French National Protocol for Diagnosis and Treatment (PNDS)

Coffin-Siris and Nicolaides-Baraitser syndromes
(BAFopathies)

Coordinating Center (Centre de Référence) for Intellectual Disabilities of Rare Causes
PNDS Project Coordinator: Dr. Cyril Mignot

DéfiScience and AnDDI-Rares rare disease networks
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<th>Description</th>
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<tbody>
<tr>
<td>ALD</td>
<td>affection de longue durée [long-term illness]</td>
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<tr>
<td>ARID</td>
<td>AT-rich interaction domain</td>
</tr>
<tr>
<td>ARID1A</td>
<td>ARID-containing protein 1A</td>
</tr>
<tr>
<td>ARID1B</td>
<td>ARID-containing protein 1B</td>
</tr>
<tr>
<td>ARID2</td>
<td>ARID-containing protein 2</td>
</tr>
<tr>
<td>ASD</td>
<td>Autism spectrum disorder</td>
</tr>
<tr>
<td>BAF</td>
<td>BRG1/BRM-Associated Factor complex; also known as SWI/SNF</td>
</tr>
<tr>
<td>BICRA</td>
<td>BRD4-interacting chromatin remodeling complex-associated protein</td>
</tr>
<tr>
<td>CAMSP</td>
<td>Centre d’Action Médico-Sociale Précoce [center for early sociomedical intervention]</td>
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<tr>
<td>CSS</td>
<td>Coffin-Siris syndrome</td>
</tr>
<tr>
<td>DPF2</td>
<td>D4, zinc and double PHD Fingers family, member 2</td>
</tr>
<tr>
<td>FAM</td>
<td>Foyer d’Accueil Médicalisé [group home or residential facility]</td>
</tr>
<tr>
<td>ID</td>
<td>intellectual disability</td>
</tr>
<tr>
<td>IME</td>
<td>Institut Médico-Educatif [special school]</td>
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<tr>
<td>MAS</td>
<td>Maison d’Accueil Spécialisée [group home or residential facility]</td>
</tr>
<tr>
<td>MDPH</td>
<td>Maison Départementale des Personnes Handicapées [Local disability center]</td>
</tr>
<tr>
<td>NBS</td>
<td>Nicolaides-Baraitser syndrome</td>
</tr>
<tr>
<td>PMR</td>
<td>physical medicine and rehabilitation</td>
</tr>
<tr>
<td>PNDS</td>
<td>Protocole National de Diagnostic et de Soins [French national protocol for diagnosis and treatment]</td>
</tr>
<tr>
<td>SESSAD</td>
<td>Service d’Éducation Spécialisée et de Soins à Domicile [home- and school-based treatment and specialized education service]</td>
</tr>
<tr>
<td>SMARC</td>
<td>SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin</td>
</tr>
<tr>
<td>SMARCA2</td>
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</tr>
<tr>
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<td>SMARCE1</td>
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</tr>
<tr>
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<td>SRY-related HMG-box, gene 11</td>
</tr>
<tr>
<td>SOX4</td>
<td>SRY-related HMG-box, gene 4</td>
</tr>
<tr>
<td>SWI/SNF</td>
<td>switch / sucrose non-fermenting complex</td>
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</table>
Summary for primary physician

- **Disease characteristics**
  Coffin-Siris syndrome (CSS) is a developmental disorder of genetic origin whose main signs are intellectual disability and certain tell-tale physical traits, occasionally including congenital abnormalities. Facial hirsutism and low hairlines, but sparse scalp hair, are typical of CSS. The most common congenital abnormalities are agenesis of the corpus callosum and hypoplasia of the distal phalanx (and nail) of the fifth fingers or toes. Rarer and less specific abnormalities—including some affecting the heart and kidneys—are also among the signs that may be observed in individuals with this disease.
  CSS is most often caused by pathogenic variants in the *ARID1B* gene. More rarely, other genes are involved. In addition, *ARID1B* variants are one of the most frequent causes of nonsyndromic intellectual disability of genetic origin. While CSS exhibits autosomal dominant inheritance, the causal gene variant is most often a *de novo* (i.e., uninherited) mutation.
  Nicolaides-Baraitser syndrome (NBS) is rarer than CSS and caused by pathogenic missense variants in the helicase domain of the *SMARCA2* gene. NBS patients share morphological and developmental traits with those who have CSS, which is very similar in terms of nosology and physiopathology.

- **Clinical suspicion, diagnosis, and treatment plan**
  A diagnosis of CSS and NBS is suggested by identification of:
  - (fetuses and all ages) agenesis of the corpus callosum (for CSS but not NBS), because CSS is the leading cause of the abnormality in syndromic cases (i.e. with intellectual disability, but agenesis of the corpus callosum may appear isolated antenatally);
  - (in infants) hypotonia, and possibly, laryngomalacia and/or feeding problems requiring nutritional support;
  - (in children) delayed psychomotor skill acquisition or difficulty adapting to school suggestive of intellectual disability
  In such situations, which are not specific to CSS, it is necessary to seek the opinion of a developmental specialist—a child neurologist or geneticist—who will rely on clinical examination and/or genetic testing to diagnose CSS. In children of all ages and in adults, typical facial/hand dysmorphism suggests the diagnosis of CSS/NBS.

- **Follow-up and role of primary physician**
  The primary physician or pediatrician plays an important role in the follow-up of a patient with CSS or NBS, who may develop epilepsy, scoliosis, behavior disorders, and possibly endocrine disorders such as hypothyroidism and diabetes mellitus. Follow-up is conducted in cooperation with a developmental specialist, usually based at a hospital, who should see the patient annually.
Useful information
AnDDI-Rares national rare disease network: http://www.anddi-rares.org
Association Coffin-Siris France (French Coffin-Siris syndrome patient organization): https://coffinsiris.fr/
Alliance Maladies Rares (Rare disease alliance): http://www.alliance-maladies-rares.org
UNAPEI (Federation of French organizations representing interests of people with mental disabilities and their families): http://www.unapei.org
Coffin-Siris Syndrome Foundation: https://www.coffinsiris.org/
Dutch ARID1B gene-dedicated site: arid1bgene.com
1 Introduction

Coffin-Siris syndrome (MIM Number: 135900 and others; CSS) is a rare genetic syndrome described by Drs. Coffin and Siris in 1970, based on their observation of three patients. Initially called “fifth-digit syndrome,” CSS is typically characterized by developmental delay or intellectual disability (ID), hypo- or aplasia of the nails or phalanges of the fifth fingers or toes, facial dysmorphism and thin hair. Other clinical signs were later described. CSS may be diagnosed clinically, but diagnostic clues differ according to stage of development. Increasingly the diagnosis is made after genome-wide genetic testing, leading to a broadening of the phenotype.

