

Regression in Persons with Down Syndrome: Current Consensus Update for Families

What is Regression?

Regression is a term for the loss of previously acquired developmental skills in an individual. This can be in the areas of daily living, language, motor abilities/function, or social interaction. Regression can occur, over weeks to months, or more quickly and time course may help in determining the likely cause of the regression. *Regression can be caused by many things and is associated with a marked decline in previously established function.*

Regression can also be referred to Down syndrome regression disorder (DSRD), Down syndrome disintegrative disorder (DSDD) or unexplained regression in Down syndrome (URDS) and these terms are sometimes used interchangeably.

What are Some of the Symptoms Associated with Regression in Persons with Down Syndrome?

Frequently reported symptoms are:

- Social withdrawal from friends, family, and school/classmates
- Loss of language or diminished language
 - Decreased speaking, loss of certain word use, sentence structure changes, “baby talk”, speaking in a whisper
- Loss of previously acquired developmental milestones or abilities
- Loss of independence in activities or need for significant assistance with activities (e.g., can no longer toilet or use the bathroom independently, feed self, dress self, or bathe self when previously able)
- Development of autism-like features that were not previously present (onset over weeks, not chronic)
 - Decreased eye contact, repeating things that other people say or repeating lines from movies/television, decreased showing of empathy or emotions towards others, anger or frustration with or without behavioral outbursts, stereotypy (repetitive hand or body movements), lack of interest in others
- Changes in motor activity (stiffness, slow movements, freezing, tics and/or extra movements that are not purposeful)
 - Repetitive purposeless (random) movements, resistance to passive movement (stiffness), and sudden loss of tone (cataplexy) can sometimes be seen as well
 - “Freezing” or slowness in moving. This can sometimes look like a slow and shuffling gait where the feet don’t lift off from the floor
 - Catatonia is a term that describes stiffness or rigidity of the muscles when placed in certain positions (like moving a mannequin). Persons with catatonia can also

move slow or not initiate movements well, or may have repetitive or purposeless overactivity

- Change in eating patterns (e.g., not wanting or not having interest in eating, extreme slowness with eating)
 - This may or not be associated with weight loss.
- Insomnia and difficulty sleeping
- Compulsive and/or obsessive behaviors (e.g., lining up toys, rigidity with routines not previously present, only talking about one specific show/activity/game)
- Facial grimacing (contorted face as if in pain or tasting something sour) or repetitive movements of the mouth that can mimic chewing behavior
- Bizarre thought content or experiences (psychosis)
 - This can include hallucinations (seeing or feeling things that are not there), delusions (belief in things that are not true), altered awareness, or distortions of memories/historical knowledge.
- Inappropriate mood and affect (crying for seemingly no reason, laughing uncontrollably to themselves even in an otherwise solemn situation)
- Aggressiveness towards self or others
- Increased self-talk

Of note, persons with regression often have a sub-acute (less than 3 month) onset of these symptoms as opposed to more gradual decline. If you or a loved one has a constellation of any of these symptoms, we recommend expedited evaluation by an expert. The presence of “triggers” that precede the onset of symptoms can be present and can include negative life events, changes in the home/school environment, and medical illness or hospitalization disease.

Do I Need to Get Evaluated?

If your loved one is experiencing any of these symptoms, quick evaluation is recommended. Although doctors don't know for certain, it is presumed that early diagnosis and treatment, may improve outcomes.

What are the Causes of Regression in Persons with Down Syndrome?

At this time, it appears that there may be several causes of regression in persons with Down syndrome. As regression is a description of the symptom (what is happening), this label does not always describe the cause. There are several ideas about the cause of regression in persons with Down syndrome:

- Medical: Individuals with Down syndrome are at an increased risk for developing several medical conditions. This can include obstructive sleep apnea (OSA), hypothyroidism, cervical spine disorders and celiac disease, to name a few. While a direct association has

not been made with these medical conditions and regression, it is very important that you work with your medical provider to rule out any possible medical diagnoses that may be a contributing factor to symptom presentation. For example, a sleep study may be recommended to determine if a person with Down syndrome has sleep apnea. Treatment of sleep apnea may then result in improvement of regression symptoms.

