Review

Differential gene expression studies to explore the molecular pathophysiology of Down syndrome

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Abstract

Trisomy 21, which causes Down syndrome, is the model human disorder due to the presence of a supernumerary chromosome. The completion of the sequence of chromosome 21 and the development of appropriate animal models now provide the molecular infrastructure and the reagents to elucidate the molecular mechanisms of the different phenotypes of Down syndrome. The study of the overexpression of single genes, and the dysregulation of global gene expression will enhance the understanding of the pathogenesis of the cognitive impairment of this syndrome. © 2001 Elsevier Science B.V. All rights reserved.

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Topic: Developmental disorders

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1. Introduction

Down syndrome (DS), caused by trisomy for chromosome 21 (T21), is the most common genetic cause of mental retardation with an incidence of approximately 1/700 live births. Changes in the neuropathology, neurochemistry, neurophysiology, and neuropharmacology of DS patient brains indicate that there is probably abnormal development and maintenance of CNS structure and function [11]. In addition to the mental retardation and facial characteristics, there are numerous other phenotypes...
associated with DS including congenital heart disease, early onset Alzheimer’s disease and an increased risk of childhood leukemia. With the development in recent years of mouse models of DS, the completion of the chromosome 21 (HC21) sequence, and the development of tools to measure global gene expression it is likely that in the near future we will gain a greater insight into the underlying molecular biology of DS.

2. Trisomy 21 and Down syndrome

2.1. Hypotheses for the molecular mechanisms of phenotypes

There are two elementary working hypotheses for how trisomy 21 leads to DS. First, the presence of an extra copy of certain but not all of the approximately 225 HC21 genes contributes to aspects of the complex DS phenotype. Second, the products of these genes act directly or, perhaps more likely, indirectly through processes that affect the expression of other genes or gene products (Fig. 1). These hypotheses require different experimental approaches to fully understand DS. For the first, it is necessary to identify all HC21 genes and their mouse homologues, know their spatial and temporal expression patterns and, importantly, identify the developmental stages where they are overexpressed and thus likely to contribute to DS phenotypes. Secondly, we need to understand the changes in global gene expression caused by the overexpression of HC21 genes.

2.2. The sequence of HC21 and the whole genome — tools for discoveries

On May 18, 2000, the (almost) entire sequence of the

Fig. 1. Models for the pathogenesis of Down syndrome. The genes of HC21 are depicted as green and red boxes. Some of the ‘red-type’ genes contribute directly to the pathogenesis of DS, while other ‘red-type’ genes contribute via a more general dysregulation of gene expression. ‘Green-type’ genes do not contribute to any of the phenotypes of DS.
long arm of HC21 was made freely available in a landmark publication [17]. The completion of the HC21 sequence was the fruit of an international collaboration with leading contributors from Japan and Germany, but was the conclusion of research efforts of many investigators that studied HC21 over the last 15 years. By allowing the rapid identification of all HC21 genes, it is anticipated that the availability of the sequence will now accelerate and facilitate discoveries concerning the disease mechanisms of trisomy 21, including the mental retardation, HC21 monogenic disorders and susceptibility genes for common polygenic traits.

The determination of the sequence was achieved using previously mapped BAC and cosmids clones, either by shotgun sequencing or by serial deletions using transposon insertions [17]. The sequence is of high quality (error rate less than 1 in 10,000 nucleotides), with only 3 cloning gaps on 21q, each of which has been estimated by interphase FISH to be no more than 30–40 kb. There are therefore 4 contigs for 21q (from 21cen to 21qter) of lengths 28515, 219, 1378, and 3429 kb, for a total of 33,546,361 nucleotides. Only approximately 3% of the sequence encodes for proteins. Approximately 38% of the sequence is interspersed repeat: 10.8% SINEs, 15.5% LINEs, and 11.7% are other repeats. In addition 1.3% encodes for short sequence repeats that may be polymorphic in human populations. The remainder are gene flanking regions, introns and other DNA of unknown function.

