**Five microRNAs Encoded on Chromosome 21**

Author: Dacey Hutcheson
Major: Microbiology
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

**Key Words:**

Down’s syndrome, gene dosage, microRNA

**Down’s syndrome, sometimes referred to as trisomy 21, is due to the triplication of all or some portion of chromosome 21. The Down’s syndrome phenotype is generally characterized by intellectual disabilities and cognitive deficits. Although the extent and severity of these abnormalities varies with each individual it affects, each abnormality results in cognitive disruption. Since the discovery of the extra copy of chromosome 21, it has been demonstrated that these disruptions are attributed to a naturally-occurring abnormality of the gene dosage. A recent discovery of a cluster of five microRNAs, microRNA let-7c, micrRNA-99a, microRNA-125b, microRNA-155, and microRNA-802, that are encoded and clustered on chromosome 21 have proved to be potential contributors to the remarkably diverse phenotype. Research has yet to find any effective treatment for this diversely complex neurological disorder. The continued study and understanding of this five-member cluster is likely to provide insight into potential beneficial therapeutic strategies to treat Down’s syndrome and many other diseases often associated with it.**

**Introduction**

Upon Jerome Lejeune’s discovery of the extra copy of chromosome 21, Down’s syndrome became the first neurological disorder with a direct link to a chromosome dosage imbalance [4]. Since then, researchers have been looking for answers to the overexpression of trisomic genes. Upon recent discovery, it is believed that trisomy 21 is not a condition that can be easily defined, instead it is a condition of immeasurable diversity in the phenotypic spectrum. A large majority of Down’s syndrome patients exhibit symptoms which lead them to suffer from disorders linked to neurodevelopment, inflammatory neurodegeneration, and carcinogenesis. Some include, but are not limited to: Alzheimer’s disease, various cancers, congenital heart disease, diabetes, visual problems (such as near-sightedness, crossed eyes, and rapid involuntary eye movement), and mental and emotional issues such as depression, aggression, autism, and motor disorders. Not only is their chance of displaying any of these diseases elevated, but the majority of Down’s syndrome patients suffer from two or more of these diseases concurrently. Chromosome 21 triplication occurs in 1/750 live births [3]. Chromosome 21 consists of 48 million base pairs and represents a total of 1.5% DNA. It contains a relatively low number of identified genes (~225) when compared to other chromosomes [1]. The rather high frequency of postnatal survival for trisomy 21 is believed to be due to the small number of genes on the human chromosome [3]. This brings us to the question: how can the 225 encoded protein genes on chromosome 21, one of the smallest human chromosomes, have such a highly complex phenotypic spectrum?

**Recent Progress**

Recent research has shown this may be due to a five-member cluster of microRNAs including let-7c, micrRNA-99a, microRNA-125b, microRNA-155, and microRNA-802 [4]. Because of the extra copy of chromosome 21 in Down’s syndrome patients, there is an extra dosage of each of these microRNA’s in Down’s syndrome tissues. Three of these microRNA, microRNA-99a, microRNA-125b, and microRNA-155 are under nuclear factor kappaB (NF-kB) transcriptional control [4]. Nf-kB proteins make up a family of structurally similar eukaryotic transcription factors involved in a wide variety of cellular processes such as immune responses and cellular growth. These factors are active in many disease states including cancer, heart diseases, and neurodegenerative diseases [2]. Since their discovery, microRNA have come to play a much more appreciated and unforeseen role for RNA. MicroRNAs make up an interesting group of small non-protein-coding RNAs [1]. When binding to their target messenger RNA, they decrease the expression of that target messenger RNA. In doing so, they act as negative post-transcriptional regulators of gene expression. In many neurological diseases it has been shown that up-regulated microRNAs act primarily to decrease their target messenger RNA levels [4]. This is believed to be the principle explanation for reductions in gene expression characteristic of Down’s syndrome and Alzheimer’s disease. One microRNA can regulate multiple target messenger RNAs from genes throughout every somatic chromosome. This allows them to interfere in a number of signaling pathways. Common algorithms of bioinformatics have calculated over 3630 genes that have potential to be regulated by the five-member microRNA cluster on chromosome 21 [4]. As with any other disease, the progression and intensity of Down’s syndrome fluctuates significantly. Many neurological disorders associated with aging, Alzheimer’s disease, and Down’s syndrome share a significant commonality. Each show a deposition of 40-42 amino acids amyloid beta peptides from a 770 amino acid beta amyloid precursor protein encoded as a single copy gene on chromosome 21. MicroRNA-155 is encoded on chromosome 21 in very close proximity of the beta amyloid precursor protein gene [4]. It is believed this accumulation may be a consequence of the extra gene dosage on chromosome 21.

**Discussion**

As our knowledge continues to advance in the understanding of the molecular genetics and neurobiology of the Down’s syndrome genetics, it becomes apparent just how multifaceted this human genetic syndrome is. This research accumulated multiple findings that could lead to the discovery of potential treatments for an otherwise untreatable genetic disorder. For the first time the presence of five microRNAs encoded on the long arm of the extra copy of chromosome 21 have shown they have the ability to regulate the expression of over 3630 genes of the somatic chromosomes. This rather large number of protein-coding genes affected by the presence of the microRNAs may be the start to understanding the tremendous variability and diversity of the conditions associated with chromosome 21 triplication. The cluster of microRNA has the ability to regulate expression in many other genes linked to other diseases interfering with neurodevelopment, brain aging, and neurodegeneration. Because of these specific microRNA’s association with multiple other diseases, this finding is a potential contributor to an improved list of potential therapeutic targets for not only those who suffer from trisomy 21, but for diseases in multiple other major organ systems as well. The importance of the microRNA cluster with respect to the relative proximity of the beta amyloid precursor protein has yet to be determined. Examining the expression and targeting of messenger RNA networking by microRNA let-7c, micrRNA-99a, microRNA-125b, microRNA-155, and microRNA-802 have the potential to evolve into treatment strategies to treat Down’s syndrome and other diseases linked to this complex phenotypic spectrum. Engaging anti-microRNA-based therapeutic strategies focused on designated chromosome 21 microRNAs could restore essential expression patterns. Only the continued advancement of understanding the multidimensional phenotype can provide more effective treatment and clinical management to this serious and often terminal neurological disorder.

**References**

1. Alexandrov PN, Percy ME, Lukiw WJ. Chromosome 21-Encoded microRNAs (mRNAs): impact on Down's syndrome and trisomy-21 linked disease. Cell Mol Neurobiol. 2017; doi: 10.1007/s10571-017- 0514-0. [PubMed PMID:28687876]
2. Beyaert R (editor) (2004). Nuclear Factor-kappaB: Regulation and Role in Disease. Kluwer Academic Publishes, Dordrecht, The Netherlands. 426 pages
3. Roper RJ, Reeves RH (2006) Understanding the Basis for Down Syndrome Phenotypes. PLoS Genet 2(3): e50. https://doi.org/10.1371/journal.pgen.0020050
4. Zhao, Y., Jaber, V., Percy, M. E., & Lukiw, W. J. (2017). A microRNA cluster (let-7c, miRNA-99a, miRNA-125b, miRNA-155 and miRNA-802) encoded at chr21q21.1-chr21q21.3 and the phenotypic diversity of Down’s syndrome (DS; trisomy 21). Journal of Nature and Science, 3(9), e446.