Beyond Traditional Therapies: Targeting the *DYRK1A* Gene and Emerging Technologies for Improving Cognitive Function in Children with Down Syndrome

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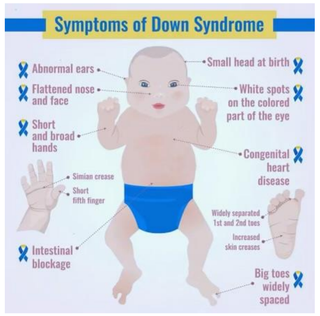
Introduction

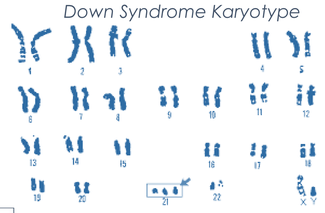


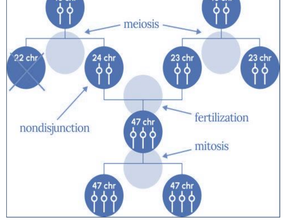
- Down syndrome is the leading genetic cause of intellectual disability, affecting 1 in 700 live births in the United States.
- The disorder results in a wide range of cognitive challenges and delays in developmental milestones.

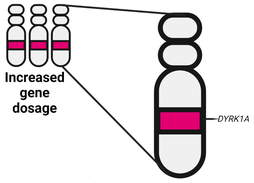
Genetics: Root Cause of Down Syndrome

A full Trisomy 21 is the most common cause of Down syndrome, which is caused by nondisjunction of homologous chromosomes (failure to separate) during cell division.

Down Syndrome Karyotype



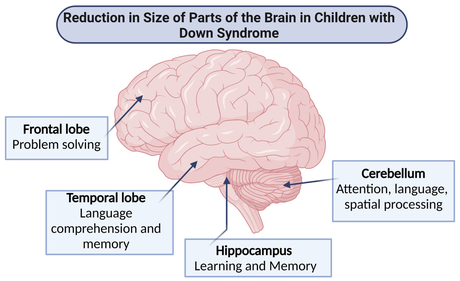




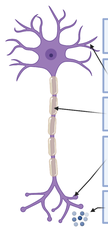
Three copies of Chr 21 increase gene expression, disrupting cellular regulatory mechanisms and affecting various aspects of development.

Brain and Neurodevelopmental Alterations

- Brain development is affected leading to processing and retention deficits.



- Neuronal growth, connectivity, and function are impaired contributing to intellectual disabilities.



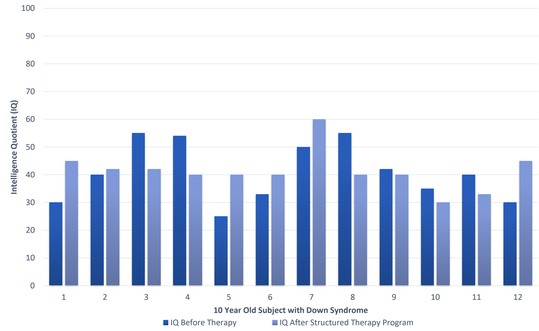
- Decrease in total number of **neurons** → makes cognitive tasks difficult. Decrease in neurogenesis → limits brain adaptation/plasticity.
- **Dendritic Trees** (responsible for receiving information) → atrophic just four months after birth in most DS individuals.
- **Myelination** (protects and insulates axons) → delayed → decreases the conduction velocity of action potentials.
- Fewer **Synapses** (place where neurons communicate with each other) → present ones have abnormal pre- and postsynaptic parameters → disrupts the electrophysiological membrane properties and overall efficiency.
- **Neurotransmitters** (chemical messengers between neurons) → imbalanced.

Current Therapy to Enhance Neurodevelopment

Speech-language and occupational therapy help improve early cognitive and language skills.

Therapies include picture exchange, sign language, communication boards, and cognitive games to enhance learning, memory, and communication.

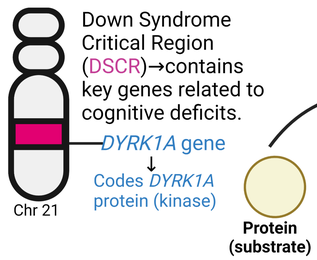
These interventions fall short of alleviating many challenges of the disorder because they address neurodevelopmental barriers, but do not tackle the underlying cause.



Current structured multimodal intervention therapy programs do not significantly help in closing the IQ gap between children with Down syndrome and their normally developing peers.

Figure 1. Comparing the IQ of children with DS before and after Therapy

Inhibiting the *DYRK1A* gene via EGCG to Restore Cognitive Function

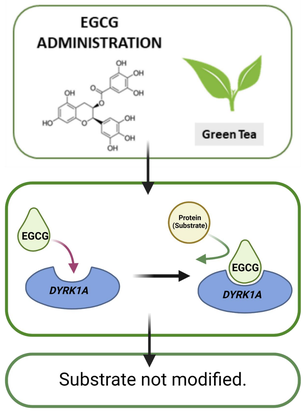


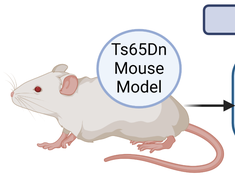
Normal- 2 copies of *DYRK1A* gene

- Regulation of cell growth/division.
- Cells proliferate.
- Extensive networks of neurons with proper connections.

