 or are transgenic animals used to investigate overexpression of a single gene[16-22]. The Tc1 mouse model, with which we mainly work, carries a freely segregating almost complete copy of Hsa21, in addition to a normal complement of the mouse chromosome[23].

In this review, we highlight recent developments in understanding how overexpression of Hsa21 genes leads to many of the features of DS. We focus on key areas including brain, heart and cancer, as these are currently the most developed in our understanding of the molecular pathogenesis of DS.

RECENT BREAKTHROUGHS IN OUR UNDERSTANDING OF PHENOTYPES ARISING FROM TRISOMY HSA21

Learning and Memory

People with DS have learning and memory problems and exhibit differences in brain structure compared to the euploid population[24-29]. Mouse models of DS recapitulate these neuroanatomical changes and behavioural deficits, and thus can be used to further our understanding of learning and memory in people with DS[25]. The Ts65Dn mouse model of DS is trisomic for approximately 136 genes on Mmu16 that have homologues on Hsa21[25] (Fig. 1). These mice have learning and memory phenotypes and it has been proposed that excess inhibition of synaptic transmission may contribute to their deficits[25,26]. Recent papers have shown that the
structure of receptors and their abundance at inhibitory synapses is altered in the hippocampus of Ts65Dn mice, which provides insight into the neurological changes that may underlie their DS-associated memory problems\(^{41,42}\). In addition, impaired synaptic plasticity was recently demonstrated in Ts65Dn striatal cholinergic interneurons\(^{43}\), highlighting a potentially novel and important role for the interstitial cholinergic system in the pathophysiology of DS-associated motor and cognitive defects. The Tc1 mouse model of DS, which is trisomic for approximately 80% Hsa21 genes, has short-term but not long-term deficits in hippocampal-dependent learning and abnormalities in long-term potentiation (LTP), which is proposed to be a physiological correlate of learning\(^{33,44}\). Interestingly, although Tc1 mice display major deficits in cerebellum-dependent learning tasks, no abnormalities in synaptic function or in cerebellar long-term depression can be detected in this model\(^{45}\).

In the Ts1Rhr mouse model (Fig. 1), trisomy of 33 Mmu16 genes that are syntenic to the DSCR and include dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 1A (Dyrk1A), potassium inwardly-rectifying channel, subfamily J, member 6 Gene (Girk2) and single-minded homologue 2 (Sim2), cause alterations in dendritic spine morphology and deficits in some behavioural tests\(^{46}\) (Table 1). Trisomy of these genes is necessary but not sufficient to elicit Morris water maze learning deficits in mouse DS models\(^{13}\). These data indicate that interactions of Hsa21 trisomic genes may contribute to DS-associated learning and memory problems. Trisomy of 12 genes (Abcg1-U2af1) found on the Hsa21 sub-telomeric region in Ts1Yah mice (Fig. 1), produced cognitive defects in working and short-term recognition memory, but an enhancement of hippocampal-dependent spatial learning\(^{22}\). This study is pivotal in showing that variation in copy number is not always deleterious.

The over-expression of a number of Hsa21 genes has been implicated in learning and memory deficits in single gene transgenic mouse models, suggesting that trisomy of these genes may contribute to learning disability in DS individuals. These genes include Dyrk1A, synaptopodin 1 (SYNJ1) and SIM2\(^{22,26-28,47,49}\). Recent evidence has emerged for a possible role in brain function of dopa

Neurodevelopment

Neurodevelopment is known to be altered in people with DS. Already by mid-gestation the brains of
Fetuses with DS are smaller than those which do not have the condition. Cerebellar granule cells in Ts65Dn mice have reduced proliferation rates and elongation of the cell cycle length which could potentially result in a decrease in brain mass\[^{[51]}\]; the number of these cells is also reduced in the Tc1 mouse model\[^{[33]}\]. Neural progenitor cells (NPCs) from the Ts1Cje mouse model also exhibit similar defects as well as an increase in cell death\[^{[52]}\]. The Ts1Cje and Ts2Cje mouse models have smaller brains, hypoplasia of the cerebellum, enlarged ventricles and decreased neurogenesis compared to euploid littermates\[^{[53]}\]. The common region that is trisomic between these two mouse models contains approximately 86 genes (Fig.1), suggesting that this trisomic segment contains the causal dosage-sensitive genes for these detrimental developmental phenotypes\[^{[53,54]}\]. The decreased proliferation of cerebellar granule cells observed in the Ts65Dn mice has been attributed to a deficient mitotic response to the Sonic hedgehog (Shh) growth factor\[^{[55]}\]. An altered response to Shh has also been demonstrated in Ts65Dn neural crest progenitor cells, and this may contribute to the craniofacial dysmorphology that is associated with DS\[^{[56,57]}\].