Comparison of the genomic sequence to full- or partial-length cDNAs, and ESTs from all species, together with the use of exon prediction programs revealed 127 known genes, 98 predicted genes (13 similar to known proteins, 17 anonymous ORFs featuring modular domains, and 68 anonymous transcription units with no similarity to known proteins) and 59 pseudogenes. Annotation of the genes on HC21 recognized several criteria: category 1 genes were those with identity or extensive homology to known genes; category 2 were those with similarity to cDNAs or ORFs (open reading frames) from other organisms; category 3 those with predicted amino acid similarity to a recognized protein domain or region; category 4 those identical to spliced ESTs or only predicted by exon recognition computer programs.

There exists striking differences in gene density throughout the length of 21q. For example, the proximal half of 21q contains only 58 genes, while the distal half contains 167 genes. Remarkably, in the proximal half there is a region of about 7 Mb containing only 7 genes. An intensive international effort is now directed towards the revision and update of the gene catalogue with the experimental confirmation and the discovery of previously unrecognized genes. This is possible because of the accumulation of additional ESTs, the sequence of the genome of other organisms, and the 'wet lab' experiments (e.g. RT-PCRs, 5’ and 3’ RACE). Indeed at our most recent count we could recognize 156 known genes, and 72 predicted genes for a total of 228 genes.

More detailed annotations of these gene predictions are obviously necessary. For example genes can also be categorized according to the function of their predicted protein; there are 17 genes that encode transcription regulators, 8 kinases, 4 adhesion molecules, etc. [14]. Among the HC21 genes, approximately 35% are homologous to genes in Drosophila, 35% to C. Elegans, and 18% to yeast Saccharomyces cerevisiae. Importantly for the use of the mouse as a model of DS, there is no example in which a human gene does not have a mouse homologue.

The HC21 gene catalogue needs to be completed soon with the description of the full-length sequences of all genes, their alternative splicing variants, and their temporal and tissue distribution of expression. After this initial phase of characterization, a serious and long term effort needs to be directed towards the elucidation of the function of each gene product. The availability of the HC21 gene catalogue now permits the development of testable hypotheses regarding the contribution of certain genes to selected phenotypes of DS. This will frequently be performed by using transgenic mice overexpressing single and/or multiple genes, and comparison of the phenotypes of these transgenic mice to the phenotype of the partial trisomies (see below).

Besides gene identification, the sequence of HC21 also provided information on very long repeats that may predispose to unequal crossing over and deletion/duplication syndromes [21]. In addition, by comparison of the genotyping data in the members of the CEPH families over the last 15 years, with the nucleotide sequence, we now know the patterns of meiotic recombination on the different parts of the chromosome [24]. The recombination rate varies considerably between genders across 21q but is the greatest (eightfold) in the pericentromeric region, with a rate of approximately 250 kb/cM in females and approximately 2125 kb/cM in males. We have also been able to use the genomic sequence as a framework for identifying coding single nucleotide polymorphisms (cSNPs), which can be used in mapping genetic disease and identifying susceptibility genes in multigenic disorders [9].

3. Mouse models of Down syndrome

As three copies of many genes contribute to DS, mice trisomic for regions syntenic to HC21 can serve as models for overexpression of selected chromosomal regions. HC21 is homologous to segments of three mouse chromosomes: from 21cen to 21qter, about 30 Mb are homologous to mouse chromosome 16, 2 Mb to mouse chromosome 17, and 2 Mb to mouse chromosome 10 (Fig. 2). Although we might expect to see species-specific differences, an underlying assumption in using mouse models of DS is that many of the genetic pathways are conserved, and this will be mirrored in the phenotypes caused by imbalances in gene dosage.

Current mouse models of DS can be split into two
groups (Table 1). Segmental trisomy mice for chromosome 16 have a triplication of many genes, and may be considered an adequate model because they accurately reflect the triplication of a large chromosomal region (Fig. 2). In contrast, mice overexpressing single genes can be used to directly test the gene dosage/phenotype hypothesis for a particular gene, but aspects of the DS phenotype caused by imbalance of a number of HC21 genes will be lost.

