A MOLECULAR PANORAMA OF DOWN SYNDROME- À LA MODE
EVIDENCE AND FUTURE IMPLICATION

1*Pramod Singh Khatri and 2Dr. Sumit Kumar

1*Research Scholar, Shri Venkateshwara University, Gajraula, Uttar Pradesh.
2Associate Professor, IAMR College, Ghaziabad, Uttar Pradesh.

ABSTRACT
Down syndrome brought on by chromosome 21 (trisomy) is the most well-known genetic reason of mental hindrance in human population. Interruption of the phenotype is assumed to be the aftereffect of gene dose unevenness. Therefore, the majority of the chromosome 21 transcripts are attuned for the gene dose impact. Overexpressed gene are most likely to be responsible for the Down syndrome phenotype. Profoundly variable genes could represent phenotypic varieties found in such patients. Down syndrome influences many infants worldwide independent of race, ethnicity, and maternal age at gestation. Much investigation has been done to focus precisely how the additional chromosome 21 leads severe fatal symptoms.

KEYWORD: Down Syndrome, HSA21, MTHFR, DYRK1A, Folate Metabolism.

INTRODUCTION
Down syndrome is the phenotypic appearance of trisomy of human chromosome 21 and is the most well-known genetic issue of intellectual disability, portrayed by dysmorphic features that are ordinary to all influenced individuals, including craniofacial anomalies and hypotonia. As described, the normal pervasiveness is 1 in 550\(^1\) and, in the dominant part of DS cases (90%), the chromosomal nondisjunction event is of maternal origin, happening fundamentally amid meiosis I in the developing oocyte. Down syndrome is a complex hereditary and metabolic issue connected to the vicinity of three duplicates of chromosome 21(figure: 1). the additional chromosome gets from the mother in 93% of gestation cases and
is because of irregular chromosome isolation amid meiosis (nondisjunction). With the exception of advanced age at gestation, maternal risk elements for meiotic nondisjunction are not entrenched.[2] A latest clinical study proposed that abnormal folate breakdown and the 677 CRT polymorphism in the MTHFR gene may be maternal risk variables for Down syndrome. Methionine synthase reductase (MTRR) is an alternate enzyme crucial for folate metabolism.[3-5] A typical polymorphism in this gene was recently associated with increased risk for Down syndrome. In a few studies, progressed maternal age at conception (35 years or above) has been connected with increased risk of Down syndrome births globally.[6] Nonetheless, a few women below 35 years at conception have had DS kids and are additionally discovered to be inclined to early chromosomal nondisjunction. In year 1999, James et al. were the first to propose the role of irregular folate metabolism in chromosome 21 nondisjunction instead of maternal age.[7]

![Figure: 1 Presence of extra chromosome 21](image)

**Folate Metabolism and Down syndrome Risk**
Folate metabolism will be obliged for the synthesis of the major DNA-methylating agent S-adenosylmethionine (SAM).[8] Past 10 years, it was recommended that debilitated folate metabolism, resulting because of the vicinity of a practical polymorphism of the methylenetetrahydrofolate reductase quality (MTHFR), may be a maternal risk factor for having a Down syndrome infant. The speculation was that a stable centromeric DNA chromatin may rely upon the epigenetic legacy of particular centromeric methylation designs and on the coupling of particular methyl-sensitive proteins so as to keep up the higher-order
DNA modeling essential for kinetochore association.\textsuperscript{[9-11]} In this way, it was proposed that peri centromeric hypo methylation, ensuing because of lacking folate intake or debilitated folate metabolism, could disable the development of the kinetochore, bringing about chromosomal nondisjunction.

