Down Syndrome and Theoretical Treatments

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Introduction:

Around 0.1% of the world have Down Syndrome, a genetic condition caused by Trisomy 21, where there is an extra copy of chromosome 21. Instead of having 2 chromosomes there, the cell has 3. This predominantly occurs in a reproduction cell, either the egg or the sperm. Due to it appearing in the sex cells, it will end up appearing in all the cells of the child.

Symptoms of Down Syndrome:

Down Syndrome has a wide variety of symptoms. Some of these symptoms include physical differences such as a short neck, flattened facial features, and a small head, ears, and/or mouth [1]. Additionally, a child with Down Syndrome may have reduced muscle tone when younger, but it will become less obvious as the child becomes older [6]. More than half of the people with Down Syndrome can also experience vision and over 3/4 of them experience hearing loss [7]. Alongside physical effects, many children with down syndrome reach developmental milestones later than other children [6]. Additionally, people with Down Syndrome may have higher susceptibility to some conditions such as Leukemia [7]. Something to note is that everyone with Down Syndrome is different, and they may not have all of these characteristics.

Genetics of Down Syndrome

Chromosome 21, the replicated chromosome, is known as the HSA21 chromosome. Due to this chromosome having an extra copy, there is overexpression of approximately 30-50% of HSA21 genes [5]. This contributes to causing the differences present in persons with Down Syndrome.

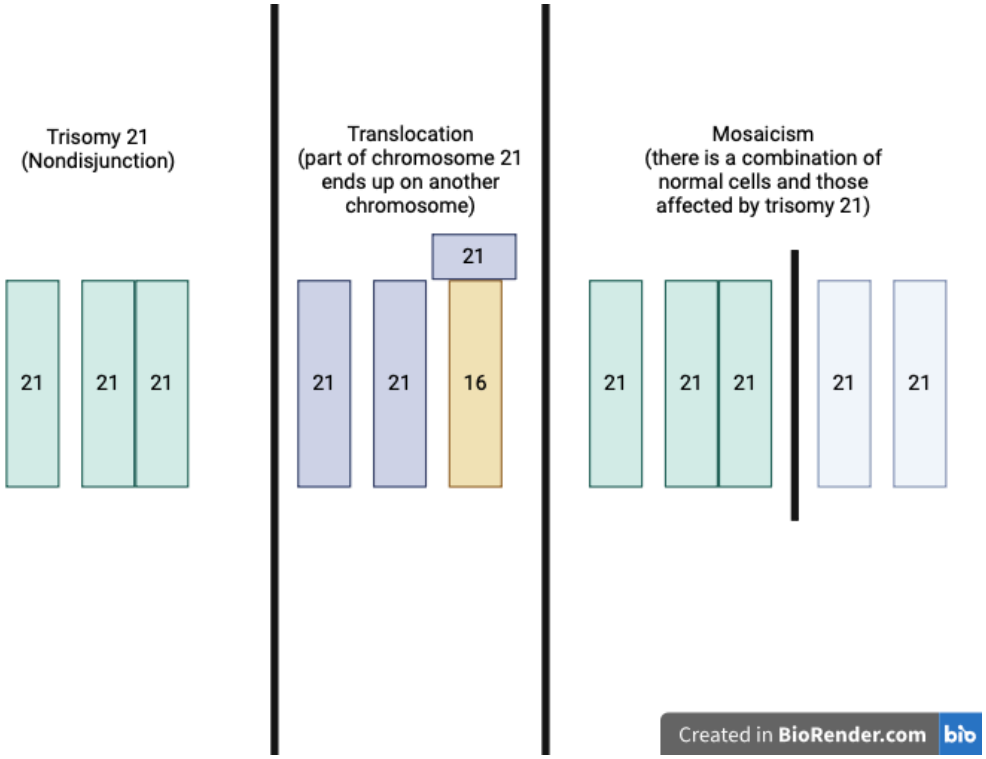

Figure 1. A visual detailing how the various types of Down Syndrome happen. Created in BioRender.com