Elevated rates of neuronal apoptosis related to oxidative stress have been reported in DS\[^{[58]}\]. Recent work suggests that Hsa21-encoded proteins PREP1, a transcription factor involved in the regulation of organism size\[^{[59]}\], and tetratricopeptide repeat domain 3 (TTC3), an E3 ubiquitin ligase that targets AKT, a serine/threonine-protein kinase, may contribute to this phenotype\[^{[60]}\]. Moreover, recent research provides evidence that oxidative stress is elevated in the Ts1Cje mouse, suggesting that one or more genes trisomic in this model, likely contribute to DS-associated oxidative stress\[^{[61]}\]. Interestingly, aneuploidy of chromosomes other than Hsa21 also results in elevated apoptosis and reduced cellular proliferation\[^{[62,63]}\].

Recently, it was proposed that DYRK1A contributes to DS neural phenotypes, such as impaired dendritic growth, by disturbing neuron-restrictive silencer factor (REST/NRSF) levels\[^{[27,64]}\]. MicroRNAs encoded by Hsa21 may also influence development of the brain; specifically trisomy of miR-155 and miR-802 has been suggested to regulate the expression of the methyl-CpG-binding-protein gene (MECP2), which is known to be important in neurodevelopment\[^{[65]}\].

### Table 1 Chromosome 21 genes implicated in the pathogenesis of DS phenotypes

| DS Phenotype                  | Implicated Hsa21 Genes | References |
|-------------------------------|------------------------|------------|
| Learning and Memory           | DOPEY2                 | Rachidi et al., 2009\[^{[49]}\]; Yu et al., 2009\[^{[29]}\]; Altafaj et al., 2001\[^{[34]}\]; Meng et al., 2006\[^{[41]}\]; Voronov et al., 2008\[^{[29]}\] |
| Neurodevelopment              | DSCAM                  |            |
|                               | DYRK1A                 |            |
|                               | SIM2                   |            |
|                               | SYNJ1                  |            |
|                               | PREP1                  | Micai et al., 2010\[^{[47]}\]; Suizu et al., 2009\[^{[46]}\] |
|                               | TTC3                   |            |
|                               | APP                    | Rovelet-Lecrux et al., 2006\[^{[28]}\]; Sieggers et al., 2006\[^{[38]}\]; Cabrejo et al., 2006\[^{[49]}\]; Salehi et al., 2006\[^{[30]}\]; Cataldo et al., 2003\[^{[24]}\]; Jiang et al., 2009\[^{[35]}\]; Ryoo et al., 2009\[^{[42]}\]; Ryoo et al., 2008\[^{[41]}\]; Liu et al., 2008\[^{[43]}\] |
|                               | DYRK1A                 |            |
|                               | ITSN1                  | Chang & Min, 2009\[^{[41]}\] |
|                               | RCAN1                  | Chang & Min, 2009\[^{[41]}\] |
|                               | SYNJ1                  | Voronov et al., 2008\[^{[29]}\]; Chang & Min, 2009\[^{[41]}\] |
| Cancer and Leukemia           | ERG                    | Ng et al., 2009\[^{[44]}\]; Sussan et al., 2006\[^{[41]}\]; Baek et al., 2009\[^{[41]}\]; Edwards et al., 2009\[^{[34]}\] |
|                               | ETS2                   |            |
|                               | RCAN1                  |            |
|                               | RUNX1                  |            |
| Heart Defects                 | Region between DSCAM-ZNF295 | Korbel et al., 2009\[^{[44]}\] |
Pharmacological interventions to tackle brain and cognition in DS

This is a relatively new area of research in DS that is rapidly gaining momentum, and which arises from experiments carried out in mouse models in which behavioural, neurophysiological and cellular biology changes can be quantitatively assessed during development and ageing, and then modified through pharmacological intervention.