- Psychiatric/Psychologic: Persons with Down syndrome are known to have higher rates of depression, anxiety, catatonia, autism spectrum disorders, and attention-deficit disorder than neurotypical persons. The presence of these psychiatric conditions in an individual with Down syndrome is complicated by the fact that intellectual disability is nearly always present as well, limiting an individual's ability to express what he/she is experiencing, thinking, or feeling. One hypothesis of regression is that it is triggered by or a result of psychiatric illness. This has been observed in persons with Down syndrome who have a prominent life stressor that is temporally associated with (triggers) regression. Some examples of life stressors include loss of a loved one, change in school, moving to a new home, sibling moving away from home, divorce of family members and/or a physical accident).
 - There is no "blood test" for diagnosing psychiatric/psychologic disorders. A psychiatric or psychological professional may utilize screening tools, symptom checklists, interviews, and some formalized evaluation to determine what diagnosis fits. A medical professional outside of the field of psychology will often make a diagnosis after ruling out physical causes through a good history, physical examination, and appropriate labs and x-ray.
 - Catatonia has been recognized as a common feature of regression. Catatonia can be caused by psychiatric and/or medical conditions. It is not featured on any psychiatric screening tools and can be overlooked. Catatonia is important to detect because there are specific treatments for catatonia. Benzodiazepines (like Lorazepam/Ativan) are effective for the treatment of catatonia, but other psychiatric medications can also be helpful. A treatment called electroconvulsive therapy (ECT) is also used to treated individuals with regression.
 - Individuals with psychiatric/psychologic mediated regression may also respond to anti-depressants, anti-convulsant medications (seizure medications/mood stabilizers), anti-psychotic medications and/or electroconvulsive therapy (ECT).
 - Consultation with a specialist is recommended prior to starting these interventions. Every patient is unique and there is no single medication or intervention that is best, which may require trying multiple different medications before finding a positive response.

- Autism spectrum disorders are prevalent in young individuals with Down syndrome as well. For chronic or slowly developing regression, co-morbid autism may be a possible explanation especially when other causes are ruled out. This form of regression is more frequently diagnosed in younger persons. Autism spectrum disorder itself is also associated with a higher incidence of catatonia.

- **Neurologic:** Persons with Down syndrome are at risk for multiple neurologic diseases. Ruling out common entities like seizure (also sometimes called epilepsy), dementia (also called Alzheimer's disease), stroke, and mitochondrial disease. Given the higher prevalence of these disorders, we generally recommend that all persons with Down syndrome experiencing regression be evaluated by a neurologist, preferably one familiar with assessing people with Down syndrome, or a physician familiar with Alzheimer's disease in Down Syndrome.
 - Some of the testing that neurologists may order include an EEG (which evaluates for seizures and/or epilepsy), MRI (done with and without contrast to evaluate for structural causes of regression) and sometimes a spinal tap (also called a lumbar puncture) which helps evaluate for infection and inflammation. Doctors may also order a special type of MRI called an MRA which is used to look at the blood vessels, specifically in the brain and neck. Sometimes patients will receive a special type of CT scan called a CTA instead. These studies are faster but provide the same type of information.
 - Some families have been told that their loved one with Down syndrome and regression has "early onset Alzheimer's disease". This is *very rare* in persons less than 40 years old and other causes should be ruled out prior to arriving at this diagnosis.

- **Neuro-Immunologic:** In a small subset of individuals with Down syndrome and regression, inflammation of the brain has been found. This is typically identified through a spinal tap (also called a lumbar puncture). Spinal taps (in spite of the name) require a needle to be inserted into a fluid filled space *beneath* the spine to look at the fluid surrounding the brain under a microscope. Looking at these cells can tell doctors if there are inflammatory cells present or if there are immune cells that could be causing regression.
 - If inflammation is found there is some case-based evidence to suggest the use of immune-based therapy may be helpful although consultation with a specialist in this area is strongly recommended. The causes of inflammation are variable and sometimes the term "autoimmune encephalitis" may be applied. Although that term may be used for descriptive purposes, it remains unclear if this process is

actually an autoimmune encephalitis or not. Testing for specific antibodies as noted above can be helpful in cases where there is a suspicion for neuro-immunologic phenomenon.