The first mouse model of DS reported was the trisomy 16 (T16) mouse [13]. Although the T16 mouse showed some characteristics of DS [8], its value was limited because of early postnatal lethality and the fact that mouse chromosome 16 contains many genes found on human chromosomes other than HC21.

A mouse with partial T16 has been generated using a reciprocal chromosomal translocation that contains a region of chromosome 16 corresponding to HC21 from...
Table 1
Mouse models of DS

<table>
<thead>
<tr>
<th>Model</th>
<th>Genotype</th>
<th>Neurological phenotype</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Segmental trisomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ts16</td>
<td>Trisomy 16</td>
<td>Reduced brain size and some structural changes</td>
<td>[7]</td>
</tr>
<tr>
<td>Ts65Dn</td>
<td>Trisomic for <em>App-Tmprss2</em> (&gt;65 known genes)</td>
<td>Learning and behavioural deficits, degeneration of basal forebrain cholinergic neurons</td>
<td>[28]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduction of the cerebellar volume and granule cell density</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced cell number and volume in the hippocampal dentate gyrus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduction in excitatory (asymmetric) synapses in the temporal cortex at advanced ages</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age-related degeneration of basal forebrain cholinergic neurons</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Astrocytic hypertrophy and increased astrocyte numbers</td>
<td></td>
</tr>
<tr>
<td>Ts1Cje</td>
<td>Trisomic for <em>Tmprss2-Sod1</em> (&gt;53 known genes)</td>
<td>Learning and behavioural deficits (&lt;less severe than in Ts65Dn)</td>
<td>[32]</td>
</tr>
<tr>
<td>Ms1Ts65</td>
<td>Trisomic for <em>App-Sod1</em> (&gt;14 known genes)</td>
<td>Learning deficits (&lt;less severe than in Ts1Cje)</td>
<td>[31]</td>
</tr>
<tr>
<td><strong>Single gene</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TgSod1</td>
<td>Transgenic for human <em>SOD1</em></td>
<td>Learning defects</td>
<td>[12]</td>
</tr>
<tr>
<td>TgPfk1</td>
<td>cDNA, highly overexpressed</td>
<td>–</td>
<td>[10]</td>
</tr>
<tr>
<td>TgS100β</td>
<td>2–12 copies</td>
<td>Astrocytosis, neurite degeneration</td>
<td>[29]</td>
</tr>
<tr>
<td>TgApp</td>
<td>YAC, low copy</td>
<td>Cognitive/behavioural defects</td>
<td>[23]</td>
</tr>
<tr>
<td>TgEts2</td>
<td>cDNA, highly overexpressed</td>
<td>–</td>
<td>[34]</td>
</tr>
<tr>
<td>TgHmg14</td>
<td>2–6 copies</td>
<td>–</td>
<td>[4]</td>
</tr>
<tr>
<td>TgMnb</td>
<td>YAC, 1–3 copies</td>
<td>Learning/memory defects</td>
<td>[33]</td>
</tr>
<tr>
<td>TgSim2</td>
<td>BAC, 1–2 copies</td>
<td>Behavioural defects</td>
<td>[5]</td>
</tr>
</tbody>
</table>

markers *App* to *Tmprss2* [28] (Fig. 2). Because of the availability of the HC21 sequence, we know that this region contains 65 known genes and 44 predicted genes. Another translocation model, Ts1Cje, is partially trisomic for a syntenic region from *Sod1* to *Tmprss2*, a region with at least 53 genes [32]. In addition, a mouse trisomic for the segment *App* to *Sod1* named Ms1Ts65 has been generated and partially characterized [31]. Both Ts65Dn and Ts1Cje mice display a variety of phenotypic abnormalities possibly similar to human DS phenotypes. Interestingly, Ts1Cje mice show only a subset of Ts65Dn phenotypes as detected by Morris water maze and even a milder deficit is present in the Ms1Ts65 mice [31]. The differences between these models will prove useful in testing contributions of gene to phenotype; for example, both *Synj1* and *Girk2* genes are triplicated in Ts65Dn and Ts1Cje mice, but *Girk1* is only triplicated in Ts65Dn and Ms1Ts65 mice.

