

## Down syndrome and Alzheimer's disease

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

### **About dementia**

Dementia is an umbrella term that describes a decline in memory, thinking and reasoning abilities and is severe enough to interfere with daily life. Dementia is not a single disease.

There are many possible causes of dementia, including Alzheimer's disease, Frontotemporal disease and Lewy body disease. Dementia is usually caused by abnormal brain changes. These changes are associated with decline in thinking skills, also known as cognitive abilities, severe enough to impair daily life and independent function. They can 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 factors such as the underlying cause of the dementia, the age at diagnosis and any coexisting health conditions.

### **Down syndrome (Trisomy 21) and Dementia**

The most common form of Down syndrome is known as trisomy 21 and accounts for 95% of individuals living with Down syndrome. Trisomy 21 occurs when a person is born with an extra copy of chromosome 21, one of the 23 human chromosomes. All human chromosomes 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 two. Scientists think the extra copy results from a random occurrence that takes place during cell division that produces the 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 of the body's structures and functions. So far, researchers have 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 disabilities and various health issues even

though all three copies of the genes carry protein codes. Down syndrome nearly always affects learning, language and memory, but its impact varies widely from person to person. Other common health issues experienced by individuals with Down syndrome include heart conditions 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 contribute to these health issues.

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 with Down syndrome have a greatly increased risk of developing a type of dementia that is either the same as or similar to Alzheimer's disease. In fact, dementia has become a leading cause of death for people with Down syndrome.

Autopsy studies show that by age 40, the brains of virtually all individuals with Down syndrome have significant levels of brain changes consistent with Alzheimer's disease, including beta-amyloid plaques and tau tangles. But despite the near-universal presence of these brain changes, not everyone with Down syndrome develops the symptoms seen in Alzheimer's in their lifetime, while others develop these symptoms at a younger age. Researchers are working to understand why.

### **Prevalence**

As with all adults, advancing age increases the chances a person with Down syndrome will develop dementia that is either the same as or similar to Alzheimer's. Studies suggest that people with Down syndrome have a 90% lifetime risk of developing dementia. For most people with Down syndrome, this occurs in their 50s, although there is a broad age range.

### **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 genes on chromosome 21 of interest in the Down syndrome/Alzheimer's connection codes for 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 increases production of beta-amyloid, and this may contribute to the chain of biological events leading to Alzheimer's-related brain changes.

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The APP gene is further implicated in Alzheimer's through its connection to rare, inherited forms of younger-onset (early-onset) Alzheimer's disease known as Dominantly Inherited Alzheimer's disease (DIAD).

Genetic variations that almost guarantee a person will develop Alzheimer's, including those in APP, are extremely rare.

## **Symptoms**

In people with Down syndrome, early signs of the brain changes that cause dementia may include changes in personality, cognition or behavior compared to a person's previous functioning.

Early symptoms may include:

- Difficulty remembering new information.
- Decline in ability to pay attention.
- Struggling to find the right word.
- Difficulty following instructions or completing routine tasks.
- Taking longer to respond to new situations or information.
- Withdrawal from social situations and favorite activities.
- Irritability, uncooperative behavior or aggression.
- Changes in walking, coordination or motor skills.
- Changes in mood, such as sadness, fearfulness or anxiety.
- Increased noisiness or excitability.
- Seizures that begin in adulthood.

## **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 changes in thinking skills in those with intellectual disabilities. However, recognizing cognitive change is important in order to provide appropriate services and support to 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. Typically, Alzheimer's and other dementias are diagnosed using a variety of approaches and tools, including review of the person's medical history, physical exam, lab testing and, in some cases, brain imaging.
- 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, individuals with Down syndrome continue to have a shortened lifespan. People with Down syndrome experience earlier-than-usual onset of a variety of conditions linked to aging in addition to Alzheimer's and other dementia. While people with Down syndrome currently live an average of 60 years, some live into their 70s and, rarely, into their 80s.

### **Treatment**

The U.S. Food and Drug Administration (FDA) has approved one treatment that may address the underlying biology of Alzheimer's and may be appropriate for people living in the early stages of the disease. This treatment has not been tested in people with Down syndrome. Additionally, availability of this drug is limited. Other medications may help lessen symptoms, such as memory loss and confusion. These drugs have been tested in people with Down syndrome in small studies.

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

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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 early brain changes, including those related to 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 are creating more sensitive and relevant memory and thinking assessments for people with Down syndrome.
  - **The Horizon 21 Consortium** offers consultations to people with Down syndrome. The program's objective is to prevent or delay the onset of Alzheimer's disease in people with Down syndrome by identifying the factors that influence disease development in this population.
- **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 Biomarker Consortium – Down Syndrome (ABC DS)**, funded through the National Institutes of Health, is following over 400 people with Down syndrome to learn about how and why Alzheimer's -related changes develop and to identify new biomarkers.
  - **The Down Alzheimer Barcelona Neuroimaging Initiative (DABNI)** cohort, is a comprehensive study collecting different assessments and measures, such as imaging, blood, genetics and sleep measures to improve our understanding of the mechanisms that drive Alzheimer's disease in Down syndrome.

- The **Linda Crnic Institute for Down Syndrome** is investigating the genes and related biology of specific cell types in the blood that could inform the development of Alzheimer's disease.
- **Test treatments for dementia in adults with Down syndrome.**
  - **An international clinical trial (the ABATE study)** with participants who have Down syndrome is testing the safety of a new vaccine (ACI-24.060) that may activate the immune system to attack plaques before they build up in individuals with Down syndrome.
  - **The NIH-funded Alzheimer's Clinical Trials Consortium – Down Syndrome (ACTC-DS)** is the largest clinical trials network dedicated to studying Alzheimer's disease in people with Down syndrome.
  - **The NIH-funded Trial Ready Cohort - Down syndrome (TRC-DS)** matches people with Down syndrome to clinical trials related to Alzheimer's disease.

Visit [alz.org/TrialMatch](https://alz.org/TrialMatch) to learn more about 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/medicalschool/institutes/lindacrnica/Pages/lindacrnica.aspx](https://ucdenver.edu/academics/colleges/medicalschool/institutes/lindacrnica/Pages/lindacrnica.aspx)

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