



How does a 1.5-Fold Increase in Gene Dosage in Chromosome 21 Causes the Pleiotropic Phenotypes in Down Syndrome?

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Down syndrome (DS) is caused by the presence of all or part of an extra copy of human chromosome 21 (HSA21) [1]. As many organs and systems are affected, DS patients show highly complex clinical features, such as distinctive facial morphology, intellectual disabilities, hypotonia, heart defects, as well as abnormalities of the gut and the immune system [2]. The severity of each feature, including mental retardation, is highly variable among individuals and suggests that there is an important contribution from the interaction between genetic elements and environmental factors. It has been hypothesized that the complex phenotypes in DS are caused by the overexpression of ~250 HSA21 genes. This hypothesis has been tested in the partial trisomy mouse model Ts65Dn [3]. Surprisingly of the 78 protein-coding genes triplicated in the Ts65Dn model, approximately only one third (37%) are expressed at the theoretical value of 1.5-fold. On average, while 45% of the 78 genes are expressed at levels significantly lower than 1.5-fold, 9% exhibit no change in expression. Interestingly, 18% of non-HSA21 genes are expressed at levels significantly greater than 1.5-fold [3]. A similar study found that nearly all of the genes with a dosage imbalance in the Ts65Dn model showed an increase in transcript level in the tissues tested. However, some of these genes showed down regulation, compensation or strong overexpression in a tissue-specific manner [1,4]. Together, these results indicate that gene expression levels in DS are not only related to gene copy number but may also be manipulated by complex regulation mechanisms.

In fact, the regulation of gene expression during development is a complex network, which consists of transcriptional regulation (e.g., transcription factors, co-activators, or suppressors) and posttranslational regulation (e.g., histone modifications, DNA methylation, localized translation, and non-coding RNAs) [5]. Transcriptional regulation usually works as an on-off switch, while posttranscriptional regulation serves to fine-tune gene expression profiles. It is through the combined actions of transcriptional regulation, posttranscriptional regulation and their interactions that the exquisite regulation of gene expression in 3 responses to environmental stimuli at different developmental stages is achieved [5]. Thus, to better understand the etiology that underlies the pleiotropic phenotypes in DS, the effects of imbalanced gene-dosage in HSA21 on gene expression must be put into a genomic context.

A recent study using integrated databases, which merged different data formats originating from distinct but complementary sources, demonstrated that HSA21 contains 238 coding genes and 296 noncoding genes and that both sections include genomic/structural and regulatory transcripts [6]. Given the complex regulation of gene expression, a 1.5-fold increase in gene dosage in HSA21 could alter genome-wide, gene expression profiles in multiple ways. First, some genes could be strongly overexpressed (more than 1.5-fold) by additive or synergistic effects, as well as the amplification of specific signalling cascades. Second, some genes could be expressed at the theoretical value of 1.5-fold because of their increased gene dosage. Third, some genes may not show apparent changes in their expression level. One possibility is that these genes are not affected by the increased gene dosage of HSA21, or that any effects from gene-dosage on these genes only occur in a tissue-specific or a spatiotemporal manner. For

example, if a sample analysed is neither the right tissue type nor at the right developmental stage, the expression level of certain genes might not appear significantly changed. Another possibility is that these genes are regulated by more than one mechanisms, each potentially having opposite effects on the overall gene expression, resulting in little net change. Finally, a forth group of genes could also be down-regulated in DS. Here, the gene products of HSA21 could target these genes directly or indirectly via the gene regulation network and cause their expression to be suppressed at the transcriptional or posttranscriptional level. Ultimately, all of these net changes in gene expression profiles could contribute the pleiotropic phenotypes observed in DS individuals.

