

Identifying Alzheimer's disease in Down syndrome with NGF metabolism: hope for better treatment and diagnosis?

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People with Down syndrome develop Alzheimer's disease. Alzheimer's disease starts in the brain decades before any memory loss occurs, and stopping it will require both understanding this early phase and finding ways to identify it. The disruption of how a molecule called "proNGF" is processed is an important early event in Alzheimer's disease. In Down syndrome, measuring levels proNGF in blood can tell us when memory loss (as a part of Alzheimer's disease) is going to happen. In fact, we can reliably identify people with Alzheimer's disease from the whole Down syndrome population just by measuring proNGF (and the proteins that process it) in blood and in spinal fluid. This discovery may help diagnose of Alzheimer's disease in Down syndrome and offer hope of better treatments.

Background & Problem statement

Down syndrome in the twenty-first century: progress and new challenges.

Better medical care and social programs have hugely increased the lifespan of people with Down syndrome. This remarkable success, however, has revealed an unfortunate truth: Down syndrome and Alzheimer's disease come hand in hand. While only 5-6% of the general population aged 50-60 will develop Alzheimer's disease, the rate in people with Down syndrome is a staggering 60-80% (1).

Why does this occur? Down syndrome is caused by an extra copy of the twenty-first chromosome. One of the genes on this chromosome, called Amyloid Precursor Protein, produces a protein called amyloid-beta. Amyloid-beta is considered the main cause of Alzheimer's disease, where it forms sticky globs of protein called "plaques" in the brain. People with Down syndrome get extra amyloid-beta and Alzheimer's disease follows—the

only ones spared in the long run are a rare few who lost APP from the extra chromosome 21 (1).

When does Alzheimer's disease begin—and why is that important?

We experience Alzheimer's disease by its effects: a loss of memory and an inability to think clearly that occurs in the 70s and 80s (in the general population) or in the 50s and 60s (in Down syndrome). However, decades before memory begins to decline, a characteristic set of changes are beginning in the brains of people with Alzheimer's disease. These include the build-up of amyloid plaques, as well as similar clumps of a protein called tau that form inside brain cells, a disruption of the connections between brain cells, and the over-activation of the brain's defense system. These issues build up, silently, for years and decades until they reach a critical point and begin to affect the ability to think and remember. The early stage is referred to as "prodromal" Alzheimer's disease, and virtually all people with Down syndrome have prodromal Alzheimer's disease by their 40s.



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While this is concerning, it also offers hope. Most treatments for Alzheimer's disease have been applied when brain changes have built up to the massive levels required to lose memory. But what if we treated people earlier? What if we could stop the accumulation of Alzheimer's disease in the brain before it reached that critical point?

Doing so will require an understanding of exactly what goes wrong when memory starts to decline in Alzheimer's disease, and ways to detect the disease before it reaches this point. Things that we can measure to detect Alzheimer's disease are called "biomarkers". With better biomarkers we could detect Alzheimer's earlier, treat people earlier, and maybe stop Alzheimer's disease before it starts.

When does Alzheimer's disease begin—and why is that important?

Understanding the causes of dementia in Alzheimer's disease

So what changes when Alzheimer's starts to disrupt our ability to think and remember clearly? One important part of the answer may be that that's when a specific set of brain cells called "basal forebrain cholinergic neurons" start to be damaged. Early in Alzheimer's disease, while the rest of the brain is working fine, these cells stop doing their job (2). The result is an impairment in thinking and memory.

A curious fact about these "cholinergic" cells is that they need to get a protein called Nerve Growth Factor (NGF) in order to keep working. In fact, if cholinergic cells are cut off from NGF they stop working in just the same way that they do in Alzheimer's disease.

Could a lack of NGF cause cholinergic cells to stop working in Alzheimer's disease?

Dr. Claudio Cuello's lab in Montreal, Canada, has shed light on this question by describing the way that NGF is processed in the brain, including how NGF is made from a molecule called "proNGF" as well as how it's broken down (3). In Alzheimer's disease, less NGF is created from proNGF, causing proNGF levels to rise, and more NGF is broken down (4, 5). Less NGF explains the loss of cholinergic cells—and therefore memory problems in Alzheimer's disease (6).

Methods

Nerve Growth Factor in Down syndrome: a new biomarker of Alzheimer's disease?

In the brains of people with Down syndrome, the same thing occurs: less NGF is produced, more

NGF is degraded, and proNGF levels rise. These changes occur in adults with Down syndrome, but they get more severe in those that also have Alzheimer's disease. Furthermore these changes occur early—even before birth—suggesting that these molecules could be used to tell us when Alzheimer's disease will onset in Down syndrome (6, 7).

However, we can't take parts of a living brain to analyze. But what if we could measure proNGF in blood or spinal fluid? Would that tell us about what's happening in the brain? To answer these questions, the McGill lab collaborated with Dr. Filippo Caraci of the University of Catania, Italy. Together, they showed that the NGF processing was also changed in blood from people with Down syndrome (including those with Alzheimer's disease), the same was as in the brain. Importantly, we could use proNGF to tell us when people were going to start experiencing memory loss (8).

If blood levels of the NGF metabolic pathway are a useful biomarker of Alzheimer's disease, could spinal fluid (CSF—the fluid taken in a lumbar puncture) be even better, since it's in closer contact with the brain? To answer this important question, the McGill lab embarked on a comprehensive project in collaboration with the team of Dr. Juan Fortea of the Hospital Sant Pau, Barcelona, who leads an extensive health program for people with Down syndrome to prevent Alzheimer's disease. In our joint presentation at the 3rd International Meeting of the Trisomy 21 Research Society in Barcelona, we reported that measuring proNGF in spinal fluid reflected what was happening in the brain even better than measuring it in blood. We showed that CSF MMP9 and proNGF can be used to reliably identify people with Alzheimer's disease from the rest of the Down syndrome population. This work strengthened the evidence that NGF processing is a promising source of biomarkers for Alzheimer's disease in Down syndrome.

Implications of research

New hope for early and better treatment of Alzheimer's disease in Down syndrome

Our hope is that one day, biomarkers like proNGF, perhaps in combination with others, might allow for the reliable detection of Alzheimer's disease in Down syndrome and in the general population. Identifying patients early will allow for earlier treatment and make the success of new

treatments for more likely. We will assess whether these biomarkers work differently in males and females, since they express different levels of some proteins. We also are actively assessing the ability of proNGF (in spinal fluid) to tell us when people are going to start losing their memory, or when other symptoms of Alzheimer's disease will start to occur. Finally, we are looking for new ways to fix NGF processing in Alzheimer's disease and help with memory loss.

Acknowledgements

Mild astrogliosis is found in Ts65Dn dorsal hippocampus, which may affect astrocyte-neuron networks within different layers of this particular circuit involved in learning and memory. Intrinsic neuronal properties of CA1 pyramidal neurons in Ts65Dn are preserved but their lower action potential amplitude is concordant with previous studies in human iPSCs showing astrogliosis reduction of neuronal excitability. Given that intact function of local astrocyte networks is critical for complex cerebral functions, we suggest that altered balance of astrocyte-neuronal signaling can contribute to Down syndrome cognitive impairment.

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Take home message

- New treatments for people with Down syndrome and Alzheimer's disease will depend on understanding the early phase of the disease and detecting it with biomarkers
- The abnormal processing of the molecule "proNGF" is an important and early event in Alzheimer's disease and Down syndrome
- Measuring proNGF (and related molecules) in blood and CSF can effectively detect Alzheimer's disease in Down syndrome and may prove to be effective biomarkers for this condition before memory deficits



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