Several pharmacological interventions to enhance cognition in people with DS have been suggested, based upon efficacy in the Ts65Dn mouse (Table 2). Chronic treatment with gamma-aminobutyric acid (GABA) A receptor antagonists, picrotoxin or pentlenetetrazole, improved hippocampal-based learning and LTP deficits in Ts65Dn animals\cite{30,66,67}. The GABA-ergic system regulates neuronal excitability throughout the nervous system and plays a significant role in cognition. Memantine, a non-competitive N-methyl-D-aspartic acid receptor (NMDAR) antagonist, has also been documented to improve learning in Ts65Dn mice\cite{69}, and is currently undergoing a clinical trial in a large group of DS patients\cite{72}. Some clinical trials of Donepezil, an acetylcholinesterase inhibitor that is proposed to improve cholinergic neurotransmission, have reported small improvements in a subset of measures of cognition in people with DS\cite{76-78}; however, not all Donepezil trials have demonstrated a statistically significant effect\cite{79-81}.

Recently, other pathways that modulate learning and memory have been examined with interest. Norepinephrine signaling in the hippocampus has been suggested to be impaired in the Ts65Dn mice because of degeneration of the locus coeruleus\cite{77,78}. In this model, learning deficits were reversed by treatment with a norepinephrine prodrug, L-DOPS, or

### Table 2 Pharmacological interventions to tackle cognitive deficits in DS

| Pharmacological Compound | Cognitive Effect                                                                 | References                                                                                           |
|--------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Donepezil                | Acetylcholinesterase inhibitor                                                    | Spiridigliozi et al., 2007\cite{70}; Johnson et al., 2003\cite{83}; Lott et al., 2002\cite{80}; Prasher et al., 2002\cite{81} |
| ECGC                     | Natural polyphenol                                                               | Guedj et al., 2009\cite{79}                                                                          |
| Fluoxetine               | Anti-depressant                                                                  |                                                                                                      |
| L-DOPS or Xamoterol      | Norepinephrine prodrug                                                           |                                                                                                      |
|                          | β, Adrenergic receptor partial antagonist                                         |                                                                                                      |
|                          | Improves hippocampal-based contextual learning deficits in Ts65Dn               | Salehi et al., 2009\cite{71}                                                                          |
| Lithium                  | Mood stabilizer                                                                  |                                                                                                      |
|                          | Prenatal treatment rescues impairments in neurogenesis                          | Bianchi et al., 2009\cite{82}                                                                          |
| Memantine                | Non-competitive NMDAR antagonist                                                  |                                                                                                      |
|                          | Improves learning in Ts65Dn                                                       | Costa et al., 2006\cite{84}                                                                          |
|                          | Currently undergoing clinical trial in DS patients                               | Mohan et al., 2009\cite{85}                                                                          |
| NAPVSIPQ & SALLRSIPA     | Neuroprotective peptides                                                          |                                                                                                      |
|                          | Prenatal treatment reverses developmental and glial deficits                      | Toso et al., 2006\cite{86}                                                                          |
| Picrotoxin or Pentlenetetrazole | GABA(A) receptor antagonists                                                   |                                                                                                      |
|                          | Improves hippocampal-based learning and LTP deficits in Ts65Dn mouse model       | Kleschevnikov et al., 2004\cite{87}; Fernandez et al., 2007\cite{88}; Reuda et al., 2008\cite{89} |
| Vitamin E                | Antioxidant                                                                      |                                                                                                      |
|                          | Partially rescues cognitive and morphological abnormalities in Ts65Dn           | Lockrow et al., 2009\cite{90}                                                                          |
|                          | Reduces oxidation state of S100β                                                | Bialowas-McGoey et al., 2008\cite{91}                                                                |
Neurogenesis impairments in the Ts65Dn mouse have been rescued by prenatal treatment with the mood-stabiliser, lithium, and by use of the antidepressant, fluoxetine. Developmental delays and glial deficits in the Ts65Dn mouse model have been demonstrated to be partially reversed through prenatal treatment with neuroprotective peptides NAPVSIPQ+SALLRSIPA. These results indicate that therapies during pregnancy could potentially improve developmental and glial deficits in DS.