Ts65Dn is by far the most studied model and recent work has shown that it is a very promising model of DS [27] (Table 2). All of these phenotypes are also present in DS individuals. Particularly striking is the report by Baxter et al. [2] on the parallels between the cerebellar pathology between DS and Ts65Dn mice. They first observed a reduction in granule cell density in Ts65Dn mice and then were able to show that this was also present in the cerebellum of DS individuals, confirming previous morphometric studies of DS brains using magnetic resonance imaging which have shown reduced size of cerebral and cerebellar hemispheres, hippocampus, amygdala and larger...
parahippocampal gyrus [1,25,26]. The precise localisation of affected structures in DS brain is of primary interest in order to understand pathophysiology of DS and to analyse the underlying molecular changes using global gene expression survey techniques as discussed below.

Single gene approaches to modelling DS in mice used several strategies (see Table 1). The advantage of this approach is the effect of gene dosage for a single gene can be studied, as pioneered by Groner et al. [12]. To achieve results of biological significance in DS, the transgene needs to be regulated by its normal promoter and other regulatory elements, and only one extra copy needs to be expressed. One such example has been described for the Sim2 gene, which shows abnormalities involving spatial exploration, social interactions and reduced nociception [5]. Considerable knowledge could also gained by multicopy overexpression of the transgene [34]. The breeding of these animal models to different mouse genetic backgrounds may uncover the contribution of the entire genome in the modification of certain DS phenotypes.

The sequence of HC21 now permits the cloning of appropriate homologous regions of the mouse genome which in turn will facilitate the creation of additional partial trisomies for mouse chromosomes 17 and 10 by Cre-loxP-mediated somatic or meiotic recombination [18,36]. The breeding of these different mouse strains will ultimately result in the creation and study of a mouse model trisomic for the entire region homologous to HC21. The contribution of the trisomy of individual genes in the mouse phenotype could further be evaluated by the deletion of one copy of the gene from the partial trisomy mouse; this could be achieved by crossing knockout mice for a particular gene to the partial trisomy mouse.

4. Consequences of aneuploidy: alterations in global gene expression in mouse models of DS

In DS it is often assumed that aneuploidy will lead to overexpression of genes on HC21. But it is not clear that all genes will be overexpressed; for example, regulatory feedback loops may ensure that many genes are expressed at normal levels. Overexpression has been reported for some genes in DS, for example MNBH [16] and APP [28], but no systematic attempt has been made to identify which genes are overexpressed, to what level, and, critically, in which tissues and which time. Interestingly, of 15 mouse chromosome 16 genes (homologous to HC21) detected by SAGE (see below) on brains of Ts65Dn mice [6], only three (Ifnar2, Ifngr2 and Cbr) showed overexpression. Although at first glance these data would suggest that the majority of HC21 genes are not overexpressed in DS, it should be remembered that this study was only on a single, and very complex organ (brain) at a single time in development. It is for this reason that more comprehensive surveys need to be performed.

4.1. Identifying gene expression differences by SAGE

We have analysed differences in the global gene expression profiles induced by the aneuploidy in brains of normal and Ts65Dn adult male mice (P30) using Serial Analysis of Gene Expression (SAGE) technique. RNAs from three Ts65Dn brains and four matched controls at postnatal day P30 were used for the SAGE protocol in order to minimize possible variability due to polymorphisms between individual mice. The Ts65Dn mouse samples were provided by Drs M. Davisson, Jackson Lab, Bar Harbor, ME, USA and X. Estivill, Barcelona, Spain. Plasmid libraries containing inserts with tags from these samples were made (as described in [35]), and individual clones were subjected to nucleotide sequencing. The resulting SAGE tags were analysed using a series of computer programs provided by Dr K. Kinzler (Johns Hopkins University).

