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## Down syndrome and Alzheimer's disease

A topic in the Alzheimer's Association® series on understanding dementia.

### About dementia

Dementia is a general term for a decline in mental ability severe enough to interfere with daily life. Dementia is not a single disease; it's the umbrella term for an individual's changes in memory, thinking or reasoning. There are many possible causes of dementia, including Alzheimer's. Disorders grouped under the general term "dementia" are caused by abnormal brain changes. These changes trigger a decline in thinking skills, also known as cognitive abilities, severe enough to impair daily life and independent function. They also affect behavior, feelings and relationships.

Brain changes that cause dementia may be temporary, but they are most often permanent and worsen over time, leading to increasing disability and a shortened life span. Survival can vary widely, depending on such factors as the cause of the dementia, age at diagnosis and coexisting health conditions.

### Down syndrome (Trisomy 21) and Alzheimer's disease

The most common type of Down syndrome is known as trisomy 21 and accounts for 95% of cases. Trisomy 21 occurs when a person is born with extra genetic material from chromosome 21, one of the 23 human chromosomes. All human chromosomes usually occur in pairs, with one copy inherited from a person's mother and one from the father. Most people with Down syndrome have a full extra copy of chromosome 21, so they have three copies instead of the usual two. Scientists think the extra copy results from a random error in the specialized cell division that produces eggs and sperm.

Human chromosomes carry about 30,000 genes coding a person's entire biological blueprint. Genes tell the body how to build proteins — the key molecules underlying all the body's structures and functions. Researchers have so far identified more than 400 genes on chromosome 21, and they expect to find more.

In ways that scientists don't yet understand, the extra copies of genes present in Down syndrome cause developmental problems and health issues even though all three copies of the genes usually carry "normal" protein codes. Down syndrome nearly always affects learning, language and memory, but its impact varies widely from person to person. Other common health issues include heart defects present at birth, conditions affecting bones and muscles, and problems with vision and hearing. A core goal of Down syndrome research is to understand how the extra copy of chromosome 21 and its genes cause problems just by existing.

Advances in medical care now have extended the average life expectancy of people with Down syndrome to age 60, revealing an additional health risk: As they age, individuals affected by Down syndrome have a greatly increased risk of developing a type of dementia that's either the same as or very similar to Alzheimer's disease.

Autopsy studies show that by age 40, the brains of almost all individuals with Down syndrome have significant levels of beta-amyloid plaques and tau tangles, which are abnormal protein deposits considered hallmarks of Alzheimer's disease. But despite the near-universal presence of these brain changes, not everyone with Down syndrome develops Alzheimer's symptoms. One of the many questions researchers hope to answer about Down syndrome is why some people develop dementia symptoms and others don't. Researchers are working to answer a similar key question about those who don't have Down syndrome: Why do some people with brain changes characteristic of Alzheimer's never show symptoms of the disease?

### **Prevalence**

As with all adults, advancing age increases the chances a person with Down syndrome will develop Alzheimer's. Studies suggest that more than 75% of those with Down syndrome age 65 and older have Alzheimer's disease, nearly six times the percentage of people in this age group who do not have Down syndrome. Because people with Down syndrome live, on average, 55 to 60 years, they are more likely to develop younger-onset Alzheimer's (occurring before age 65) than older-onset Alzheimer's (occurring at age 65 or older).

### **Causes and risk factors**

Scientists think that the increased risk of dementia — like other health issues associated with Down syndrome — results from the extra genes present. One of the chromosome 21 genes of greatest interest in the Down syndrome/Alzheimer's connection codes amyloid precursor protein (APP). Scientists don't yet know APP's function, but they've learned that day-to-day brain activity involves continuous “processing” of APP into shorter pieces. One of the brain's APP processing pathways produces beta-amyloid, a fragment that's the chief component of plaques and a prime suspect in Alzheimer's-related brain changes. Having an extra copy of the APP gene may increase production of beta-amyloid, triggering the chain of biological events leading to Alzheimer's.

The APP gene is further implicated in Alzheimer's through its connection to rare inherited forms of Alzheimer's disease. Certain small variations in the APP chemical code were the first genetic changes scientists identified that guarantee people will develop Alzheimer's if they inherit such a change from either parent. Like other

genetic variations that ensure a person will develop Alzheimer's, these APP variations are extremely rare. Few, if any, people with Down syndrome have them.

The fact that APP is strongly implicated in Alzheimer's through two different mechanisms — one involving a whole extra copy of the normal gene and the other involving specific minor changes in the gene's chemical code — makes the intersection of Down syndrome and Alzheimer's a strong focus of research.

### Symptoms

In people with Down syndrome, changes in overall function, personality and behavior may be more common early signs of Alzheimer's than memory loss and forgetfulness. Early symptoms may include:

- Reduced interest in being sociable, conversing or expressing thoughts.
- Decreased enthusiasm for usual activities.
- Decline in ability to pay attention.
- Sadness, fearfulness or anxiety.
- Irritability, uncooperativeness or aggression.
- Restlessness or sleep disturbances.
- Seizures that begin in adulthood.
- Changes in coordination and walking.
- Increased noisiness or excitability.