Methionine synthase (MTR), methionine synthase reductase (MTRR), transcobalamin 2 (TC2), cystathionine beta synthase (CBS), and methylenetetrahydrofolate dehydrogenase (MTHFD1) are critical proteins included in folate/homocysteine (Hcy) metabolism and assume fundamental role in synthesis and repair of DNA and methylation reaction\textsuperscript{[12]} (Diagram: I). The methylation of Hcy to methionine is catalyzed by MTR utilizing cobalamin (vitamin B12) as a cofactor, in which the MTR may get to be inactivated because of the oxidation of cobalamin cofactor. The trans membrane transport of cobalamin is intervened by cobalamin transporting proteins, for example, transcobalamin 2 (TC2). Recovery of latent type of MTR into its dynamic structure requires reductive methylation of vitamin B12 through a response catalyzed by MTRR in which S-adenosylmethionine (SAM) is utilized as a methyl donor.\textsuperscript{[13]}

![Diagram: 1 folate metabolism and risk of Down syndrome](image)

Cystathionine β-synthase (CBS), a catalyst included in the trans sulfuration cycle, is in charge of metabolizing Hcy into cystathionine, a center venture in the synthesis of cysteine. Furthermore, methylenetetrahydrofolate dehydrogenase 1 (MTHFD1)\textsuperscript{[14]}, a trifunctional nicotinamide adenine dinucleotide phosphate-dependent cytoplasmic protein, catalyzes the
consecutive inter conversion of tetrahydrofolate (THF) into the relating 10-formyl-THF, 5, 10-methenyl-THF, and 5, 10-methylene-THF, which assume a critical role in purine and pyrimidine biosynthesis and, in this way, the synthesis of DNA.\[15\]

Genetic polymorphisms in key catalysts of folate digestion have been recognized in the modification of the levels of folate and Hcy, in the protein activity diminish, furthermore in the Hcy remethylation rate. Subsequently, changes in folate levels may impact the DNA dependability and integrity or influence the methylation patterns and, in this way, incline it to the development of Down syndrome.\[16\]

Investigation concentrated on the genes expressed in Down's syndrome has prompted the identification of a specific locale of chromosome 21 that contains the fundamental genes involved in the pathology of this condition. The surmised location of this locale is 21q22.3 and a great part of the investigation has been completed to hunt down key genes in Down's syndrome involves the region 21q21–21q22.3.

Researchers has demonstrated that dysregulation of transcription factor may be identified with the phenotypes connected with Down's syndrome.\[17\] One of these transcription factors, NFAT, is taken care by two proteins, Down's syndrome critical region 1 (DSCR1) and double specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A).

The DSCR1 and DYRK1A genes are spotted on chromosome 21 and offer ascent to 1.5 times the typical measure of these proteins that is found in healthy cells. The high concentration of these proteins retains NFAT mostly placed in the cytoplasm as opposed to in the nucleus, which implies that NFAT is kept from enacting the translation of specific genes. The proteins that these genes code for are hence not delivered.\[18\]

Human chromosomes convey around 25,000 genes coding an individual's whole biological blueprint. Genes advise the body how to assemble proteins — the key molecule underlying all the body’s structures and function. Scientists have so far distinguished more than 400 genes on chromosome 21, and they hope to discover more.\[19\]

In ways that researchers don't yet comprehend, the additional copy of genes present in Down syndrome cause developmental problems and health problems despite of the fact that each of the three duplicates of the genes typically bear "normal" protein codes. Down syndrome almost dependably influences learning, language and memory, however its effect fluctuates
generally from individual to individual. Other health issues incorporate heart defects present during childbirth, conditions influencing bones and muscles, and issues with vision and hearing\textsuperscript{16}. A center objective of Down syndrome investigation is to comprehend how the additional duplicate of chromosome 21 and its genes cause issues just by being available. Gains in function and life span for individuals with Down syndrome have uncovered an extra health risk. As they become old, those influenced by Down syndrome have an extraordinarily increased risk of developing dementia which is much like to Alzheimer's disease.\textsuperscript{20-22}