- **Immunologic/Endocrinologic:** Persons with Down syndrome are at risk for a host of inflammatory and endocrine disorders like thyroid disease, celiac disease, rheumatologic conditions (including inflammatory skin conditions such as psoriasis), and diabetes. Although these are less linked to longstanding regression, ruling in/out these diseases is of value as they are treatable.
- **Genetic:** The majority of persons with Down syndrome have trisomy (three copies) of chromosome 21. Despite this commonality other genetic variations are present in everyone. Thus, the possibility of having more than one gene variation in a single person is well-established and reported. There are some patients with regression who may warrant an extended genetic work up as part of their evaluation. Depending on symptoms and the presence of other medical issues, testing may include a targeted panel or more broad analysis, referred to as whole exome sequencing. Metabolic testing of blood or urine can sometimes detect genetic variation but not every person with regression requires genetic or metabolic testing.
- **Nutritional/Environmental:** Some cases of regression can be caused by severe vitamin deficiencies, heavy metal or toxin exposure or infection. These are less frequently reported in persons with regression but can be evaluated as well, especially if there is a history of exposure or very restricted eating or diet.

Arriving at the most likely reason for regression in a person with Down syndrome is very important as the therapies that can be offered vary widely on what the most likely explanation is. We encourage discussion with other families about regression but please be aware that no case of regression is exactly like the next.

We as a medical community are still learning the best ways to test and treat persons with Down syndrome and regression and an open dialogue between you and your doctor is the best way to optimize care.

What Tests Should Be Done?

As there are many potential causes of regression in persons with Down syndrome, we propose a broad work up that tests for various causes based on each individual's profile of symptoms.

We suggest that you encourage your physician to read through the articles referenced at the end of this document to familiarize themselves with the regression and some of the tests that are used. It is possible (likely) that your doctor may not be comfortable with obtaining each test and they ask you to see a “specialist” doctor (or consultant) for additional evaluation and testing.

Testing may (but not always) include tests like blood work, imaging of the brain (an MRI or CT), an EEG, a sleep study (called a polysomnogram) a lumbar puncture (called a spinal tap) and sometimes genetic or metabolic testing.

Testing is based on an individual’s symptoms and the determining the most likely cause or regression. Sometimes a combination of treatments will be considered and discussed. You do not need to have all testing performed before starting a treatment.

Is There a Treatment?

There is no one singular treatment for persons with regression. However, once a source (or reason) is found for regression, your doctor(s) can work together to provide the best treatment options. We recommend seeking consultation from an expert in psychiatry, neurology, and/or a provider familiar with treating people with Down syndrome and regression before starting a therapy.

Your doctors may recommend treatment for an individual’s symptoms while still waiting to get tests done. Typically, this will not interfere with the accuracy of the testing when performed after starting a treatment.

For consideration of immune therapy (e.g. steroids, IVIg) you should be under the care of a neurologist or immunologist with prior experience in the use of immune therapy.

When considering psychiatric medications or ECT you should work with a psychiatrist or neurologist familiar with Down syndrome.

Are There Clinical Trials or Research Available for Regression in Down Syndrome?

At this time, there are no clinical trials in persons with regression and Down syndrome. Professionals working with the Down syndrome community are actively investigating the causes of and treatment for regression in persons with Down syndrome. All clinical trials (not just regression related) are listed at: <https://clinicaltrials.gov/>.

