Coffin Siris Syndrome: A Disorder of SWI/SNF Pathway

Shivani Mishra and Shubha R Phadke

Department of Medical Genetics, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow

Email: shubharaophadke@gmail.com

Abstract

Coffin-Siris syndrome (CSS) is classically characterized by aplasia/hypoplasia of the distal phalanx or nail of the fifth digit, coarse facial features and moderate to severe developmental delay. CSS is a genetically heterogeneous disorder with clinical variability. Recently, mutations in five genes which encode for subunits of the ATP dependent chromatin-remodeling complex- switch/sucrose non-fermenting (SWI/SNF): *SMARCB1, SMARCA4, SMARCE1, ARID1A* and *ARID1B*, have been found to be responsible for the disorder. The CSS phenotypes and the SWI/SNF complex are discussed in this paper.

Introduction

Coffin-Siris syndrome (CSS) also known as "Fifth digit syndrome" (OMIM#135900) is a genetic disorder, classically characterized by aplasia/hypoplasia of the distal phalanx or nail of the fifth digit, coarse facial features and moderate to severe developmental/cognitive delay. Other findings commonly include failure to thrive, feeding difficulties, frequent infections, short stature, hypertrichosis, sparse scalp hair, ophthalmologic abnormalities, microcephaly, brain malformations, speech delay and hearing loss, etc. (Figs. 1, 2, 3, 4). It was first described by Coffin and Siris in 1970 in 3 unrelated girls with severe mental retardation, absent nails and hypoplastic distal phalanges of fifth fingers (Coffin & Siris, 1970). CSS is inherited in an autosomal dominant manner. Mutations in five genes encoding subunits of the ATP dependent chromatin-remodeling complex- switch/sucrose non-fermenting (SWI/SNF): *SMARCB1, SMARCA4, SMARCE1, ARID1A,* and *ARID1B* have been found to be responsible for the disorder and have been identified by whole exome sequencing and pathway-based genetic testing (Fig. 5). Further *SOX11* mutations have been recently discovered in CSS patients with a mild phenotype. SOX11 is the downstream transcriptional factor of the PAX6-BAF complex.

Figure 1 Hypoplasia of nail of fifth digit in a patient with Coffin-Siris syndrome.

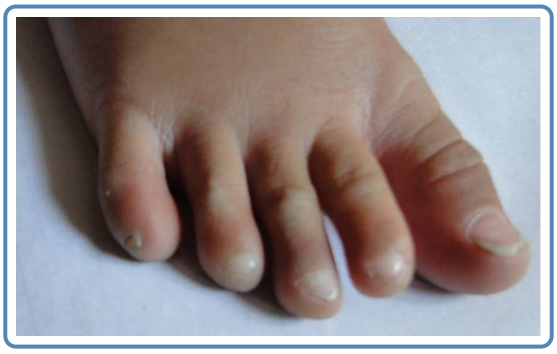


Figure 2 Hypolplasia of nail of fifth toe in a patient with Coffin-Siris syndrome.

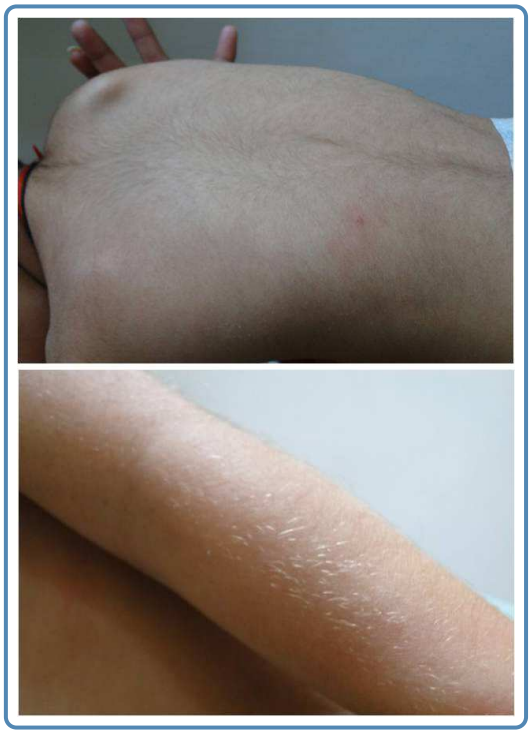


Figure 3 Increased body hairs (hypertrichosis) in a patient with Coffin-Siris syndrome.