**The Origin of Maternal Chromosome 21 Nondisjunction**

Notwithstanding, regardless of proof that advanced maternal age at pregnancy is the significant risk factor for trisomy 21, little is still thought about the molecular mechanism of chromosome 21 nondisjunction. A few studies have related adjusted levels and positioning of meiotic recombination events to human nondisjunction.\textsuperscript{23} Especially, investigations of trisomy 21 have demonstrated that changed levels or nonappearance of recombination are connected with maternal nondisjunction happening at both meiosis I and meiosis II (Diagram: 2). It was detected that about 50\% of meiosis I errors are brought on by the nonappearance of chromosome 21 recombination amid maternal meiosis, while the larger part of the remaining Meiosis I mistakes had recombination events that bunched at the telomere.\textsuperscript{24}

Conversely, nondisjunction events because of slips at maternal Meiosis II were related with recombination that bunched at the peri centromeric region of the chromosome, recommending that all nondisjunction events may be launched amid Meiosis I and basically determined at both of the two meiotic stages.\textsuperscript{25-28}

Ensuing studies have been performed to know a conceivable relationship between maternal age and altered chromosome 21 recombination designs.\textsuperscript{29} An investigation of trisomy 21 cases of maternal Meiosis I origin, grouped by maternal age, showed that, adequately in matured ladies, chromosome 21 nondisjunction could be brought about by the age-related accumulation of slips prompting a less-efficient meiotic process more inclined to chromosomal mal segregation. On the opposite, the nonappearance of recombination amid Meiosis I\textsuperscript{30-31} will be likely to be the cause of chromosome 21 nondisjunction in adolescent women. Further affirmation comes from the perception that, for maternal Meiosis I slips, a single telomeric exchange leads the same risk for nondisjunction, independent of the age of the oocyte.\textsuperscript{32}
Despite what might be expected, the investigation of Meiosis II mistakes shows that the vicinity of a solitary exchange inside the 0020 peri centromeric locale of 21q connects with maternal age-related risk factors. A latest case-control study discovered that: (a) progressed maternal age was essentially connected with both Meiosis I and Meiosis II slips, and (b) the degree of Meiosis I to Meiosis II error differ by maternal age\(^3\). The degree was lower among women <19 years old and those ≥40 years and higher in the middle-age group.

A latest hypothesis proposed that maternal trisomy 21 ovarian mosaicism may be an alternate mechanism driving to Down Syndrome. The author analyzed premeiotic ovarian cells acquired from eight phenotypically normal female embryos, showing trisomy 21 mosaicism in all patients.\(^ {34}\)

**New gene SNX27 related with Down syndrome**

In the event that individuals with Down syndrome basically have excessively of hereditary material known as miR-155 or insufficient of the protein called SNX27. In another study, a researcher group investigated this plausibility by utilizing a noninfectious virus as a vehicle to present new human genetic material called as SNX27 in the brains of Down syndrome mice(Figure:2). Also the mice's typical capacities were restored.\(^ {35}\)
By restoring the protein called as SNX27, typical brain function resumed, and the scientists saved the Down syndrome mice. So as to create enough of the protein SNX27, a mouse or a human with Down's syndrome needs a normal duplicate of the SNX27 protein-producing gene.\textsuperscript{36}

In Down's syndrome, because of the additional chromosome 21 duplicate, the brains of individuals with Down syndrome create additional miR-155, which indirectly diminishes the protein SNX27 levels, thusly diminishing surface glutamate receptors.\textsuperscript{37-38} Through this system, learning, memory, and conduct are debilitated.

With less hereditary material that has the capacity deliver the protein known as SNX27, these mice had less dynamic glutamate receptors and in this manner disabled learning and memory. That additional chromosome changes the way the cerebrum and body works.

Researchers restored a protein called SNX27 to standardize the Down's syndrome brain and enhance cognitive capacity and conduct in the mice Downs syndrome people with an additional duplicate of chromosome 21 additionally create less of the protein known as
SNX27, which thus disturbs brain capacity.\cite{39} "In the brain, SNX27 keeps certain receptors on the cell surface—receptors that are vital for neurons to flame legitimately.