Analyses of 152,791 RNA TAGs from Ts65Dn and normals, revealed 45,856 unique tags in the combined sample defining the mouse brain transcriptome corresponding to an estimated 26,652 transcripts (Fig. 3A). Expression levels of mouse genes ranging from 2 to 5252 transcript copies per cell were observed. Thirty three transcripts expressed at over 500 copies per cell comprised 11% of the cellular mRNA mass and the most highly expressed 742 transcripts/tags accounted for 37% of the cellular mRNA content. Most unique transcripts were expressed at levels equal to or lower than 5 copies per cell, with 28% of the mRNA mass comprising 81% of the unique transcripts expressed (Fig. 4). The TAGs matched approximately 4000 known genes (there are ~6000 mouse mRNA sequences in GenBank at the time of publication [6]) and approximately 10,000 EST clusters with unknown functions (out of ~70,000 mouse UniGene clusters), whereas the remaining transcript TAGs (76%), mainly among the genes with low expression levels had no matches in public databases.

The vast majority of transcripts are expressed at the same or similar levels between Ts65Dn and normals. There are 330 tags with statistically significant expression differences (P<0.05) (Fig. 3B). Approximately half of the differentially expressed TAGs (161) are under- and half are over-represented (169) in Ts65Dn male compared to normal male SAGE libraries. 112 TAGs matched known genes, 133 matched ESTs and 85 were unknown. There are 14 ribosomal protein genes (9 underepressed) among the 330 statistically significant differences between normal male and Ts65Dn male brains possibly implying abnormal ribosomal biogenesis in the development and maintenance of Down syndrome phenotypes.

Also among the differentially-expressed tags which match to known genes are many that could clearly have a pathological role in both the developmental and neurodegenerative aspects of DS. Several of these are discussed below.

Genes involved in neural development: microtubule-
Fig. 3. SAGE (serial analysis of gene expression). A. Cumulative number of unique tags in the mouse brain transcriptome as a function of total tags sampled. The rate of unique tag identification decreases as more tags are sequenced but does not reach zero [6]. B. Comparison of the observed frequencies of tags from Ts65Dn and normal mice. The vast majority of tags were expressed at the same level (blue circles), but 330 tags showed significant expression differences (red circles) [6].

**Transcript (TAG) number**

![Pie chart showing transcript (TAG) number distribution](image)

- >500/cell: 33
- 50-500/cell: 709
- 5-50/cell: 7821
- <5/cell: 37293

**Transcript (TAG) abundance**

![Pie chart showing transcript (TAG) abundance distribution](image)

- 26% (50-500/cell)
- 34% (5-50/cell)
- 28% (<5/cell)
- 11% (1-50/cell)
- 26% (1-50/cell)

Fig. 4. The mouse brain transcriptome. Tags after analysis of 45,856 unique Tags of the mouse brain transcriptome. The pie on the left shows the distribution of unique Tags according to their abundance in the average 'brain cell'. The pie on the right shows the distribution the 152,791 total 'tags' representing 45,856 unique transcripts as percentages of total cellular mRNA by mRNA expression levels (copies per cell).
associated protein 1B (Map1b; T65:N30) (OMIM 157129) is involved in cytoskeletal changes that accompany neurite extension during brain development. Mice homozygous for null Map1b alleles die during embryogenesis and heterozygotes show abnormal Purkinje cell dendritic processes, and histologic and immunohistochemical changes in the olfactory bulb and hippocampus; Dynactin 1 (Dctn1; T38:N20) (OMIM 601143) is required for the cytoplasmic dynein-driven retrograde movement of vesicles and organelles along microtubules; Synapsin I (Syn1; T14/N34) (OMIM 313440) is a neuronal phosphoprotein that coats synaptic vesicles, binds to the cytoskeleton, and is believed to function in the regulation of neurotransmitter release.