CSS-associated disorders are one of the most frequent causes—and possibly the most frequent cause—of unexplained IDs (i.e., potentially of genetic origin), accounting for up to 1% of them. Assuming an ID prevalence of 2%, we may estimate that of CSS to be approximately 2 out of 10,000, yielding an incidence of >100 children born each year in France, and >800 in Europe.

CSS is a developmental disorder exhibiting autosomal dominant inheritance. Genetic etiologies account for 50% to 70% of all cases known to date (>300 cases reported in literature). In the vast majority of cases, CSS is caused by heterozygous de novo (i.e., not inherited) deletions or mutations affecting genes for the BRG1- or BRM-associated factor (BAF) protein complex, also known as the switch/sucrose non-fermenting (SWI/SNF) complex. The SWI/SNF complex is involved in ATP-dependent chromatin remodeling. Genotype and phenotype correlate to a certain extent.

Nicolaides–Baraitser syndrome (NBS) is a clinical entity first described in 1993 that shares several clinical signs with CSS. Its phenotype includes moderate to severe ID, facial dysmorphism, thin hair, risk of epilepsy, short stature, and microcephaly. Facial features are notably similar to those in CSS. However, individuals with NBS do not exhibit hypoplasia of the nails or phalanges. Instead, their interphalangeal joints are distinctively broad. NBS is much rarer than CSS. It is exclusively due to missense variants in the helicase domain of SMARCA2. Interestingly, patients with duplications of SMARCA2 exhibit a CSS(-like) phenotype.

The phenotypic and genotypic similarities between the two syndromes have led some authors to suggest grouping them together within a single category as “BAFopathies”.

2 Objective of PNDS

This document seeks to provide medical and allied health professionals with a detailed exposition of the current, optimal approach to diagnosis and therapy, and of the care pathway, for pediatric or adult patients with CSS or NBS. It aims to ensure optimal, consistently implemented treatment and follow-up for this rare disease across France, improving the quality of life of patients and their relatives. Where applicable, this PNDS also identifies pharmaceuticals that may be administered for off-label use, and any services, medication, or other products needed to treat these patients but not usually reimbursed by the French public health insurance administration.

The present document and the accompanying list of acts and services (LAP) may guide the primary physician (who the patient must have declared as such to the public health insurance administration), working with the medical specialist, in drawing up the individualized treatment protocol (protocole de soins) with input from the physician in charge of approving public reimbursement of medical expenses (médecin conseil) and the patient’s relative or guardian. The individualized protocol must be completed to request full reimbursement of medical expenses related to CCS or NBS, which are so-called “unlisted” (hors liste) conditions, i.e., not on the French ALD 30 list of long-term illnesses.

The PNDS cannot account for every unique case, comorbidity, complication, therapeutic specificity, hospital treatment plan, etc. It cannot claim to exhaustively address all possibilities for management of CSS, nor can it replace the responsibility that the physician has towards his or her patient. Rather, it describes the standard management of patients with CSS or NBS. It must be updated to reflect new, confirmed findings.

This PNDS was prepared in accordance with the guidelines published by the French National Authority for Health (HAS) in 2012—Méthode d’élaboration d’un protocole national de diagnostic et de soins pour les maladies rares [Guide to preparing a national protocol for diagnosis and treatment of rare diseases]—which is available from the websites of the HAS (www.has-sante.fr) and DéfiScience (www.defiscience.fr/).

The present document addresses the following points for patients of all ages (fetuses, infants, older children, adolescents, and adults):

- signs suggesting CSS diagnosis
- genetic testing techniques
- patient evaluation (associated pathologies and comorbidities)
- treatment and follow-up (care pathway)
- transition to adulthood
- genetic counseling
3 Diagnosis and initial evaluation

3.1 Objectives

The diagnosis of CSS or NBS was solely clinical before the genetic bases of these conditions were identified. Currently, a diagnosis should be confirmed by determining the genetic cause. The absence of a causal variant in the known genes (see section 3.7: Genetics) does not rule out a diagnosis when clinical signs are convincing. On the other hand, a diagnosis of CSS or NBS may be reached while exploring an unexplained ID or congenital abnormality, through the identification of a variant in an associated gene. An individual with ID but none of the morphological characteristics of CSS may be found to have a pathogenic ARID1B variant. In that case, the diagnosis would be nonsyndromic ID caused by an ARID1B mutation. Since the two diagnoses are a continuum, the same investigation as for patients with CSS are recommended.

Once a diagnosis of CSS has been made, whether or not it is confirmed by molecular analysis, the patient should undergo complementary examinations (section 3.8). In addition to corroborating the diagnosis through genetic testing, the initial evaluation is also aimed at:

– detecting comorbidities that might increase the level of disability;
– informing family members, where necessary, of the need for regular follow-up, and implementing that follow-up;
– assessing the family environment and providing assistance for parents;
– informing family members, where necessary, of services and support offered by the disability center (MDPH) in the patient’s département;
– filing a request for full reimbursement of related medical expenses by the public health insurance administration.

3.2 Professionals involved

The diagnostic assessment of a patient with a developmental delay or one or more congenital abnormalities, or having difficulty adjusting to school, can be performed—at the request of the pediatrician or general practitioner—by a developmental specialist (geneticist or child neurologist). The specialist will seek to make a primary or nosological diagnosis of ID or a genetic disorder affecting development. The etiologic diagnosis of CSS or NBS demands knowledge of rare diseases and is based on either clinical examination of the patient or specific genetic testing by a clinical geneticist or pediatric specialist—from a coordinating center (centre de référence) for rare diseases, or the
DéfiScience or AnDDI-Rares rare disease networks, for example. In any case, the opinion of a geneticist should be sought for confirmation of the diagnosis and genetic counseling. Depending on the context, associated complications, and comorbidities, other specialists may intervene:

- gastroenterologist (or pediatric gastroenterologist)
- neurologist (or child neurologist)
- pediatric physiatrist or orthopedist
- dermatologist
- cardiologist (or pediatric cardiologist)
- ophthalmologist
- ENT
- endocrinologist (or pediatric endocrinologist)
- obstetrician (in event of ultrasound finding during pregnancy, such as agenesis of the corpus callosum)
- dentist
- nephrologist
- psychiatrist (or child and adolescent psychiatrist)

### 3.3 Circumstances of detection / clinical suspicion

CSS may be diagnosed or suspected under varying circumstances, depending on patient age. A prenatal ultrasound may reveal agenesis of the corpus callosum, or other organ abnormalities, in a fetus; a feeding disorder requiring nutritional support, in an infant with psychomotor delay, axial hypotonia, laryngomalacia, cryptorchism or specific morphological features; or growth delays or, more commonly, learning difficulties or problems adjusting to school, in older children. There are specific morphological traits that may suggest CSS to the examining specialist (see section 3.4).