Trisomy- 3 copies of *DYRK1A* gene

- Neurons not properly developed.
- Less extensive neural networks.
- Extra glial cells, fewer neurons.

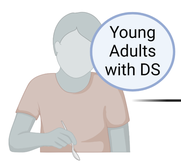




Pre-Clinical Trials

Young mice treated with small dose of EGCG for one Month.

- Rescued hippocampal neurogenesis.
- Improved neuron density.
- Normalized long-term potentiation (LTP), a cellular mechanism important in learning and memory processes.



Clinical Trials (Phase 1)

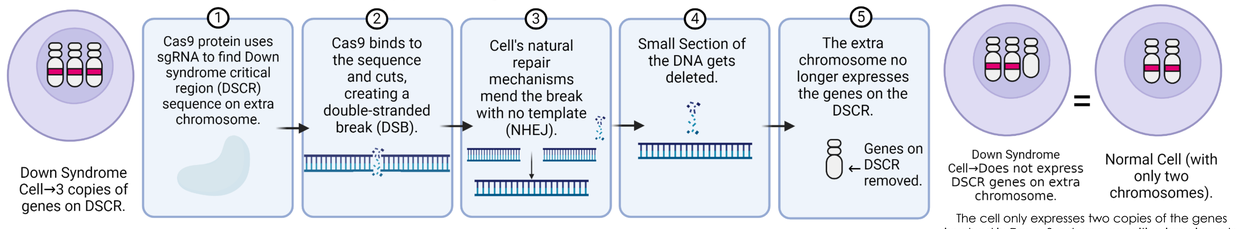
31 young adults with DS treated with EGCG for 3 months.

- Better memory performance.
- Demonstrated improvement in brain structure, synaptic plasticity, and neuron proliferation.

- EGCG is an optimal inhibitor because it has a high specificity for *DYRK1A*, and it has an established safety profile because it is derived from a natural antioxidant source.

CRISPR-Cas9 to Cut out Down Syndrome Critical Region on Extra Chromosome

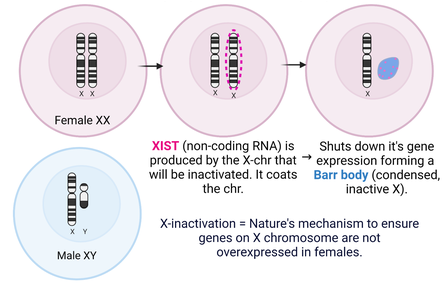
- The application of CRISPR-Cas9 for targeting specific regions on chromosome 21 to address Down syndrome focuses on editing genomic sequences to potentially eliminate the expression of genes associated with the condition.



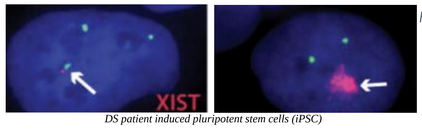
The cell only expresses two copies of the genes involved in Down Syndrome cognitive impairments.

Towards a Cure: XIST and ZFN Technology

- A Mechanism for chromosome inactivation already exists in nature to balance gene dosage of the X-chromosome between Females (XX) and Males (XY) → **X-inactivation**.

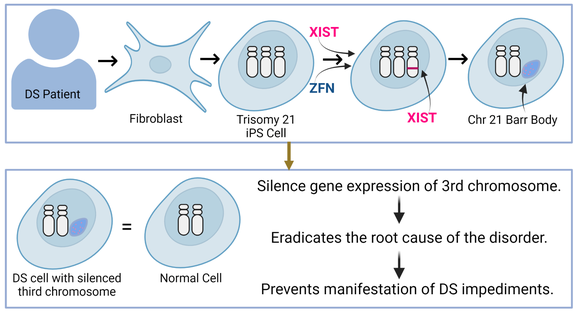


- Harness the power of the natural *XIST* RNA mechanism to inactivate the extra chromosome 21 in Down syndrome.
- The 21st chr cannot naturally create XIST, so Zinc-finger nucleases (ZFNs) create a cut in the extra chromosome and insert an *XIST* transgene.
  - This silences the extra chromosome 21 (like X-inactivation) and prevents the overexpression of its genes.



DS patient induced pluripotent stem cells (iPSC)

FISH (fluorescence in situ hybridization)- Shows the XIST RNA "paints" the extra chromosome and silences it.



Conclusions and Future Directions

- Current therapies foster neurodevelopmental progress but do not target the genetic cause.
- Targeted inhibition of the *DYRK1A* gene has emerged as a promising strategy to enhance cognition.
- CRISPR-Cas9 gene editing could remove the DSCR, eliminating the genes involved in cognitive deficits.
- The revolutionary goal is to harness XIST technology to silence the extra copy of the chromosome, leading to a cure for this condition.
- Further research is needed to confirm the safety and efficacy of these new treatments and refinement of the technologies.
- With emerging technology and continuous research, there is a potential to correct all human cells with an extra chromosome 21 without harming the remainder of the genome.

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References