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The Genetic Dosage Imbalance Linked to Clinical Brain Alterations and Mental Disability in Down Syndrome Could be Targeted for Therapeutics Development

Rachidi M*

Molecular Genetics of Human Diseases, French Polynesia and University Paris Denis Diderot, Paris, France

***Corresponding author:** Mohammed Rachidi, Molecular Genetics of Human Diseases, French Polynesia and University Paris Denis Diderot, Paris, France; Email: rachidi.med1@yahoo.com

Short Communication
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Abbreviations: DSCR: Down syndrome Chromosomal Region; NFATc: Nuclear Factor of Activated T cells.

Short Communication

Trisomy of human chromosome 21 is a major cause of Mental Disability and other clinical phenotypic abnormalities such as hypotonia, skeletal and heart defects, immunological and haematological defects, collectively known as Down syndrome, affecting 1/700 live births. The Mental Disability remains the invariable hallmark of Down syndrome and its more invalidating pathological aspect with a hard impact in the public health. This cognitive disorder is mainly a consequence of functional and developmental alterations in neurogenesis, neuronal differentiation, myelination, dendritogenesis and synaptogenesis [1].

Clinical, cytogenetic and molecular studies allowed narrowing a region of human chromosome 21 called Down syndrome Chromosomal Region (DSCR) on the distal part of the long arm, around the marker D21S55 and flanked by D21S17 and ERG. The extra copy of DSCR is associated with the expression of many features of the disease and the multiple neurological features including Mental Disability. Consequently, the major phenotypes of Down syndrome, particularly the Mental Disability, have their origin in the over-dosage of genes localized in the DSCR [2-4].

Gene expression profiling provides two kinds of information to understand Mental Disability pathogenesis in the Down syndrome [5]. On one hand, these studies allowed the identification of genes specifically expressed in the brain and, on the other hand, the genes restricted to the key brain regions involved in the cognitive functions selected as candidate genes for Mental Disability [6-10]. The majority of trisomic genes showed transcript levels increased of about 1.5 fold in human trisomic tissues and in trisomic mouse models [11-15]. Particularly, in trisomic tissues, although most of the trisomic genes show transcriptional variations on average 1.5 fold the normal level, only a subset of genes show a significant difference of expression level between trisomic and diploid individuals [15,16].

Two kinds of murine models have been developed for investigating the molecular genetics of Down syndrome, the trisomic and the transgenic mouse models that represent powerful tools to study the kinetics of early developmental phenotypes and the molecular and cellular pathogenesis of the brain abnormalities seen in Down syndrome. The trisomic mouse models carrying segmental trisomy for mouse chromosome 16 (Ts65Dn and Ts1Cje), contains the ortholog regions of the most part of human 21q and mimic the interactions between different genes present at 3 copies. These mouse models have similar clinical phenotypes seen in Down syndrome and facilitate the identification of candidate genes involved in neurological alterations including learning and memory seen in Down syndrome patients [17]. The

transgenic mouse models are also of the most interest because they have been generated to study the effect of cell-specific and stage-specific over expression of a unique gene. Among these critical genes localized in DSCR the Drosophila Minibrain homolog *DYRK1A* gene (Dual specificity tyrosine-regulated protein kinase 1) and the Down syndrome Critical Region 1 gene (*DSCR1*) [17].

DSCR1 is predominantly expressed in the brain and the RNA and protein are over expressed in the brain of Down syndrome foetuses and the transgenic mice displayed a neurological phenotype with increased locomotor activity and impaired working memory [18,19]. The transgenic mouse models over expressing *DYRK1A* showed neuro developmental delay, motor abnormalities and cognitive deficits with significant impairments in spatial learning and memory, indicating hippocampal and prefrontal cortex function alterations, comparable with those found in trisomic mouse models for Down syndrome, and suggesting a causative role of *DYRK1A* in Mental Disability in Down syndrome patients [20-22].

Interestingly, these two critical dosage sensitive genes *DYRK1A* and *DSCR1* regulate the transcription factor Nuclear Factor of Activated T cells (NFATc) and their over expression dysregulates the NFATc pathways that play a critical role in the central nervous system, giving an important view of a molecular mechanism complementary to our molecular and cellular mechanism involved in the Down syndrome pathogenesis and in the Mental Disability [23,24].

Importantly, the treatment of DYRK1A transgenic mice with injection into striatum of inhibitory Dyrk1A shRNA restores the motor coordination, attenuates the hyperactivity and improves the sensorimotor gating indicating *DYRK1A* as a potential therapeutic target [25-27]. Remarkably, genetic reductions of DYRK1A copy number in trisomic mouse models showed important corrections of Down syndrome phenotypes and showed important improvements in cognitive and behavioural phenotypes [28-30].

These potential genetic targets such as DYRK1A and DSCR1, in Down Syndrome Critical Region DSCR, and their associated pathways could be corrected and the genetic overdosage responsible of brain alterations and associated Mental Disability seen in Down syndrome could be targeted in the perspective of new therapeutic approaches.

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