In other cases the diagnosis can be made by performing broad genetic testing in a child with ID, identifying a known pathogenic mutation in a CSS-related gene (or BAFopathy-related gene). In some cases, retrospective phenotyping may reveal a missed diagnosis, but mutations may also be identified in individuals with nonsyndromic ID.

NBS is rarely suggested by prenatal signs. Agenesis of the corpus callosum is not characteristic of NBS, and feeding disorders in children with this condition less often demand nutritional support. Hence, NBS is usually diagnosed or suggested by a developmental delay or learning difficulties associated with certain morphological characteristics, and possibly, epilepsy.
3.4 Clinical aspects of Coffin-Siris syndrome (and associated disorders)

The following information concerns CSS. Corresponding information for NBS is in section 3.5. While reading this it is important to keep three things in mind: 1) there is a phenotypic spectrum within this syndrome and the range of clinical features associated is still expanding; 2) that the reported frequencies are based on recent reports and may change over time; 3) most published data concerns ARID1B patients, which is also mentioned in this text, these features may also be present among other CSS patients.

3.4.1 Developmental delay and intellectual disability

Moderate to severe ID is among the most consistent features (>95%) of CSS, irrespective of its genetic cause. The particular ID profile may vary slightly depending on the gene involved (see section 3.7.2, Genetic heterogeneity; genotype-phenotype correlations). Cognitive deficit is mainly manifested as delayed psychomotor and language skill acquisition during early years. On average, children with CSS begin to sit at 12 months of age, walk at 30 months, and utter their first words at 24 months. Oral production is more seriously affected than oral comprehension: a portion (around 20-30%) of these patients do not develop speech at all.

Skills and neurodevelopmental difficulties, which may vary independently of the etiologic diagnosis, must be assessed for an individual with ID. ID is confirmed by psychometric tests and the detection of impaired adaptive functions.

Though not characteristic of the syndrome, behavior disorders have been reported in individuals with CSS. These include hyperactivity (~25%), aggressiveness (~10%), and autistic traits (up to 50%, depending on publication and the gene).

3.4.2 Neurological involvement

Moderate infantile hypotonia is the most common neurological sign of CSS (80%, all genes combined, and in patients with ARID1B variants). With the exception of hypotonia, clinical (neuromotor) neurological signs are not typical of CSS.

Some patients, with variants in genes associated with a minority of CSS cases, exhibit microcephaly (see section 3.7.2, Genetic heterogeneity; genotype-phenotype correlations).

Seizures are reported in about 25% of patients with ARID1B variants. In 50% of the cases, they occur before 4 years of age. These epilepsies are generally responsive to treatment
and usually not very active (only one seizure, or one seizure per year). Some other causative genes are associated with higher incidences of seizures.

The most typical congenital abnormality of the CNS is agenesis of the corpus callosum, which is found in approximately one-third of patients with \textit{ARID1B} variants. Other minor abnormalities have been reported (e.g., Dandy-Walker variant, ventriculomegaly and simplified gyration).

### 3.4.3 Characteristic facial dysmorphism

A CSS diagnosis is supported by the presence of particular facial characteristics, the most common being coarse features (95%); flat, broad nasal root (50%); short nose (50%); anteverted nares (50%); broad nasal tip (75%); thick alae nasi (70%); large mouth (80%); long, broad philtrum (70%); thin upper lip (50%); thick lower lip (80%); low hairline (95%); thick eyebrows (90%); and long eyelashes (85%). These percentages are based on reports of clinically diagnoses CSS patients, and may therefore be biased.

### 3.4.4 Congenital abnormalities

Heart defects are found in 20% to 35% of CSS patients. They mostly involve ventricular or atrial septal defects. Other reported abnormalities include hypoplastic left heart tetralogy of Fallot, patent ductus arteriosus, mitral or pulmonary atresia, and dextrocardia.

Kidney abnormalities are not common (12.5% of patients with \textit{ARID1B} variant). Most are cases of hydronephrosis, and only rarely is horseshoe kidney found.

Cryptorchidism has been reported for 55% of patients with an \textit{ARID1B} variant. Hypospadias is rare.

### 3.4.5 Musculoskeletal abnormalities

Hypoplasia of the distal phalanx and fingernail of the 5th finger, a classic sign of CSS, is reported in 40% of patients with ARID1B-related CSS.

Scoliosis (25%) and joint laxity (60%) are frequent signs in patients with \textit{ARID1B} variants; scoliosis is even more frequent in those with SMARCB1 variants. Not uncommonly, there are delays in bone age (40%), deciduous dentition (45%), and permanent dentition (48%).

### 3.4.6 Dermatologic manifestations

Hypertrichosis is the most typical dermatologic sign (>90% of patients). It mostly involves the back, shoulders, and face. The hairline in CSS patients is low (75%), but the hair is
sparse (60%). Between a quarter and a third of the patients have eczema. Vitiligo has been described in some patients.

Nail hypoplasia, or anonychia, typically concerns the 5th fingers or 5th toes. Hypoplasia of all fingers or toes is reported in 20% of patients with an ARID1B variant. The reported frequency of nail hypoplasia varies between publications. It apparently affects 76% of all CSS patients (Santen et al. 2013), 68.5% of CSS patients with an ARID1B variant, and 34% of patients with an ARID1B variant who exhibit a so-called “nonsyndromic” ID phenotype.

3.4.7 Feeding problems and digestive disorders

Problems sucking or swallowing in the first months or weeks of life are among the earliest and most frequent signs of CSS in the absence of digestive tract abnormalities. They typically appear alongside axial hypotonia. Affected infants may also exhibit laryngomalacia.

These problems concern >70% of all patients and 69% of those with an ARID1B variant. They require nutritional support via nasogastric tube in 17% of CSS patients and may sometimes persist past the first year and a subset requires (temporary) gastrostomy. Half of patients with ARID1B variants suffer from constipation.

3.4.8 Endocrine and growth disorders

A third of patients with an ARID1B variant are two standard deviations below the mean height for their age. Bone age tends to be delayed. Head circumference is normal at birth and throughout life (except for some genetic etiologies, see below).

Certain hormonal and endocrinological disorders are observed in patients with ARID1B variants, including hypothyroidism (19% of cases), growth hormone deficiency (13%), and diabetes mellitus (7%).