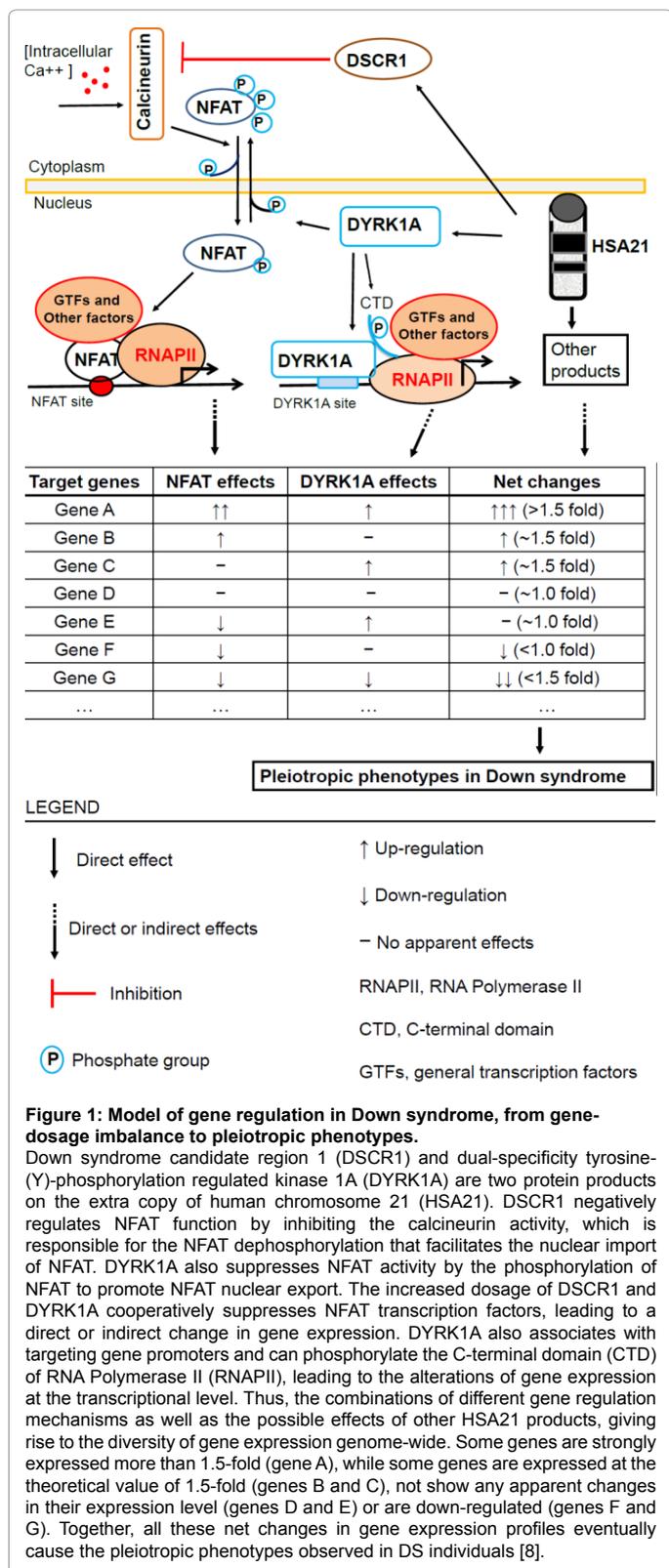
There is accumulating evidence indicating that the alterations of enzyme activities, signalling pathways, transcriptional programs, and their interactions (cooperation, additive, synergetic or compensation) are implicated in the diversity of gene expression in DS. For example, the protein products of two genes on 4 HSA21, Down syndrome candidate region 1 (DSCR1) and dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A (DYRK1A), have been shown to functionally interact [7]. Their increased dosage cooperatively leads to the dysregulation of signalling pathways controlled by the nuclear factor of activated T cells (NFAT) family of transcription factors [7]. NFAT transcription factors play important roles in development and normal physiology in mammals. Further, their activity is controlled by cycles of dephosphorylation and phosphorylation, which serves to determine the nuclear localization of the transcription factor, resulting in the final transcriptional response. The phosphatase, calcineurin, is responsible for NFAT dephosphorylation following an increase in intracellular Ca²⁺, and the subsequent nuclear import of NFAT, which leads to the up-regulation of NFAT transcriptional activity (Figure 1). On the other hand, several kinases, including glycogen synthase 3 and casein kinase 1, participate in the phosphorylation of NFAT. Together, the cycle of NFAT dephosphorylation and phosphorylation acts as a switch-off mechanism [8]. DSCR1, also named RCAN1 (regulator of calcineurin 1), works as a negative regulator of this pathway by virtue of its inhibitory activity on calcineurin. Interestingly, DYRK1A has been shown to phosphorylate NFAT family members in order to promote the nuclear export of NFAT [7] (Figure 1). Thus, DSCR1 and DYRK1A cooperatively suppress the calcineurin-NFAT signaling pathway,

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Received September 13, 2015; Accepted September 15, 2015; Published September 22, 2015

Citation: Ding B (2015) How does a 1.5-Fold Increase in Gene Dosage in Chromosome 21 Causes the Pleiotropic Phenotypes in Down Syndrome? J Down Syndr Chr Abnorm 1: e101. doi:10.4172/jdsca.1000e101

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progenitors, leading to a delay in neuronal differentiation and the alteration of their laminar fate [9]. The NFAT family of transcription factors could function to directly promote gene expression via binding the consensus sequence at target gene promoter region. However, they could also suppress gene expression via interactions with other transcription factors or transcriptional programs. For example, the nuclear factor one (NFI)-regulated developmental switch program controls the expression of several groups of genes during the postnatal development in the cerebellum. The NFI temporal occupancy of target gene promoters is one central feature of this program. NFATc4 occupation of NFI program gene promoters in immature mouse cerebellum blocks the NFI temporal occupancy of late-expressed genes and suppresses NFI transactivity 5 [10]. Thus, in response to the increased dosage of DYRK1A and DSCR1, the net change of individual gene expression could be positive or negative via cooperatively suppressing the calcineurin-NFAT signalling pathway (Figure 1).