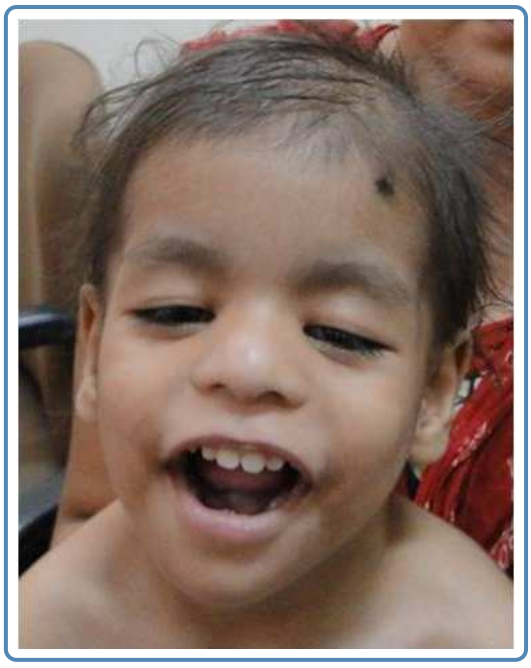


Figure 4 Coarse facial features in Coffin- Siris Syndrome- bushy eyebrows, broad nasal bridge and bulbous nasal tip.

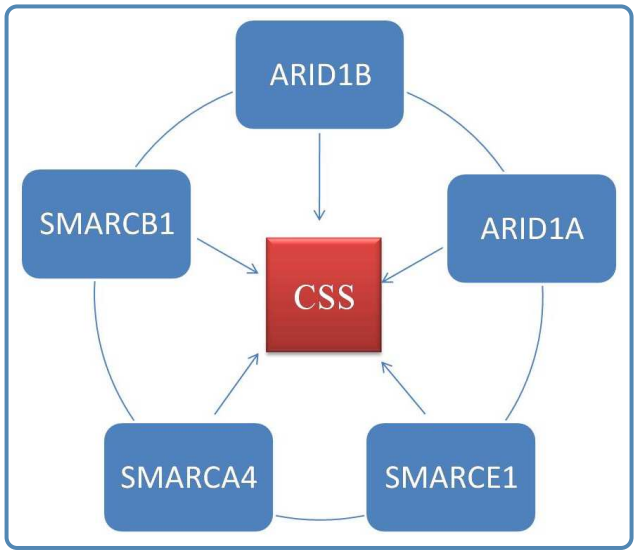


Figure 5 Genes of the SWI/SNF pathway involved in Coffin- Siris Syndrome.

CSS: A Genetically Heterogeneous Disorder

CSS has a distinct clinical phenotype. Clinical criteria of CSS include three major findings and one of each of the three minor findings. The major findings are fifth digit nail/distal phalanx hypoplasia/aplasia, developmental/cognitive delay and coarse facial features with bushy eyebrows, thick lips, broad nasal bridge with bulbous nasal tip. Minor findings include- 1) ectodermal findings like hirsutism, sparse scalp hair, dental anomalies; 2) constitutional findings like intrauterine growth retardation (IUGR), short stature, microcephaly, failure to thrive, frequent infections; 3) organ related findings like cardiac anomalies, feeding difficulties, genitourinary/renal anomalies, gastrointestinal anomalies and brain/cranial malformations.

Because molecular genetic testing has identified causative pathogenic variants in several individuals with coarse facial features and intellectual disability that overlap with classic CSS but with little or no fifth digit hypoplasia/aplasia, evaluation of individuals with a broader phenotype is required to determine the frequency of this finding in individuals with molecularly confirmed CSS. Newer diagnostic criteria are likely to evolve to include both clinical features and molecular findings to evaluate a broader phenotype for CSS. For exam-

ple *ARID1B* variants have been found in persons with intellectual disability, some without distal digital or fifth finger hypoplasia/aplasia [Halgren et al., 2012; Santen et al., 2012].

Genotype–Phenotype Correlation

Genotype-phenotype correlations in CSS have not been clearly defined. Pathogenic variants in *ARIDB1* have been identified in individuals with mild CSS and/or apparently isolated intellectual disability by exome sequencing (Hoyer et al., 2012). These individuals have many features of CSS like developmental delay, hearing loss, seizures and dysmorphic facial features but only a subset has fifth digit anomalies. In addition to classic features, individuals with *SMARCB1* mutations are associated with severe neurodevelopmental abnormalities including CNS structural abnormalities, severe intellectual disability, seizures, scoliosis and speech delay; expressive language being affected predominantly. Especially, those with a recurrent mutation "p.Lys364del" presented strikingly similar phenotypes including characteristic coarse facial features. Patients with *SMARCA4* mutations have less coarse craniofacial appearances and behavioral abnormalities. *SMARCE1* mutations have a wide spectrum of manifestations from moderate to severe intellectual disability. Patients with *ARID1A* mutations have a wide spectrum of manifestations from mild to severe intellectual disability and serious internal complications due to cardiac anomalies, feeding difficulties, genitourinary/renal anomalies, gastrointestinal anomalies and brain/cranial malformations that could result in early death.