Genes affecting cellular proliferation and viability: Calmodulin (Calm1; T23:N43) (OMIM 114180) mediates the control of a large number of enzymes by Ca\(^{2+}\), including a number of protein kinases and phosphatases. Its functions include roles in growth and the cell cycle as well as in signal transduction and the synthesis and release of neurotransmitters; Nucleosome assembly protein 1-like 2 (Nap1l2; T5:N0) (OMIM 300026) has been shown by gene targeting to be a tissue-specific factor interacting with chromatin to regulate neuronal cell proliferation. The effect of overexpression of Nap1l2 is unknown.

Genes involved in neural degeneration: Amyloid beta (A4) precursor-like protein 1 (Aplp1, T26:N9) (OMIM 104775) is related to the amyloid beta protein precursor (App) and as a member of this gene family could be involved in the Alzheimer disease neuropathology seen in DS. Microtubule-associated protein tau (T10:N1) (OMIM 157140) is a core protein of the paired helical filament of Alzheimer’s disease. It is also mutated in an autosomal dominant inherited dementia, frontotemporal dementia with Parkinsonism (also called Pick’s disease).

4.2. Identifying gene expression differences by microarray

The SAGE technique has several advantages since it provides a quantitative and comprehensive comparisons of gene expression; it has however, also disadvantages, in that it is time-consuming and expensive and cannot therefore be used to examine expression at many developmental stages. For this reason we have begun to use the recently developed microarray technology [3] (for a review of microarrays see The Chipping Forecast at www.nature.com/ng/web specials/). Microarrays experiments to assess gene expression differences in both human DS and mouse models of DS (Ts65Dn) are underway. The sources of these microarrays are shown in Table 3, and an example of a hybridization experiment is shown in Fig. 5.

5. Conclusions

The sequence of HC21 provides now the infrastructure for real progress on the understanding of the molecular pathophysiology of phenotypes of Down syndrome. The development and study of mouse models will aid in the matching of genes to certain phenotypes. Methods for assessing transcriptome and proteome differences in cells, tissues and organs with partial or complete trisomy 21 in different stages of development will generate new testable hypotheses for the pathogenesis of certain phenotypes. In addition, the functional analysis of the HC21 genes using various model organisms will elucidate the implication of certain genes in the abnormal molecular signaling and developmental pathways that are perturbed in Down syndrome.

Acknowledgements

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Table 3
Microarrays used in these studies

<table>
<thead>
<tr>
<th>Array</th>
<th>Source</th>
<th>Format</th>
<th>No. of clones</th>
<th>Hybridised with RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>GF205</td>
<td>Research Genetics</td>
<td>Nylon</td>
<td>5184</td>
<td>Human Brain normal/DS</td>
</tr>
<tr>
<td>Human UniGene set</td>
<td>RZPD (<a href="http://www.rzpd.de">www.rzpd.de</a>)</td>
<td>Nylon</td>
<td>32,000</td>
<td>Human Brain normal/DS</td>
</tr>
<tr>
<td>Micromax I</td>
<td>NEN (<a href="http://www.nen.com">www.nen.com</a>)</td>
<td>Glass</td>
<td>2400</td>
<td>Human Brain normal/DS</td>
</tr>
<tr>
<td>Mouse UniGene set</td>
<td>RZPD (<a href="http://www.rzpd.de">www.rzpd.de</a>)</td>
<td>Nylon</td>
<td>25,000</td>
<td>Mouse brain normal/Ts65Dn</td>
</tr>
</tbody>
</table>
Fig. 5. Microarray analysis of gene expression differences. A. Portion of a 25,000 transcript nylon array hybridised with whole P30 brain from a Ts65Dn mouse. This image shows only a region containing ~500 spots. B. Scatterplot comparison of the ratios in expression levels of 25,000 transcripts between Ts65Dn and normal mouse brain.

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Engineering mouse chromosomes with Cre-loxP: range, efficiency,