3.4.9 Sensory impairments

Refractive errors are frequent. They are found in 20% to 30% of patients with CSS due to an ARID1B variant. Both myopia and hypermetropia have been reported, among ARID1B patients (severe) myopia is more frequent compared to hypermetropia.

Furthermore, hearing loss—often due to recurrent otitis media, but also persistent hearing loss—is reported in 22% of patients with variants in ARID1B.
3.4.10 Infection risk

Recurrent infections are found in 57% of patients. They occur usually during childhood and are generally upper and lower respiratory tract infections. Their cause has yet to be determined.

3.4.11 Tumor risk

Somatic or constitutional pathogenic variants in several BAF-complex genes involved in CSS have been implicated in the development of various tumors and cancers. Tumors have been reported in 9 people with CSS that is due to variants in genes accounting for relatively small numbers of Coffins-Siris cases (see section 3.7.2, Genetic heterogeneity; genotype-phenotype correlations, for a description of these genes). Generally speaking, available data do not allow us to assert that CSS patients are at greater risk for tumors or cancers. Longer cohort follow-up is needed.

3.5 Clinical aspects and molecular genetics of Nicolaides-Baraitser syndrome

The first case of NBS was reported by Drs. Nicolaides and Baraitser in 1993. They initially posited a diagnosis of CSS. However, the phenotype of their patient was characterized by fingers with large joints and cone-shaped phalangeal epiphyses, and by the absence of nail abnormalities. Several later articles reported other patients with NBS. Sousa et al. (2009) reviewed previously reported NBS cases and presented new ones. At the time, the molecular bases of CSS and NBS were still unknown. The conditions are distinguished clinically by the nature of the phalangeal abnormalities: hypoplastic 5th nail with or without a hypoplastic distal phalanx, typical of CSS, versus large joints, short metacarpals and broad distal phalanges, typical of NBS.

The discovery of missense variants in the SMARCA2 gene responsible for NBS (van Houdt et al. 2012) was reported shortly before the announcement of the discovery of variants in genes coding for SWI/SNF-complex proteins in CSS patients (Tsurusaki et al. 2012, Santen et al. 2012, Hoyer et al. 2012). Together these data explained the similarities between the two syndromes but did not elucidate their differences, which became less categorical with the identification of many CSS patients lacking 5th-nail anomalies.

Patients with SMARCA2 duplications exhibit features of the CSS phenotype. Yet most people with pathogenic SMARCA2 variants within the helicase domain have the NBS phenotype. Sousa et al. (2014) described the following features of NBS, based on their
study of 61 patients clinically diagnosed with the syndrome and having pathogenic
SMARCA2 variants:

– severe (45% of patients), moderate (36%), or slight (18%) ID
– head circumference 2 standard deviations below the mean (65%)
– epilepsy (64%), the first seizures occurring at age 2, on average
– delayed growth in stature (half of patients) and delayed bone age (41%)
– feeding problems (46%), not usually requiring nutritional support
– large finger joints (85%) and broad distal phalanges (68%)
– cryptorchidism (59%), umbilical and inguinal hernias (46%)
– minor heart defects (10%)

Overall, the neurodevelopmental phenotype is more pronounced in NBS patients with
SMARCA2 variants than in those with a CSS phenotype, especially if it is due to an
ARID1B variant.

3.6 Confirmation of diagnosis and differential diagnosis

3.6.1 Confirmation of diagnosis

While a diagnosis of CSS may be clinically supported, a genetic cause must be identified
to achieve certainty. This means genetic testing to identify a pathogenic variant in one of
the known CSS-related genes [i.e., ARID1A, ARID1B, ARID2, BICRA, DPF2, SMARCA2
duplication], SMARCA4, SMARCB1, SMARCC2, SMARCD1, SMARCE1, SOX4, or
SOX11]. Many means of testing are available, including array CGH to detect gene
deletions, ID gene panels, and exome or genome sequencing, or even karyotyping to
detect translocations. The choice of method is based on the expertise of the requesting
physician. In any case, the pathogenicity of an identified variant must be discussed by the
molecular biologist and the requesting clinician together before an appointment with the
patient and his or her family to announce test results. Because it is difficult to exhaustively
examine certain regions (e.g., introns, 3’ and 5’ untranslated regions, and GC-rich
regions) of the genes behind this syndrome, failure to detect a variation does not exclude
a CSS diagnosis that is supported clinically. Genome sequencing might resolve this
problem.

If, when CSS is not initially suspected, a gene variant is nonetheless identified, the
diagnosis must be discussed in light of the clinical and genetic findings together. The
absence of typical CSS signs does not exclude the pathogenicity of an ARID1B variant,
which is also associated with a nonsyndromic form of ID.

In some cases, analysis of the DNA methylation profile (episignature) can help determine
whether a variant of unknown significance is pathogenic or confirm a BAFopathy
episignature in case of a clinical diagnosis without a genetic variant by array and genome-wide screening.

3.6.2 Differential diagnosis

CSS is a possible diagnosis when agenesis of the corpus callosum is detected in a fetus, but other potential causes exist. In such cases, it is necessary to consult a geneticist in order to investigate the etiology of the brain malformation.

In infants, hypotonia, feeding problems, and certain morphological traits may suggest a RASopathy—Noonan syndrome in particular.

Hypoplasia or aplasia of the 5th-finger nails is suggestive of CSS, but all nails may be affected. Other syndromes combining a neurodevelopmental disorder with nail hypoplasia may be considered for differential diagnosis by the patient's examiner. They include DOORS syndrome, tied to TBC1D24 variants; Mabry syndrome, linked to defective formation of the GPI anchor and involving various genes; and Temple-Baraitser syndrome, caused by variants in the KCNH1 gene, where the thumbnail is typically affected.

While the combination of hypertrichosis and a neurodevelopmental disorder is common in CSS, these signs may point to other rare syndromes, such as Cornelia de Lange syndrome, mostly associated with the NIPBL gene; Wiedemann-Steiner syndrome, caused by KMT2A variants; and FHEIG, which is the result of KCNK4 variants.

3.7 Genetics

3.7.1 Fundamentals of the SWI/SNF (BAF) pathway

DNA methylation, posttranslational modification of DNA-bound histones, and ATP-dependent chromatin remodeling are all epigenetic mechanisms that regulate gene expression. The SWI/SNF complex identified in yeast is involved in ATP-dependent chromatin remodeling. Its equivalent in mammals is the BAF complex, but other complexes having a similar function exist. This complex relaxes the chromatin structure, which gives proteins access to the DNA or histones, to activate or suppress gene transcription. The BAF complex can contain up to about fifteen subunits, whose combination varies across developmental stages, including during brain organogenesis.
CSS and NBS are due to variants in genes encoding BAF-complex subunits. The physiopathology of these two syndromes thus probably involves deregulation of gene expression. Future research will allow us to better understand the phenotypic effects of this deregulation.