Mutation in genes involved in CSS also causes cancer. *ARID1B* truncating mutations (and one small in-frame deletion) were identified in breast cancer tissue. Inactivating mutations of *ARID1A* are a common feature of gastric cancer and truncating somatic mutations of endometriosis-associated ovarian clear cell and endometrioid carcinoma. Recently, missense mutations of *SMARCA4* were identified in medulloblastoma and *SMARCB1* in meningiomas. Truncating as well as missense mutations in *SMARCB1* in the germline are associated with Schwannomatosis, a tumor suppressor syndrome. *SMARCE1* mutations have not been unequivocally linked to tumor formation, but two truncating mutations which are thought to lead to haploinsufficiency were reported in the breast cancer tissue (Santen et al., 2012).

SWI/SNF Complex and its Function

The DNA in human chromosomes is packed in the cell nucleus in the form of nucleosomes, which are formed by ~147 bp of DNA wrapped around histone proteins. Nucleosomes are assembled into condensed chromatin which inhibits access to DNA for cellular proteins that drive chromatin-based processes, including transcription and DNA repair. An important step in the regulation of these nuclear processes is the modulation of chromatin structure. It can be achieved by two mechanisms either by involving the modification of residues in the histone tails or by the activity of ATP-dependent chromatin remodeling complexes (Santen et al., 2012). SWI/SNF (Switch/Sucrose Non-Fermentable) are the chromatin remodeling complexes present in human cells and play an important role in transcription, cell differentiation, DNA repair, and tumor suppression.

The SWI/SNF complex was first discovered in the yeast, Saccharomyces cerevisiae and is named after yeast mating types switching (SWI) and sucrose non-fermenting (SNF). The SWI/SNF complex in yeast contains the ATPase Swi2/Snf2p, two actin-related proteins (Arp7p and Arp9) and other subunits involved in DNA and protein-protein interactions which causes alteration of nucleosome structure in an ATP-dependent manner. RSC (Remodeling the Structure of Chromatin), a closely related complex, was also identified in yeast. This complex is composed of 17 subunits and shows similarities to the SWI/SNF complex. The structures of the SWI/SNF and RSC complexes are highly conserved, but their compositions are not identical, reflecting an increasing complexity of chromatin through evolution. SWI/SNF and RSC complexes in higher eukaryotes maintain core components to maintain overall shape and remodeling activity and also substitute or add on other components with more specialized or tissue-specific domains. As in yeast, humans contain two distinct remodeling complexes homologous to SWI/SNF and RSC, respectively. These two complexes are called BAF (BRG1 Associated Factors) and PBAF (Polybromo-associated BAF) (Table 1).

SWI/SNF complex consists of 15–20 subunits and is thought to remodel chromatin through ATP-dependent sliding of nucleosomes along the DNA. It binds near promoters to facilitate the binding of transcription factors and regulate the expression of genes in yeast, including those involved in sugar and iron uptake. In humans, its mode of action is

Table 1 SWI/SNF and RSC components during evolution.

	S.cerevisae		H.sapiens	
COMPLEX	**SWI/SNF**	**RSC**	**BAF**	**PBAF**
	Swi2/Snf2	Sth1	BRG1/hBRM	BRG1
	Swi3	Rsc8/Swh3	BAF155/BAF170	
	Swi1/Adr6		BAF250 a,b	
		Rsc9		BAF200
		Rsc1,2,4		BAF180
	Swp73	Rsc6	BAF60 a,b,c	
	Snf5	Sfhl	INI1/BAF47/hSNF5	
			BAF57	
			BAF45 a,b,C,d	
	Arp7,9		Beta actin	
			BAF53a,b	
				BRD7
	Swp82			
	Snf6			
	Snf11			
	Taf14			
		Rsc3-5,7		
		Rsc10,30		
		Ht11		
		Ldb7		

less clear. Many SWI/SNF complexes do not bind near promoter sites, but a substantial number of genes involved in cellular processes are controlled by this complex, like those involved in cell adhesion and cell differentiation. The catalytic subunits of SWI/SNF complex, the SMARCA2 and SMARCA4 ATPases, as well as structural components, ARID1A and ARID1B, are required for transcription regulation. Moreover, these subunits can exert antagonistic effects on transcription regulation of cell cycle regulators, like c-Myc, illustrating their importance in determining SWI/SNF activity. It has been shown that the structure of the complex changes upon differentiation of cells, suggesting that distinct SWI/SNF complex may be important for cell differentiation. SWI/SNF also plays important role in DNA repair. Its inactivation leads to impaired DNA repair and reduced cell survival after exposure to genotoxic agents. Defects in DNA repair often lead to genomic instability, which is one of the hallmarks of cancer. This explains why inactivating mutations in SWI/SNF components results in genomic instability and could lead to cancer development.