The current findings are based on a thorough understanding of neuronal and cognitive deficits in mouse models of DS and are exciting in the therapeutic opportunities they offer. However, as with all pharmacological interventions, caution must be taken in translating findings from mice to humans.

**Alzheimer Disease in DS**

A high incidence of early-onset Alzheimer Disease (AD) occurs in people with DS, with 30-70% of DS individuals developing dementia by the age of 60. AD pathology is characterized by brain atrophy, extracellular β-amyloid (Aβ) deposits and the accumulation of neurofibrillary tangles (NFTs) that are composed of hyperphosphorylated Tau. The amyloid precursor protein, amyloid precursor protein (APP), from which Aβ is produced, is encoded on Hsa21. In DS, the triplication of APP is proposed to be the underlying mechanism through which trisomy 21 individuals demonstrate an increased frequency of dementia.

Neurodegenerative phenotypes have also been observed in animal models of DS. In particular, the loss of basal forebrain cholinergic neurons (BFCNs) occurs early in AD and is also observed in the Ts65Dn mouse. Degeneration of these cells is related to a failure in the retrograde transport of nerve growth factor (NGF), and may arise from trisomy of APP. Increased APP expression is also linked to enlargement of early endosomes. Recently, it was reported that lowering the expression of APP or beta-site APP-cleaving enzyme 1 (BACE-1), reversed endocytic abnormalities in fibroblasts derived from people with DS, and the over-expression of APP alone resulted in early endosome enlargements. These data suggest that triplication of APP is sufficient to cause endosomal deficits, in contrast to previous reports. Hsa21 genes other than APP may also contribute to endosomal phenotypes, in particular, overexpression of Hsa21 gene homologues in Drosophila, dap160/ITSN1 (intersectin1), synj/SYNJ1 and nla/RCAN1 (runtr-related transcription factor 1), results in abnormal synaptic morphology and impaired vesicle recycling.

Other Hsa21 trisomic genes may also contribute to AD through different mechanisms. DYRK1A, an Hsa21 encoded kinase, phosphorylates Tau at a key priming site which may mediate its AD-related hyperphosphorylation in people with DS. DYRK1A can also phosphorylate APP. Indeed, increased phosphorylation of Tau has been reported in the Ts1Cje mouse model of DS that is not trisomic for APP (Fig. 1). Mis-regulated splicing of Tau may contribute to NFT formation in AD. . PCBP3, an Hsa21 protein, modifies splicing of Tau and may contribute to the expression of AD associated Tau isoforms in people with DS. Recently, degeneration of Purkinje cells in the cerebellum of aged Ts65Dn mice, proximal to deposits of Aβ and Tau, has been observed.

**Other neurological disorders**

Six percent of children and adolescents with DS have epileptic seizures. Children with DS are also susceptible to infantile spasms, however little is known about the molecular mechanisms underlying this. Treating Ts65Dn mice with GABA(B) receptor agonists induced a phenotype reminiscent of infantile spasms, providing a model to further understand the pathogenesis of this phenotype. Moyamoya syndrome, a cerebrovascular condition that is characterized by reduced blood flow predisposing to stroke, has been reported to occur with a higher frequency in people with DS than in the general population. Recently, the expression of β-catenin was found to be increased in brain capillary endothelial cells in the Ts65Dn mouse model, however whether this finding is linked to Moyamoya syndrome is as yet unclear.

People with DS have been reported to experience disturbed sleeping patterns. Studies of circadian activity in the Ts65Dn mouse model have reported...
conflicting results of both intact\textsuperscript{[25,115,116]} and disturbed rhythms\textsuperscript{[117]}. Future studies of this phenotype in alternative mouse models of DS will thus be of value.