The physiopathologic mechanisms of variants in SOX4 and SOX11, two genes that are associated with CSS and do not encode BAF-complex proteins, are unknown, but may interact with the complex.

### 3.7.2 Genetic heterogeneity; genotype-phenotype correlations

Because of the number of patients harboring variants in the gene, the phenotype associated with ARID1B mutations has been well described, while our understanding of any distinctive effects of variants in other BAF-complex genes is relatively limited. Nevertheless, some authors have attempted to correlate phenotype with the gene in question.

Clinical characteristics associated with variants in SMARCA2 are presented in section 3.5 (Clinical aspects and molecular genetics of NBS).

#### 3.7.2.1 ARID1A

Fewer than twenty-some patients heterozygous for variants in ARID1A have been reported. These variants mostly lead to loss of function. Some missense variants have also been reported.

The reported severity of ID linked to ARID1A variants varies between publications. Some authors (Kosho et al. 2013) indicate that individuals with these variants have the most severe ID, while others (Santen et al. 2013) report that ID ranges from slight to severe—though this variability could reflect mosaicism. The typical morphological features of CSS (agenesis of the corpus callosum and nail abnormalities) are usually found in patients for whom defects of the heart (e.g., aortic coarctation, ventricular septal defects, and atrial septal defects) and urogenital system (cryptorchidism, hypospadias, and ectopic ureters) are also reported.

Cancers have been described in two patients with CSS due to an ARID1A variant: one acute lymphoblastic leukemia (Diets et al. 2018) and one hepatoblastoma (Tsurusaki et al. 2012).

Les microduplications comprenant le gene ARID1A sont responsables d’un syndrome associant déficience intellectuelle et microcéphalie.

#### 3.7.2.2 ARID1B

More than 200 reported pathogenic variants of the ARID1B gene are known. They are mostly truncating variants. Deletion of this gene may cause CSS. The nature of the variant
does not appear to impact phenotype, and it does not determine whether the individual will exhibit syndromic CSS or nonsyndromic ID. Associations between ARID1B-related CSS and tumoral diseases have been reported for two patients: one lacking ARID1B due to a 6q25 deletion had papillary thyroid cancer; the other, with a truncating variant, developed a Sertoli cell tumor and then a glioneuronal tumor.

### 3.7.2.3 ARID2

There have been at least 15 reported patients with pathogenic, usually truncating, ARID2 variants. Nosographic discussions in articles offering clinical descriptions of these patients conclude that a diagnosis of CSS may be made for some, but not all: thus, other phenotypes are also associated with this gene. Wormian bones have been described as a characteristic of the ARID2 CSS phenotype.

### 3.7.2.4 BICRA

Twelve patients with a deletion of or a de novo variant in the BICRA gene have been reported. Seven point variants were truncating and two were missense. BICRA protein is a component of SWI/SNF subcomplexes, thus these patients had a new type of BAFopathy. All of these patients had a neurodevelopmental phenotype including developmental delay, ID and/or ASD. 4/12 patients had microcephaly, fifth nail hypoplasia was reported in three and facial dysmorphism was not typically suggestive of CSS/NBS. Most patients' phenotype is related to BICRA loss-of-function, but it is unclear whether the phenotype of patients with missense variants has similar physiopathology. The authors conclude that “haploinsufficiency of BICRA leads to a unique [BAFopathy] whose phenotypes overlap with those previously reported”.

### 3.7.2.5 DPF2

At least nine patients with CSS linked to pathogenic variants in DPF2 have been reported. These are missense variants in the sequence encoding the functional domain of the protein (6 cases) or truncating variants (3 cases). The CSS phenotype seems to be milder for DPF2 variants than for variants in other CSS-related genes. ID is less severe: one patient had none, two had borderline ID, and the others exhibited slight to moderate ID. These patients have nail abnormalities, 4th-ray brachymetatarsia (in one patient), and other morphological features of CSS. Three patients exhibited craniosynostosis, which is uncommon in CSS.
3.7.2.6 SMARCA4

There are >25 known CSS patients with SMARCA4 gene variants. They account for a little over 10% of all CSS cases. The vast majority of these variants are missense mutations. Heterozygous deletions encompassing the gene have also been described (Mitrikos et al. 2020).

SMARCA4 variants are associated with the typical CSS phenotype. The degree of ID ranges from moderate to severe in these patients. Heart defects (e.g., ventricular septal defect or complex defect) have been reported in these patients. Some exhibit microcephaly.

SMARCA4 variants, mostly truncating, have been described in patients with various tumors, notably including small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT), of which it is the only known cause. This cancer was reported in a patient with a constitutional truncating variant responsible for CSS and another truncating variant within the ovarian tumor, in trans. In light of current knowledge one cannot rule out greater tumor risk in patients with CSS related to a missense variant in SMARCA4, although no other cases have been described.

3.7.2.7 SMARCB1

There are 13 known patients with CSS due to SMARCB1 variants. Most of these pathogenic variants (9 out of 13) are missense mutations; some are truncating variants. The CSS phenotype in patients with pathogenic variants in SMARCB1 is considered more severe than for the CSS patient population as a whole. More severe ID is a neurological feature in this subgroup, and epilepsy and microcephaly are more common. Delayed growth and scoliosis is also more frequently reported among these patients. Furthermore, the frequency of congenital abnormalities (e.g., horseshoe kidney, dextrocardia, or ventricular septal defect) appears to be higher.

Somatic truncating variants in SMARCB1 have been reported in association with certain tumors—including rhabdoid tumors. Constitutional SMARCB1 variants are associated with higher risk of rhabdoid tumors, and with familial schwannomatosis (Holsten et al. 2018). The association of SMARCB1-related CSS and schwannomatosis has been reported in a single patient. The tumor contained a constitutional variant of the SMARCB1 gene; a chromosome 22 deletion eliminating one copy of SMARCB1 and of NF2, which is the principal gene behind schwannomatosis; and a truncating variant in the remaining NF2 allele.

Hence, it is difficult to attribute the schwannomatosis to the SMARCB1 variant because the NF2 defects in this patient might explain the tumoral disease.

Similar to SMARCA4, current data do not permit us to exclude the possibility of greater tumor risk in patients with CSS related to a SMARCB1 missense variant.
Finally, a unique phenotype, distinct from CSS, combining severe ID and hydrocephalus associated with hyperplasia of the choroid plexuses, has been observed in 4 patients carrying the variant p.Arg37His.