Chromatin Remodelling

Chromatin remodeling is an enzyme-mediated process which facilitates access of nucleosomal DNA by remodeling the structure, composition and positioning of nucleosomes. Nucleosomal DNA is accessed by two major classes of protein complexes: 1) Covalent histone-modifying complexes, 2) ATP-dependent chromatin remodeling complexes. Histone-modifying complexes are specific protein complexes that catalyze addition or removal of various chemical elements on histones. These enzymatic modifications include methylation, acetylation, phosphorylation, and ubiquitination and primarily occur at N-terminal histone tails. These enzymatic modifications affect the binding affinity between histones and DNA, and thus, loosening and tightening of the condensed

DNA wrapped around histones. ATP-dependent chromatin-remodeling complexes regulate gene expression by either moving, ejecting or restructuring nucleosomes. These chromatin-remodeling complexes have a common ATPase domain. Energy from the hydrolysis of ATP allows these chromatin-remodeling complexes to reposition nucleosomes (slide, twist or loop) along the DNA or remove histone from DNA, or causes exchange of histone variants (Fig. 6). This creates nucleosome-free regions of DNA for gene activation. SWI/SNF is an ATP-dependent nucleosome remodeling complex. Two mechanisms of chromosome remodeling by SWI/SNF have been proposed. The first model involves a unidirectional diffusion of a twist defect in the nucleosomal DNA that starts at the DNA entry site of the nucleosome and results in a corkscrew-like propagation of DNA on the histone octamer surface. The second model involves "loop-recapture" mechanism. It involves the dissociation of DNA from the edge of the nucleosome and reassociation of DNA inside the nucleosome, resulting in a DNA bulge on the octamer surface. The DNA loop then propagates over the surface of the histone in a wave-like manner and results in the repositioning of DNA to histone without changes in the total number of DNA-histone contacts. A recent study has concluded strong evidence against the twist diffusion mechanism and has further strengthened the loop-recapture model (Tang et al., 2010).

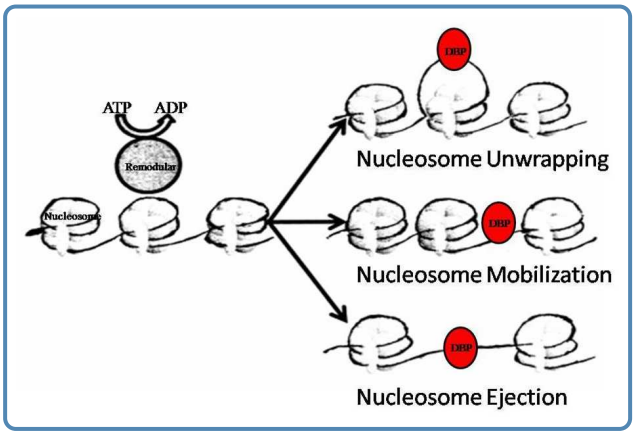


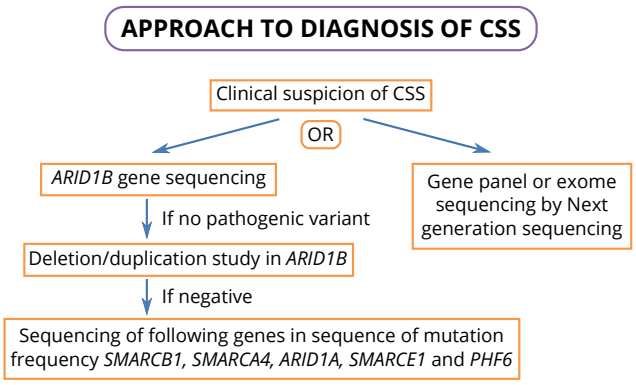
Figure 6 Different effects of ATP-dependent chromatin remodeling activity of remodelers (SWI/SNF) on nucleosomal DNA.