**Cancer and leukemia**

Children with DS have a greatly elevated risk of developing the otherwise very rare transient myeloproliferative disorder (TMD), as well as acute megakaryocytic leukemia (AMKL) and acute lymphoblastic leukemia (ALL)\textsuperscript{[6,118,119]}. Trisomy of Hsa21 leads to an expansion of the megakaryocyte-erythroid progenitor population\textsuperscript{[120,121]}, which precedes the development of TMD. The development of TMD and AMKL is almost always associated with stereotypical mutations in exon 2 of the \textit{GATA binding protein 1} (\textit{GATA1}) gene resulting in the synthesis of a truncated \textit{GATA1} protein termed \textit{GATA1s}\textsuperscript{[122,123]}. Mutations in Janus kinase 3 (JAK3) have also been reported by several groups to be associated with AMKL\textsuperscript{[119,124-126]}. Additionally, one fifth of DS-ALL cases have been associated with janus kinase 2 (JAK2) point mutation\textsuperscript{[129,130]}. DS-ALL is also associated with aberrant expression of cyto kine receptor-like factor 2 (\textit{CRLF2}) linked to genomic rearrangements\textsuperscript{[130-132]}. Trisomy of an Hsa21-encoded gene, \textit{v-ets erythroblastosis virus E26 oncogene homolog} (ERG), is required for development of the myeloproliferation defect in the Ts65Dn model\textsuperscript{[133]}. The Hsa21 gene \textit{run-related transcription factor 1} (\textit{RUNX1}) has also been proposed to regulate hematopoiesis via the phosphoinositide 3 (PI3) kinase/AKT pathway\textsuperscript{[133-136]}.

Despite perturbations of hematopoietic development in the Ts1Cje, Ts65Dn and Tc1 models of DS, these mice do not develop leukaemia, even when the trisomic models also express disease-associated \textit{GATA1} mutations\textsuperscript{[137-139]}. It is possible that trisomy of Hsa21 genes other than those encoded in these models, in concert with mutations in non-Hsa21 encoded genes such as \textit{GATA1}, JAK3 or \textit{CRLF2}, may be required for the development of leukaemia.

Although DS is associated with a predisposition to leukaemia, people with DS have a reduced risk of developing most solid tumours\textsuperscript{[21,140]}. Crossing a mouse model of colon cancer, \textit{Apc}\textsubscript{min}, with mouse models of DS resulted in reduced formation of tumors, dependent on the trisomy of the Hsa21-encoded \textit{ETS2} gene\textsuperscript{[141]}. Recently overexpression of the Hsa21 gene, \textit{regulator of calcineurin} (\textit{RCAN1}), was shown to be sufficient to suppress tumour growth by attenuating angiogenesis via the regulation of vascular endothelial growth factor (VEGF) signaling\textsuperscript{[142]}. However, in a Ts65Dn trisomic background removal of one copy of \textit{Rcan1} did not completely abrogate the effect of trisomy on tumour formation, suggesting that other Hsa21 genes also contribute to this phenotype\textsuperscript{[143]}.

**Heart defects**

Congenital heart defects (CHD) are prevalent in 40% of children with DS and over 50% of all atrioventricular septal heart defects (AVSDs) in infancy are attributed to trisomy Hsa21\textsuperscript{[5,144]}. Mutations in \textit{cysteine-rich with EGF-like domains 1} (\textit{CRELD1}), a non-Hsa21 gene, contribute to the occurrence of AVSD in DS\textsuperscript{[144]}. Several DS mouse models exhibit heart defects reminiscent of those in DS\textsuperscript{[12,33-35,145]}, suggesting that trisomic genes common to these models influence the development of the heart. Analysis of the occurrence of CHD in people who have partial trisomies of Hsa21 has suggested that trisomy of genes within a 1.77 Mb region [\textit{DSCAM-ZNF295} (\textit{zinc finger protein 295})] of Hsa21 may be sufficient for the development of CHD\textsuperscript{[145]}.

**CONCLUSION**

DS is complex disorder and dissecting the genetic and molecular processes underlying the syndrome requires many different complementary approaches, including the study of human data and mouse and other model organisms. However, several recent breakthroughs have increased our understanding of the effects of Hsa21 trisomy. Combining information from studies of people with DS with the power of mouse models of trisomy has enabled genetic associations to be tested and continues to lead to the identification of genes that cause DS-associated pathology. Significant advances in basic research have been instrumental in determining the molecular mechanisms underlying these phenotypes leading to useful therapeutic interventions. However, many aspects of DS crucial to the health and well-being of people with the condition remain to be investigated and require study at all levels.

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