### 3.7.2.8 SMARCC2

Fifteen patients with CSS phenotypes due to heterozygous, usually *de novo*, pathogenic variants in *SMARCC2* are known. These are missense, truncating, or splicing variants (Machol et al. 2019). Their description does not yet permit a distinction to be made between these patients and those with CSS related to other BAF-complex genes.

### 3.7.2.9 SMARCD1

Missense and truncating variants, most often *de novo*, have been reported in six patients with IDs (Nixon et al. 2019). The phenotype of some, but not all, of these patients overlaps with that of CSS. To better understand this, more patients must be studied.

### 3.7.2.10 SMARCE1

Seven patients with CSS due to pathogenic *SMARCE1* variants (one being a splice-site variant and all others missense) have been described. The phenotype they present includes a higher frequency of heart defects (e.g., patent ductus arteriosus, valve stenosis, and dextrocardia), fetal growth retardation, and microcephaly. Nail abnormalities are more common than for the CSS population as a whole.

Constitutional truncating variants in *SMARCE1* have been reported in cases of familial and sporadic multiple spinal meningiomas. One case of *SMARCE1*-related CSS in association with a brain tumor (anaplastic astrocytoma) and a missense variant in *SMARCE1* is known. Transcriptome analyses of the tumor revealed fusion of *MYBL1* and *MAML2* that adequately explains the neoplasm.

Two patients with a splicing variant in *SMARCE1* have also been reported whose phenotype is not CSS, but Angelman-like syndrome and autism.

### 3.7.2.11 SOX4

Unlike the genes responsible for most cases of CSS, *SOX4* does not encode a BAF-complex subunit. *De novo* missense variants in *SOX4* have been identified in 4 patients with IDs ranging from slight to severe. Some aspects of their phenotype (e.g., 5th-finger anomalies and facial dysmorphism) are suggestive of CSS. More patients are needed to confirm an association between *SOX4* and CSS.
3.7.2.12  **SOX11**

Like *SOX4*, this gene does not code for a BAF-complex subunit. Nine patients with a neurodevelopmental disorder tied to pathogenic *SOX11* variants—6 missense and 3 truncating—have been described. Some of these patients have CSS-like phenotypes, including facial dysmorphism and phalangeal abnormalities (5th-finger clinodactyly or nail hypoplasia). The *SOX11*-associated phenotype and its relationship to genotype need further study.

3.8  **Evaluation of disease severity or extent, detection of comorbidities, and determination of prognosis**

The proposed initial evaluation of patients with CSS includes

- an assessment of ID severity—relying on the medical history, clinical examination, and documents available from the different professionals involved—and of the need for any further evaluations
- an assessment of the need for school (or workplace, depending on the patient’s age) adaptations or therapy, based on the evaluation of cognitive functions (e.g., treatment by medical neurodevelopment specialists, psychomotor therapists, speech-language pathologists, or occupational therapists)
- screening for visual or hearing impairments
- echocardiogram and abdominal ultrasound to detect congenital abnormalities
- dental examination, depending on age

Additional evaluations in the following specialized areas may be required, according to the context:

- neurology (or child neurology)—essential if patient has epilepsy
- endocrinology—to evaluate bone age, thyroid function, and growth hormone secretion when growth is delayed
- gastroenterology—for feeding problems or growth disorders
- physical medicine and rehabilitation (PMR) or orthopedics—in the presence of joint or spine deformities
- psychiatry (or child and adolescent psychiatry)—in the event of behavior disorders
- immunology—when the patient has a conspicuous history of infection

3.9  **Announcement of diagnosis and provision of information to patient**

The announcement of the diagnosis must be made in an undisturbed setting, preferably in the presence of the patient’s parents, and should not be rushed. It can rely on the
participation of the prescriber of the molecular analysis and, depending on the context, another member of the therapeutic team (e.g., psychologist, genetic counselor, or nurse).

During this meeting,
- the diagnosis, laboratory results, and other findings are explained
- information on the disease, including the pattern of inheritance (may concern siblings), is provided
- information about the need for regular follow-up and multidisciplinary treatment is provided
- planned treatment is described
- a psychologist must be present—or the psychologist may meet with the patient immediately after the meeting, or during follow-up

the family is provided with the contact information of patient organizations

3.10 Genetic counseling and prenatal diagnosis

3.10.1 Genetic counseling of probands and their relatives

To date, most of the probands reported have *de novo* pathogenic variants, and the risk of recurrence in a later pregnancy with the same parents is very low but still exists. Molecular analyses are therefore needed for the parents, to search for the same variant found in the proband. This can detect somatic mosaicism but cannot exclude potential germline mosaicism, which determines the risk of recurrence for a future pregnancy (±1%).

Causal variants may be inherited from a parent with a milder CSS phenotype. In such cases, a 50% risk of recurrence must be announced. The same applies for the offspring of a proband. The risk of CSS in the offspring of unaffected siblings is the same as for the general population.

3.10.2 Prenatal testing and preimplantation genetic diagnosis

Prenatal testing of the parents of the proband, to screen for the same pathogenic variant identified in the latter, is an option to consider, given the risk of germline mosaicism and the disability associated with CSS. The same holds for a proband with a mild form of CSS. Preimplantation genetic diagnosis may be warranted when one of the parents has proven mosaicism for the causal variant.
3.10.3 Special case of pregnant women

Today, detection in a fetus (in utero) of a genetic variant that can cause CSS is rare. Yet it is becoming more common with prenatal array, whole-genome/exome sequencing, especially when congenital abnormalities such as agenesis of the corpus callosum are found. Genetic consultation is followed by genetic testing and possible discovery of a variant in a CSS-related gene. After detecting a variant, an appointment must be planned for announcing the results and explaining the potential consequences of the variant. In some cases prospective parents may choose to terminate the pregnancy.

4 Treatment and follow-up for a patient with Coffin-Siris syndrome

There is currently no specific treatment for CSS. There are no particular dietary recommendations for people with this condition. Vaccinations are not contraindicated.