Role of BAF Complex in Neural Development

In mammalian neural development, developmental stage-specific BAF assemblies are found in embryonic stem cells, neural progenitor cells and postmitotic neurons. Particularly, the neural progenitor-specific BAF (npBAF) complexes are essential for controlling the neural progenitor cell division, while neuronal BAF (nBAF) function is necessary for the maturation of post-mitotic neurons as well as long-term memory formation. Transition from npBAF to nBAF complexes is a microRNA-mediated mechanism and is instructive for the neuronal fate and can even convert fibroblasts into neurons. In neurological disorders, the frequency of BAF subunit mutations is high. This underscores the rate-determining role of BAF complexes in neural development, homeostasis, and plasticity (Sony et al., 2014).

Approach to Diagnosis

Diagnosis of CSS is based on both clinical features and molecular testing. The frequency of mutations in different genes in a study of 109 patients is as follows: *ARID1B1* (65%), *ARID1A* (7%), *SMARCB1* (12%), *SMARCA4* (11%), *SMARCE1* (2%) and *PHF6* (2%) (Kosho et al., 2014). The following flowchart outlines the diagnostic approach to a patient with clinically suspected CSS.



Genetic Counseling

CSS is inherited in an autosomal dominant manner. Till date, all the pathogenic variants detected have been *de novo* mutations. If the pathogenic variant found in the proband is not detected in either parent, the risk to sibs is low but greater than that

of the general population because of the possibility of germline mosaicism. However, there has been no instance of germline mosaicism reported thus far in molecularly confirmed CSS patients. Prenatal testing for pregnancies at increased risk is possible after identifying the causative gene mutation. With the exception of one report of parental transmission, typically individuals with CSS do not reproduce.

Management of CSS

Management of CSS is basically supportive. Occupational, physical and/or speech therapies are required to optimize developmental outcomes. Supplementation of nutrients and/or gastrostomy tube placement may be required to meet nutritional needs. Routine management of hearing loss and ophthalmologic abnormalities is required.

SWI/SNF Targeted Therapy for Cancers

There is growing evidence for mutations in the BAF complex genes to be causal for CSS. The biology of BAF is very complicated and still remains unknown. According to recent studies SWI/SNF-mutant cancers depend on residual SWI/SNF complexes for their aberrant growth, revealing synthetic lethal interactions that could be used for therapeutic purposes. Certain cancers like small cell lung cancers and acute leukemias lack SWI/SNF mutations and are vulnerable to inhibition of the SWI/SNF ATPase subunit BRG1, whereas several other cell types do not show this sensitivity. There is emerging evidence that implicates SWI/SNF as a candidate drug target in human cancer.

Further research is required to reveal the importance of the SWI/SNF and BAF complex in human development, which could lead to the development of new targeted therapies for CSS in the future.

Conclusion

CSS is a heterogeneous disorder that can be diagnosed by clinical and molecular genetic testing. At present no definitive treatment is available. Therapies targeting the SWI/SNF pathway need further research.

References

1. Coffin GS, Siris E. Mental retardation with absent fifth fingernail and terminal phalanx. Am J Dis Child 1970; 119: 433-439.
2. Haspeslagh M et al. The Coffin-Siris syndrome: report of a family and further delineation. Clin Genet 1984; 26: 374–378.
3. Kosho T, et al., Coffin-Siris syndrome and related disorders involving components of the BAF (mSWI/SNF) complex: historical review and recent advances using next generation sequencing. Am J Med Genet C 2014; 166C: 241-251.
4. Kosho T et al. Genotype-phenotype correlation of Coffin-Siris syndrome caused by mutations in SMARCB1, SMARCA4, SMARCE1, and ARID1A.Am J Med Genet C 2014; 166C: 262-275.
5. Santen GW, et al. Mutations in SWI/SNF chromatin remodeling complex gene ARID1B cause Coffin-Siris syndrome. Nat Genet 2012; 44: 379-380.
6. Santen GW, et al. SWI/SNF complex in disorder: SWItching from malignancies to intellectual disability. Epigenetics 2012; 7: 1219-1224.
7. Sony EY, et al. The role of BAF (mSWI/SNF) complexes in mammalian neural development.Am J Med Genet C 2014; 166C: 333-349.
8. Tang L et al. Structure and function of SWI/SNF chromatin remodeling complexes and mechanistic implications for transcription. Prog Biophys Mol Biol 2010; 102: 122-128.
9. Tsurusaki Y, et al. Coffin-Siris syndrome is a SWI/SNF complex disorder. Clin Genet 2014; 85: 548-554.