# CSS Fast Facts and FAQs

### What is Coffin-Siris Syndrome?

Coffin-Siris Syndrome (CSS; fifth digit syndrome) was first reported in 1970 by Drs. Coffin and Siris to describe individuals with a shortened or underdeveloped fifth digit or fifth digit nail, along with developmental and learning differences, and a variety of organ-system issues. For many years, the diagnosis was made solely on clinical features; in 2013, the first genes associated with CSS were discovered. As more individuals with CSS are being diagnosed, the clinical picture has broadened; we are finding that not all individuals have the classic fifth digit finding, and that the extent of learning, developmental, and growth differences vary among children. Other terms that have been proposed for the syndrome include 'BAFopathies' and 'SWI-SNF related disorders.'

### What causes CSS?

Genes that cause CSS have been linked to the BAF molecular pathway, which is responsible in part for the 'packaging' of genetic information in our cells. Specific genes that have been shown to cause CSS include ARID1A, ARID1B, ARID2, BICRA, DPF2, SMARCA2, SMARCA4, SMARCB1, SMARCC2, SMARCD1, SMARCE1, SOX4, AND SOX11. It is likely that further genes may be linked to CSS as researchers discover more about our genes.

## How common is CSS?

The true prevalence of CSS is unknown, and numbers described online (and likely communicated to you by your doctor) are determined by those actually represented in research and in the IRB-approved clinical registry. That number currently sits around 550 worldwide (as of Fall 2024), though we know from our community that it is much bigger than that (best estimation is a few thousand, but concrete and documented cases in research is what speaks). This is why we push for participation in the registry so heavily! Every step forward in research helps! (To join the registry, please email CSSregistry@seattlechildrens.org)

As genetic testing technology continues to expand, doctors will certainly be able to diagnose more individuals with the condition.

## What is ARID1B-related disorder? Is it the same as CSS?

*ARID1B*-related disorder has been described as slightly different from CSS, as some individuals with changes in the *ARID1B* gene are only affected with learning or developmental differences, without significant medical issues. Clinicians are still divided as to what is properly termed 'CSS' vs. 'ARID1B related disorder', but this does not change the underlying cause or how we care for individuals with either.

## Can CSS be passed down?

Theoretically, yes. There have been several reports of individuals with CSS passing down CSS to their children. Oftentimes if a child is found to have a change in one of the genes that cause CSS, his or her parents may be tested. It is possible that a parent may have a change in one of the CSS genes, but if the parent is healthy, that variant is likely not causing CSS in that parent. Children who have CSS have a 50% chance of passing down their altered CSS gene to any future children.

## If I have one child with CSS, could any additional children I birth also have CSS?

Short answer is yes. If a parent has a change in any of the genes associated with CSS, and has a child with CSS, this indicates a 50% chance of passing those gene changes on to any future children. Assuming your child with CSS is due to a "de novo" change (or randomly occurring), which is far and away most common, the answer is still... technically yes. With any genetic syndrome, there is a very low, but not zero, chance that additional children may be affected (due to a phenomenon known as gonadal mosaicism). However, if a healthy parent does not have the same gene change as their

CSS child, the likelihood of having another child with CSS is <1%. Please consult a genetic counselor if you would like to ask specific questions regarding your family planning and/or any testing you have had done.

### Did anything I do cause my child to have CSS?

No. We have no control over the genetic material that we either pass down to our children or that is created when they are conceived. CSS is not caused by anything that a mother or father did or didn't do while or before they became pregnant.

### Is there treatment for CSS?

Because CSS is caused by a genetic change that is present in all the cells of the body, there is no medicine or treatment that will 'undo' that change. However, individuals with CSS should be monitored for various health concerns and should be evaluated by several specialists depending on their unique medical needs. All children with CSS have some degree of learning or developmental differences, and benefit from individualized education plans as well as speech, feeding, occupational, or physical therapies. A comprehensive list of articles related to CSS can be found at www.coffinsiris.org/programs, and some of the recent articles include recommendations for treatment and ongoing care.

### I've heard information about gene therapy or genetic therapeutics for certain diseases. Is this an option for CSS?

Gene therapy is a rapidly evolving field of research which may involve alteration of the transcription or translation of DNA to change protein production. While gene therapy is beginning to be used for a number of different conditions, it is unclear at this time how or if gene therapy would serve individuals with neurodevelopmental conditions such as CSS. We don't have good information as a scientific community about how genetic therapy may benefit or harm these individuals. More research needs to be done in order to make safe and educated decisions about such therapy for individuals with CSS.

As a Foundation, our statement on the matter stands as such: "The Coffin-Siris Syndrome Foundation is committed to supporting and expanding the ongoing research base around CSS and related disorders. Our highest priority remains the inclusion and well-being of those with CSS and their devoted caregivers. We believe disability is an inherent part of the human condition and is not an abnormality that must necessarily be fixed. Disability comes with RIGHTS, as well as community, belonging, and pride, and we will always place these values highest. To that end, we will support, both financially and

otherwise, research that strives to bring better understanding and diagnosis, better quality of life, and better treatments and modalities for the care of those with Coffin-Siris Syndrome. We will continue to pursue, explore, and understand research efforts being made, assess how we can engage and help further these efforts, and grapple with (our own and society's) internalized ableism and the ever-growing body of ethics as they arise.”