4.1 Objectives

Management of CSS is aimed at fostering optimal intellectual development, avoiding complications, and detecting comorbidities. This requires regular appointments, their frequency depending on the unique characteristics of each patient. For stable patients, an annual appointment may reasonably suffice. CSS must be addressed early, demands sustained and continuous care, and requires attentiveness towards the patient.
## 4.2 Intervening professionals and roles in management

<table>
<thead>
<tr>
<th>Professionals involved</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>General practitioner or pediatrician</td>
<td>General follow-up, at local level, and coordination</td>
</tr>
<tr>
<td>Neurologist (or child neurologist)</td>
<td>General follow-up and coordination</td>
</tr>
<tr>
<td></td>
<td>Developmental follow-up and adaption of care and schooling</td>
</tr>
<tr>
<td></td>
<td>Follow-up for neurological complications (epilepsy)</td>
</tr>
<tr>
<td>Clinical geneticist</td>
<td>General follow-up and coordination</td>
</tr>
<tr>
<td></td>
<td>Diagnosis and genetic counseling</td>
</tr>
<tr>
<td>Neonatologist, pediatric intensivist</td>
<td>Neonatal or intensive care (e.g., for malnutrition or heart complications)</td>
</tr>
<tr>
<td>Cardiologist (or pediatric cardiologist)</td>
<td>Follow-up for heart abnormalities and prevention</td>
</tr>
<tr>
<td></td>
<td>Pre- and postsurgical follow-up for congenital heart diseases</td>
</tr>
<tr>
<td>Gastroenterologist (or pediatric gastroenterologist)</td>
<td>Management and follow-up of feeding problems and use of feeding tube (especially for infants)</td>
</tr>
<tr>
<td>Endocrinologist (or pediatric endocrinologist)</td>
<td>Treatment and follow-up for any growth disorder</td>
</tr>
<tr>
<td>Pediatric surgeon (general surgery)</td>
<td>Treatment of any congenital abnormalities</td>
</tr>
<tr>
<td>Pediatric orthopedic surgeon, physiatrist</td>
<td>Treatment of scoliosis and joint abnormalities</td>
</tr>
<tr>
<td>Dermatologist</td>
<td>Treatment of pathological conditions of skin appendages, hyperkeratosis, or hyperhidrosis</td>
</tr>
<tr>
<td>Psychiatrist (or child and adolescent psychiatrist)</td>
<td>Follow-up of behavior disorders and autistic manifestations</td>
</tr>
<tr>
<td>ENT</td>
<td>Detection and follow-up of hearing impairment where appropriate</td>
</tr>
<tr>
<td>Ophthalmologist</td>
<td>Detection and follow-up of refractive errors and strabismus</td>
</tr>
<tr>
<td>Nephrologist, urologist</td>
<td>Treatment of congenital anomalies of kidneys and urinary tract or vesicoureteral reflux</td>
</tr>
<tr>
<td>Dentist, orthodontist</td>
<td>Dental and orthodontal care</td>
</tr>
<tr>
<td>Physical therapist, hearing aid specialist, orthoptist, etc.</td>
<td>Treatment of various complications by allied health professionals</td>
</tr>
<tr>
<td>Psychomotor therapist, speech-language pathologist, special educator, psychologist, etc.</td>
<td>Treatment of ID or more specific disorders by allied health professionals</td>
</tr>
<tr>
<td>Sociomedical institutions: center for early sociomedical intervention (CAMSP), special school (IME), home- and school-based treatment and specialized education service (SESSAD), and group home or residential facility (MAS; FAM)</td>
<td>Support for individuals with intellectual disability provided by allied health professionals</td>
</tr>
<tr>
<td>Health-care social worker</td>
<td>Facilitation of relationship between medical teams and both patient and patient’s family</td>
</tr>
<tr>
<td></td>
<td>Orientation towards available social support services</td>
</tr>
</tbody>
</table>
4.3 Cognitive development, behavior, and neurological disorders

At the minimum, neurodevelopmental follow-up should involve annual appointments. During each appointment, the clinician assesses whether additional examinations for neurological investigation (e.g., EEG or brain MRI) are needed, as to address potential epilepsy.

An evaluation by a child and adolescent psychiatrist—before commencing school, for example—may be necessary to detect ADD/ADHD, behavior problems, or an ASD. Neurodevelopmental assessments by medical specialists and allied health professionals will help define the rehabilitative measures and educational adaptations patients require.

4.4 Ophthalmologic and auditory problems

An annual ophthalmologic appointment to detect any vision problems is recommended. Due to the frequency of refractive errors and strabismus, examination by a pediatric ophthalmologist after administration of atropine must be performed at least once, and as early as possible.

Hearing may be tested during this follow-up if a loss of auditory acuity is suspected.

4.5 Growth and feeding

Delayed growth and feeding problems warrant a gastroenterological assessment, which may require analysis of swallowing, imaging of the upper digestive system, or endoscopy. Early dental examinations may help to identify any tooth crowding or problem related to delayed dentition. An endocrinologic evaluation at any point in the follow-up of a child CSS patient may be justified by growth retardation, particularly because of possible hypothyroidism/growth hormone deficiency, and because diabetes mellitus may occur.

4.6 Orthopedic problems

Orthopedic or PMR follow-up is recommended for CSS patients with spine or joint abnormalities.

4.7 Patient education and lifestyle changes

Patient education is aimed at helping patients and their relatives acquire or maintain the skills they need to optimize living with a long-term illness. These skills do not differ between CSS and other development diseases characterized by ID, a risk of orthopedic
disorders, feeding problems, etc. See Déficiences Intellectuelles, Synthèse et Recommandations—Expertise Collective [Intellectual disabilities: overview and recommendations—collective expert review] (INSERM 2016).

4.8 Turning to patient organizations

Patient organizations are essential partners of the multisite coordinating center (centre de référence) and regional centers of excellence (centres de compétence). They play a fundamental role by educating, supporting, and assisting families.

In addition to being an important source of information, they help patients and their relatives feel less alone by allowing them to interact with others in the same situation, who can share practical advice to ease day-to-day living with the condition.

In cooperation with the coordinating center and the centers of excellence, they complement and reinforce the aid provided to patients, with support from the DéfiScience network. These organizations participate in research projects and may even finance projects of particular relevance to patients. Though they are always provided with the contact information for patients’ organizations, patients and their families alone decide whether to reach out to them.

(See Appendix 2.)

4.9 Prognosis

In the absence of long-term studies, we lack data on the life spans of individuals with CSS. One case report describing a 69-year-old diagnosed with CSS did not indicate any particular complication related to aging (Määttänen et al. 2018).

Prospective follow-up studies are currently under way to acquire a better understanding of prognoses for people with CSS.
Appendix 1. Authors and contributors

Dr. Cyril Mignot of the Coordinating Center for Intellectual Disabilities of Rare Causes (Pitié-Salpêtrière and Trousseau Hospitals, AP-HP / Sorbonne University) acted as PNDS project coordinator, working alongside Dr. Ponha Heng, DéfiScience PNDS project manager.