**Classification of HSA21 Genes**

By use of this new protocol, human chromosome 21 genes can now be positioned into four classes by their expression levels in Down Syndrome cell lines with respect to controls. This protocol could be connected to expression information acquired from other human tissues, to validate the classification.

Class I contains 30 genes with expression degree of Down syndrome/ control near 1.5 (ranging 1.3–1.67), related to the vicinity of three genomic duplicates. These class I genes could be in charge of the phenotype available in Down syndrome, either specifically or by implication through a secondary impact of cis or trans-acting genes.\cite{40}

Class II contains nine genes with expression ratio(11.64) of Down Syndrome, relating to an amplification of the enacted kinase amplification of SNF1LK gene expression could in this manner result from the overexpression of DYRK1A acting as a regulatory element on SNF1LK in the course, and DSCR3 could act as a scaffolding protein.

Class III is the most rich and consists 77 genes, with a huge extent of gene prediction and antisense transcripts with Down syndrome. These class III genes are likely to be remunerated in Down syndrome. Notwithstanding, the presence of polymorh alleles related to diverse levels of expression ought not represent gene amplification in given population of patients with Down Syndrome.\cite{41-43}

Class IV contains 15 genes and 5 gene forecasts that have Down Syndrome/control expression degree not quite the same as either 1 or 1.5. These class IV genes will be therefore very variable between people with Down syndrome and control individuals.

**Distinguishing between detection and prevention**

The vicinity of a surprising number of chromosomes is shockingly normal among human pregnancy— influencing maybe 20% of all fertile eggs. Numerous fail to survive amid the early weeks of pregnancy. Pregnancies influenced by Down syndrome are generously more prone to lose regularly than unaffected pregnancies.\cite{44} A synopsis assessment recommends that 43% of infants diagnosed with Down syndrome at around 11 to 13 weeks gestation and around 23% of those diagnosed at around 16 to 18 weeks characteristically fail to survive till
birth (figure:3). Misfortune rates give off an impression of being higher among older women. It is hard to create exact figures in the nonappearance of studies including an extensive population of prenatally diagnosed pregnancies with complete follow up.[45] It appears likely that premature deliveries are all the more regularly underreported than terminations or live births. Pregnancies influenced by Down syndrome that are not prenatally diagnosed (false screen-negatives) and don't bring about a live conception are likewise excluded and represent an alternate source of inclination in comparisons of pervasiveness at diverse gestations and live births.[46]

**Figure:3 Oxidative stress in Down Syndrome**

The natural misfortune rate implies that pre-birth recognition and termination is not the same as live conception prevention (as a large number of those ended would not have survived if took off alone).[47] The regular misfortune rate likewise implies that screening prior in pregnancy (for instance, by embracing the first-trimester combined test) will identify relatively more influenced pregnancies that would not have characteristically survived, accordingly substituting terminations for miscarriages.[48]

**The future outlook**

A battle is on to dependably remove fetal DNA from maternal blood specimen whereas, an alternate battle is moving towards decreasing the expenses of entire genome sequencing to under $800. At the point when these two races impact, it will be conceivable to furnish couples with a thorough report of
a risk variables for a bunch of conceivable results in life that may or may not be affected with Down syndrome.

Pre-birth screening for Down syndrome was presented with insufficient open and political debate for more than 20 years. At the point when pre-birth whole genome screening turns into a probability, a large number of the disturbing issues raised by our encounters of screening for Down syndrome will be brought into sharper target. The smart technology may be with us inside 5 years.

Generally, the conception of a down syndrome younger appears to result from hereditary (i.e., polygenic commitment of maternal and fetal folate–metabolizing genes and chromosomal transformation, meiotic chromosome blending, recombination) and ecological elements (maternal age, maternal grandma diet at pregnancy), as well as epigenetic (DNA methylation). In this way, further studies will be obliged in request to comprehend the single contribution of every of them. In the light of an fascinating point of perspective that depicts human nondisjunction likely as a multifactorial trait.

Conflicts of Interest Statement
The Authors declare no conflicts of interest.

REFERENCES