A recent genome-wide analysis of DYRK1A-associated loci reveals that the kinase is recruited preferentially to the promoters of genes actively transcribed by RNA polymerase II (RNAPII), which is functionally associated with translation, RNA processing, and the cell cycle. DYRK1A-bound promoter sequences are highly enriched in a conserved palindromic motif, which is necessary to drive DYRK1A-dependent transcriptional activation. Furthermore, DYRK1A phosphorylates the C-terminal domain (CTD) of RNAPII at Ser2 and Ser5 to facilitate the transcriptional elongation of target genes [11] (Figure 1). These results provide further insight into how a 1.5-fold dosage of a single gene causes the diversity of expression profiles at genome-wide via transcriptional regulation. Although the target genes of DYRK1A need to be verified, it is not surprising that some genes will be identified as common targets of both DYRK1A and NFAT transcription factors. Therefore, the interactions between different regulatory mechanisms could give rise to more complex outcome on gene expression, resulting in the ultimate pleiotropic phenotypes observed in DS.

To further elucidate the pathological mechanisms of DS and develop effective intervention treatments, it is important to decipher the physiological functions of individual transcripts in HSA21. However, the final phenotypic outcome cannot be foreseen on the basis of analysing the overexpression of single genes. Therefore, the genome-wide interactions between HSA21 products, HSA21 products and non-HSA21 genes, and even the interactions between genetic elements and environmental factors become more important. This kind of interactome analysis could provide further insight into the etiology of DS. 6

References

1. Antonarakis SE, Lyle R, Dermitzakis ET, Reymond A, Deutsch S, et al. (2004) Chromosome 21 and down syndrome: From genomics to pathophysiology. *Nat Rev Genet* 5: 725-738.
2. de la Luna S, Estivill X (2006) Cooperation to amplify gene-dosage-imbalance effects. *Trends Mol Med* 12: 451-454.
3. Lyle R, Gehrig C, Neergaard-Henrichsen C, Deutsch S, Antonarakis SE, et al. (2004) Gene expression from the aneuploid chromosome in a trisomy mouse model of down syndrome. *Genome Res* 14: 1268-1274.
4. Kahlem P, Sultan M, Herwig R, Steinfath M, Balzereit D, et al. (2004) Transcript level alterations reflect gene dosage effects across multiple tissues in a mouse model of down syndrome. *Genome Res* 14: 1258-1267.
5. Ding B (2015) Gene expression in maturing neurons: Regulatory mechanisms and related neurodevelopmental disorders. *Sheng Li Xue Bao* 67: 113-133.
6. Margherita Scarpato, Roberta Esposito, Daniela Evangelista, Marianna Aprile, Maria Rosaria Ambrosio, et al. (2014) AnaLysis of Expression on human

amplifying the effects of their 1.5-fold gene dosage in HSA21. This additive or synergistic effect has been verified in Ts1Cje mice, another DS mouse model [9]. In particular, the cooperative actions of DYRK1A and DSCR1 have been shown to suppress NFAT activity in neural

- chromosome 21, ALE-HSA21: A pilot integrated web resource. Database (Oxford), 2014 10.1093/database/bau009.
7. Arron JR, Winslow MM, Polleri A, Chang CP, Wu H, et al. (2006) NFAT dysregulation by increased dosage of DSCR1 and DYRK1A on chromosome 21. *Nature* 441: 595-600.
 8. Hogan PG, Chen L, Nardone J, Rao A (2003) Transcriptional regulation by calcium, calcineurin, and NFAT. *Genes Dev* 17: 2205-2232.
 9. Kurabayashi, N, Sanada K (2013) Increased dosage of DYRK1A and DSCR1 delays neuronal differentiation in neocortical progenitor cells. *Genes Dev* 27: 2708-2721.
 10. Ding B, Wang W, Selvakumar T, Xi HS, Zhu H, et al. (2013) Temporal regulation of nuclear factor one occupancy by calcineurin/NFAT governs a voltage-sensitive developmental switch in late maturing neurons. *J Neurosci* 33: 2860-2872.
 11. Di Vona C, Bezdán D, Islam AB, Salichs E, López-Bigas N, et al. (2015) Chromatin-wide profiling of DYRK1A reveals a role as a gene-specific RNA polymerase II CTD kinase. *Mol Cell* 57: 506-520.

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