The following individuals contributed to the PNDS:

Authors
- Dr. Cyril Mignot, Department of Genetics, Pitié-Salpêtrière and Trousseau Hospitals, AP-HP / Sorbonne University, Paris, France
- Dr. Ponha Heng, pediatrician and DéfiScience PNDS project manager, Paris, France
- Dr. Gijs Santen, Clinical Geneticist, Leids Universitair Medisch Centrum, Leiden, Pays-Bas

Multidisciplinary working group
- Dr. Alexandra Afenjar, Department of Genetics, Trousseau Hospital, AP-HP / Sorbonne University, Paris, France
- Dr. Béatrice Dubern, pediatric gastroenterologist, Trousseau Hospital, AP-HP / Sorbonne University, Paris, France
- Dr. Delphine Héron, pediatrician and geneticist, Pitié-Salpêtrière Hospital, AP-HP / Sorbonne University, Paris, France
- Dr. Hina Simonnet, PMR Unit, Trousseau Hospital, AP-HP / Sorbonne University, Paris, France

Review committee
- Association Coffin-Siris France
- Dr. Thierry Bienvenu, molecular biologist, Cochin Hospital, AP-HP / Centre–Université de Paris, Paris, France
- Dr. Frédéric Brioude, endocrinologist, Trousseau Hospital, AP-HP / Sorbonne University, Paris, France
- Dr. Joseph Bursztyn, ophthalmologist, private practice (22 rue Monsieur Le Prince, 75006 Paris, France)
- Dr. Angèle Consoli, child and adolescent psychiatrist, Pitié-Salpêtrière Hospital, AP-HP / Sorbonne University, Paris, France
- Dr. Vincent des Portes, Professor of Medicine, child neurologist, HCL-GH Est, Bron, France
- Dr. Salima El Chehadeh, geneticist, Hautepierre Hospital, Strasbourg, France
- Ms. Anne-Claire Gélineau, neuropsychologist, Pitié-Salpêtrière Hospital, AP-HP / Sorbonne University, Paris, France
- Dr. David Germanaud, child neurologist, Debré Hospital, AP-HP / Nord–Université de Paris, Paris, France
- Dr. Mary Hully, pediatrician, Necker Hospital, AP-HP / Centre–Université de Paris, Paris, France
- Ms. Emmanuelle Lacaze, neuropsychologist, Trousseau Hospital, AP-HP / Sorbonne University, Paris, France
- Dr. Mathieu Milh, Professor of Medicine, child neurologist, La Timone University Hospital, Marseille, France
- Dr. Laurent Pasquier, geneticist, Rennes University Hospital (Pontchaillou), Rennes, France
- Dr. Sylvaine Peudenier, child neurologist, Morvan Hospital, Brest, France
- Dr. Marlène Rio, geneticist, Necker Hospital, AP-HP / Centre–Université de Paris, Paris, France
- Dr. Annick Toutain, Professor of Medicine, geneticist, Bretonneau Hospital, Tours, France
- Dr. Stéphanie Valence, child neurologist, Trousseau Hospital, AP-HP / Sorbonne University, Paris, France
- Dr. van der Sluijs, Clinical Geneticist, Leids Universitair Medisch Centrum, Leiden, Pays-Bas
- Dr. Alain Verloes, Professor of Medicine, geneticist, Debré Hospital, AP-HP / Nord–Université de Paris, Paris, France
- Dr. Dorothée Vile, child neurologist, HCL-GH Est, Bron, France
- Dr. Marie Vincent, geneticist, Nantes University Hospital (Hôtel-Dieu), Nantes, France
- Dr. Sandra Whalen, geneticist, Trousseau Hospital, AP-HP / Sorbonne University, Paris, France
- Dr. Marjolaine Willems, geneticist, Arnaud de Villeneuve Hospital, Montpellier, France

Conflicts of interest
The authors and all contributors have completed conflict of interest forms.
Appendix 2. Contact information for multisite coordinating center (*centre de référence*), centers of excellence (*centres de compétence*), and patient organizations

**Multisite Coordinating Center (*centre de référence*) for Intellectual Disabilities of Rare Causes**

**Main site**
Dr. Delphine Héron, clinical geneticist, Head Physician of Coordinating Center

Address: AP-HP, Hôpital Pitié-Salpêtrière; Département de génétique et cytogénétique; 47-83, boulevard de l'Hôpital; 75651 Paris cedex 13

Contact: Anne Faudet; anne.faudet@psl.aphp.fr; tel.: (+33) 0 142 161 387

**DéfiScience, French national rare disease network for brain development disorders and intellectual disability** *(http://www.defiscience.fr)*

**Branch sites**
Hospices Civils de Lyon
La Timone Hospital (AP-HM)
Trousseau Hospital (AP-HP)
Necker Hospital (AP-HP)
Dijon University Hospital
Necker Hospital (AP-HP)
Debré Hospital (AP-HP)
Brest Regional University Hospital
Rennes University Hospital
Strasbourg University Hospital

Dr. Vincent des Portes, Professor of Medicine
Dr. Mathieu Milh, Professor of Medicine
Dr. Thierry Billette de Villemeur, Professor of Medicine
Dr. Nadia Bahi Buisson, Professor of Medicine
Dr. Christel Thauvin, Professor of Medicine
Dr. Marlène Rio
Dr. David Germanaud
Dr. Sylviane Peudennier
Dr. Laurent Pasquier
Dr. Salima El Chehadeh
Centers of Excellence (centres de compétence) for Intellectual Disabilities of Rare Causes

Tours University Hospital  Dr. Annick Toutain, Professor of Medicine
Kremlin-Bicêtre Hospital (AP-HP)  Dr. Anya Rothenbuhler Pen
Lille University Hospital  Dr. Audrey Riquet
Amiens University Hospital  Dr. Patrick Berquin, Professor of Medicine
Besançon University Hospital  Dr. Lionel Van Maldergem, Professor of Medicine
Nancy University Hospital  Dr. Bruno Leheup, Professor of Medicine
Nantes University Hospital  Dr. Bertrand Isidor
Nice University Hospital  Dr. Fabienne Giuliani
Pointe-à-Pitre University Hospital  Dr. Marilyn Lackmy-Port-Lis
Reims University Hospital  Dr. Nathalie Bednarek
Toulouse University Hospital  Dr. Caroline Karsenty
Bordeaux University Hospital  Dr. Cyril Goizet, Professor of Medicine
Montpellier University Hospital  Dr. Pierre Meyer

Patient organizations

Association Coffin-Siris France  
(https://coffinsiris.fr/)

For further information

Réseau Maladies Rares Méditerranée rare disease management network  
(https://www.reseau-maladies-rares.fr/)

Orphanet  
(https://www.orpha.net)

Genetic and Rare Diseases Information Center  
(https://rarediseases.info.nih.gov/)

Online Mendelian Inheritance in Man  
(https://www.omim.org/)

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