Trisomy 21 can be caused by a variety of genetic events (Figure 1). The predominant version of Down Syndrome is caused by nondisjunction in chromosome 21, which occurs when Chromosome 21 doesn't break up properly in one parent's sperm or egg cell, meaning the child is given 3 copies of Chromosome 21. Down Syndrome can also result from two less frequent genetic events: translocation and mosaicism. Translocation, occurring for 4% of the patients [2], happens when part of chromosome 21 breaks off and becomes attached to another chromosome, resulting in symptoms very similar to that of normal nondisjunction Down Syndrome. Mosaicism, occurring for 1% of the patients [2], happens when there are some cells with Down Syndrome symptoms and others without it. This means that some people with mosaicism may have very few cells with Down Syndrome, meaning they won't even know they have it [3]. On the other hand, someone else could have a large amount of Down Syndrome cells, leaving their condition indistinguishable from those with normal Down Syndrome [3].

Current Treatments for Down Syndrome

Due to gene therapy treatments not existing yet for Down Syndrome, treatments that are more physical in nature are used to help a patient get to any developmental thresholds they haven't gotten to yet.

Therapies such as occupational therapy, physical therapy, or speech therapy are used to help with any physical or speech deficiencies to help the person live on their own [8]. These therapies can be more difficult to get access to though, meaning not every patient will have access to them.

In school, they may be in a Special Education class if they have a learning disability, but they may be in a normal class if there is no learning disability present [8].

The person will have glasses or hearing aids prescribed for any vision or hearing impairments present [8]. An issue with this approach though is that any aids can cost a lot based on healthcare coverage, meaning they may not be accessible to everyone that needs them.

Experimental Non-Gene Therapy Treatments:

With Down Syndrome, lots of patients have various neurotransmission systems upgraded or downgraded due to their condition [4]. Using this information, scientists are trying to use medications to reduce the effects of the changes to these neurotransmission systems, making it so that the brain of a Down Syndrome patient is closer to that of a normal human [4].

Gene Therapy for Down Syndrome:

At the moment, there are not currently any gene therapies available for people with Down Syndrome. This is due to the complexities and intricacies present in the expression of genes affected by the presence of a third chromosome. There are, however , multiple forms of gene therapies being researched for Down Syndrome.

#1: Another strategy could be to remove it by using a gene therapy based on Crispr-Cas9 to cut out a copy of the gene [4]. Alternatively, a piece of non-coding RNA used for gene regulation could be used to deactivate the extra copy of chromosome 21 [4]. This removes the extra chromosome or at least reduces its usability to the point that Chromosome 21 usage levels are similar to that of a normal patient with no Down Syndrome [4]. This approach would only be useful in nondisjunction cases of Down Syndrome though, as it requires every cell to have an extra Chromosome 21.

#2: Instead of cutting out the entire chromosome, another option could involve cutting out the problematic genes in Chromosome 21 that have the most detrimental effects by using Crispr-Cas9 [4]. This could reduce the overexpression of various genes, therefore solving the problem. An issue with this process is that it would be difficult to cut out specific parts of the genes without significantly damaging Chromosome 21.

Feasibility:

While there are various treatments that are all promising in their own ways, there is little available at the moment. Based on how lots of Gene Therapy and medication based treatments are hypothetical, or at best being tested on small animals, treatment seems far away.
While removing an extra Chromosome or at least the most active parts of the Chromosome seem like the simplest solution, there are still various issues, mainly regarding chromosome targeting and effects that occur due to removal of parts of the chromosome actively being used. Additionally, the same issues exist for gene suppression. Gene suppression does seem like a less damaging solution though, as it uses systems the body already has in place, making it the least changing while still theoretically achieving the goal.

Looking at the results and difficulties of the various methods, the first method listed for Gene Therapies seems to hold the most promise, whether it be by cutting or suppressing genes. For the foreseeable future though, only treatments such as forms of physical and speech therapy alongside visual or hearing aids are the only viable options.

Conclusion:

While the field has advanced a lot in recent years and we are seeing progress on extremely promising therapies, little will be made available soon due to the various difficulties and nuances when it comes to treating the components causing Down Syndrome and also the effects of Down Syndrome.

As technology advances though, I believe that the most promising aspect to look into is that of suppressing a Chromosome, as that will be minimally changing to the cells, limiting any side effects.

Sources:

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