### Diagnosis

Most adults with Down syndrome will not self-report concerns about memory. Diagnosing dementia in a person with Down syndrome can be difficult, in part because of the challenges involved in assessing thinking-skill changes in those with intellectual disabilities. Yet, recognition of adult cognitive change is important for providing appropriate services and support for individuals with Down syndrome and their caregivers. Experts recommend the following principles as key to person-centered diagnosis in those with Down syndrome:

- Document baseline adult function by age 35. Ongoing evaluation of intellectual, behavioral and social function is important for everyone with Down syndrome. By age 35, each individual's medical record should ideally include detailed information on his or her adult abilities. The person with Down syndrome, family members and other reliable individuals are helpful sources for this information.
- Watch for changes in day-to-day function. Reduced enthusiasm for daily activities, loss of interest in social interactions and changes in personality and behavior are often early signs of an underlying decline in thinking skills.

- Consider professional assessment by a dementia expert. A variety of cognitive tests have been used to evaluate thinking changes in adults with Down syndrome. However, experts caution that cognitive tests should never be used as the only benchmark to diagnose dementia.
- Rule out other causes of symptoms. It's important to rule out other medical conditions commonly associated with Down syndrome as the cause of changes in thinking and function, including thyroid problems, depression, chronic ear and sinus infections, vision loss and sleep apnea.

### Outcomes

Despite modern improvements in quality and length of life, Down syndrome remains a condition that shortens life span. People with Down syndrome experience earlier-than-usual onset of a variety of conditions linked to aging in addition to Alzheimer's disease. People with Down syndrome currently live an average of 60 years, although some live into their seventies and, rarely, into their eighties.

### Treatment

The U.S. Food and Drug Administration (FDA) has not approved any drugs specifically to treat dementia associated with Down syndrome. In the United Kingdom, cholinesterase inhibitors, a class of drugs approved in the United States and many other countries to treat Alzheimer's disease, are approved to treat dementia in people with Down syndrome. An analysis by the Cochrane Reviews, an extensive series of reports by international experts evaluating treatment effectiveness, found that there isn't enough evidence to reach a conclusive judgment about the benefit of cholinesterase inhibitors for people with Down syndrome.

An international randomized trial has shown no benefit for the Alzheimer's drug memantine in adults with Down syndrome. Experts urge more research and clinical studies to identify effective treatments for dementia in those with Down syndrome. Because there may be differences in the way people with Down syndrome process medications, experts advise caution about using any drug that has not specifically been shown to be safe and effective in this group.

### Research

Because people with Down syndrome are at such high risk of dementia, they are a key group of people to help researchers understand Alzheimer's, beginning decades before symptoms start. The research aims to:

- **Measure cognitive changes over time.** First, cognitive assessment tests specifically developed for use with individuals with Down syndrome must be validated. Tracking cognitive changes in this population may be useful in

preventative treatment trials for the greater Alzheimer's population and make it easier to detect early signs of dementia.

- The LonDownS Consortium researchers — a group made up of clinicians, geneticists, developmental psychologists, psychiatrists and cellular scientists — are creating more sensitive and relevant memory and thinking assessments for people with Down syndrome.
- **Improve our understanding of the genetic and biological causes of brain abnormalities** that lead to Alzheimer's may help diagnose it — even before symptoms appear—and show brain changes as people with Down syndrome age.
  - The Alzheimer's Biomarkers Consortium – Down Syndrome (ABC-DS), currently funded at \$46 million through the National Institutes of Health, published research in July 2020 that showed that people with Down syndrome who are at risk for, or have, Alzheimer's disease experience the same metabolic (biochemical processes that occur in living cells) changes as people with late-stage Alzheimer's disease. Knowing this, scientists may be able to identify potential blood-based biomarkers (measurable biological changes that can show if a disease is present or a person is at risk) to track progression of disease — from no symptoms to mild cognitive impairment to Alzheimer's. The LonDownS Consortium is conducting similar research.
  - A team of researchers in the U.K., Europe and the U.S. now suggest that three copies of chromosome 21 genes other than APP may influence Alzheimer's disease pathogenesis in Down syndrome patients. Their 2018 results showed that extra copies of non-APP genes are associated with increased amyloid-beta aggregation and plaque deposition, and worsening cognitive deficits.
  - Other researchers are investigating Down syndrome's molecular alterations in the brain.
  - The Linda Crnic Institute for Down Syndrome is investigating the genome and epigenome of specific cell types in the blood that could inform the development of Alzheimer's disease.
  - The Alzheimer's Association, the Crnic Institute and the Global Down Syndrome Foundation are funding efforts to develop a blood test to identify individuals at high risk for developing Alzheimer's.

- **Test treatments** for dementia in adults with Down syndrome. One national clinical trial with participants who have Down syndrome is testing the safety of a new vaccine (ACI-24) that may activate the immune system to attack the plaques before they build up.
  - Researchers have confirmed that people with Down syndrome who develop dementia can benefit from the drugs commonly used to Alzheimer's disease.

Visit [nia.nih.gov/alzheimers/clinical-trials](https://nia.nih.gov/alzheimers/clinical-trials) to find a complete list of Alzheimer's trials involving people with Down syndrome.

### **Additional resources**

#### **National Down Syndrome Society**

[NDSS.org](https://ndss.org)

#### **Global Down Syndrome Foundation**

[globaldownsyndrome.org](https://globaldownsyndrome.org)

#### **National Down Syndrome Congress**

[ndscenter.org](https://ndscenter.org)

#### **National Association for Down Syndrome**

[NADS.org](https://nads.org)

#### **Linda Crnic Institute for Down Syndrome**

[ucdenver.edu/academics/colleges/medicalschoo/institutes/lindacrnic/Pages/lindacrnic.aspx](https://ucdenver.edu/academics/colleges/medicalschoo/institutes/lindacrnic/Pages/lindacrnic.aspx)

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