Selected Reading Materials: *(listed alphabetically)*

1. Akahoshi K, Matsuda H, Funahashi M, Hanaoka T, Suzuki Y. Acute neuropsychiatric disorders in adolescents and young adults with Down syndrome: Japanese case reports. *Neuropsychiatr Dis Treat.* 2012;8:339-45. doi: 10.2147/NDT.S32767. Epub 2012 Jul 30. PMID: 22888254; PMCID: PMC3414247.
2. Cardinale KM, Bocharnikov A, Hart SJ, Baker JA, Eckstein C, Jasien JM, Gallentine W, Worley G, Kishnani PS, Van Mater H. Immunotherapy in selected patients with Down syndrome disintegrative disorder. *Dev Med Child Neurol.* 2019 Jul;61(7):847-851. doi: 10.1111/dmcn.14127. Epub 2018 Dec 12. PMID: 30548468.
3. Castillo H, Patterson B, Hickey F, Kinsman A, Howard JM, Mitchell T, Molloy CA. Difference in age at regression in children with autism with and without Down syndrome. *J Dev Behav Pediatr.* 2008 Apr;29(2):89-93. doi: 10.1097/DBP.0b013e318165c78d. PMID: 18367994.
4. Dykens EM, Shah B, Davis B, Baker C, Fife T, Fitzpatrick J. Psychiatric disorders in adolescents and young adults with Down syndrome and other intellectual disabilities. *J Neurodev Disord.* 2015;7(1):9. doi: 10.1186/s11689-015-9101-1. Epub 2015 Mar 1. PMID: 25810793; PMCID: PMC4373108.
5. Ghaziuddin N, Nassiri A, Miles JH. Catatonia in Down syndrome; a treatable cause of regression. *Neuropsychiatr Dis Treat.* 2015 Apr 2;11:941-9. doi: 10.2147/NDT.S77307. PMID: 25897230; PMCID: PMC4396650.
6. Jacobs J, Schwartz A, McDougle CJ, Skotko BG. Rapid clinical deterioration in an individual with Down syndrome. *Am J Med Genet Part A.* 2016 Jul; 170A(7):1899-1902. PMID: 27149638.
7. Miles JH, Takahashi N, Muckerman J, Nowell KP, Ithman M. Catatonia in Down syndrome: systematic approach to diagnosis, treatment and outcome assessment based on a case series of seven patients. *Neuropsychiatr Dis Treat.* 2019 Sep 20;15:2723-2741. doi: 10.2147/NDT.S210613. PMID: 31571888; PMCID: PMC6759875.
8. Mircher C, Cieuta-Walti C, Marey I, Rebillat AS, Cretu L, Milenko E, Conte M, Sturtz F, Rethore MO, Ravel A. Acute Regression in Young People with Down Syndrome. *Brain Sci.* 2017 May 27;7(6):57. doi: 10.3390/brainsci7060057. PMID: 28555009; PMCID: PMC5483630.
9. Poumeaud F, Mircher C, Smith PJ, Faye PA, Sturtz FG. Deciphering the links between psychological stress, depression, and neurocognitive decline in patients with Down syndrome. *Neurobiol Stress.* 2021 Feb 5;14:100305. doi: 10.1016/j.ynstr.2021.100305. PMID: 33614867; PMCID: PMC7879042.
10. Rosso M, Fremion E, Santoro SL, Oreskovic NM, Chitnis T, Skotko BG, Santoro JD. Down Syndrome Disintegrative Disorder: A Clinical Regression Syndrome of Increasing Importance. *Pediatrics.* 2020 Jun;145(6):e20192939. doi: 10.1542/peds.2019-2939. PMID: 32471843.
11. Santoro SL, Cannon S, Capone G, Franklin C, Hart SJ, Hobensack V, Kishnani PS, Macklin EA, Manickam K, McCormick A, Nash P, Oreskovic NM, Patsiogiannis V, Steingass K, Torres A, Valentini D, Vellody K, Skotko BG. Unexplained regression in Down syndrome: 35 cases from an international Down syndrome database. *Genet Med.* 2020 Apr;22(4):767-776. doi: 10.1038/s41436-019-0706-8. Epub 2019 Nov 26. PMID: 31767984.
12. Worley G, Crissman BG, Cadogan E, Milleson C, Adkins DW, Kishnani PS. Down Syndrome Disintegrative Disorder: New-Onset Autistic Regression, Dementia, and Insomnia in Older Children and Adolescents With Down Syndrome. *J Child Neurol.* 2015 Aug;30(9):1147-52. doi: 10.1177/0883073814554654. Epub 2014 Nov 3. PMID: 25367918.