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Saul-Wilson Syndrome

Synonym: Microcephalic Osteodysplastic Dysplasia

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Summary

Clinical characteristics

Saul-Wilson syndrome (SWS) is a skeletal dysplasia characterized by profound short stature, distinctive craniofacial features, short distal phalanges of fingers and toes, and often clubfoot. Early development (primarily speech and motor) is delayed; cognition is normal. Other findings can include hearing loss (conductive, sensorineural, and mixed), lamellar cataracts, and/or rod-cone retinal dystrophy. To date, 16 affected individuals have been reported.

Diagnosis/testing

The diagnosis of SWS is established in a proband with marked short stature, typical facial and skeletal features, and a heterozygous pathogenic variant in *COG4* identified by molecular genetic testing. To date only two *COG4* variants, both resulting in a p.Gly516Arg missense change, have been reported.

Management

Treatment of manifestations: Skeletal dysplasia or physiatry clinic (orthopedist, OT/PT/ rehabilitation specialist) to address repair of clubfoot, possible C1-C2 subluxation and/or spinal cord compression, mobility issues in those with residual foot deformities (post clubfoot repair), osteoarticular pain; standard treatment for feeding issues, speech delay, cataracts and retinal dystrophy, and hearing loss.

Surveillance: Routine follow up of growth and feeding, developmental progress and educational needs, musculoskeletal issues including mobility, osteoarticular pain, bone fragility, possible cataracts and/or retinal dystrophy, hearing loss.

Agents/circumstances to avoid: Participation in gymnastics and jumping on a trampoline until atlanto-axial instability is excluded.

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Genetic counseling

SWS is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Sib recurrence has been observed in one family and is thought to result from germline mosaicism in a parent. The risk to offspring of an individual with SWS of inheriting the *COG4* pathogenic variant is 50%. Once the *COG4* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria for Saul-Wilson syndrome have not been established.

Suggestive Findings

Saul-Wilson syndrome **should be suspected** in individuals with the following clinical, laboratory, and imaging findings [Ferreira et al 2018].

Clinical findings

- Skeletal
  - Profound short stature (typically of prenatal onset)
  - Clubfoot
  - Short distal phalanges of fingers and toes (See Figure 1.)
- Distinctive craniofacial features (See Figure 1.)
  - Progeroid facial appearance (more striking during infancy)
  - Sparse hair and sparse eyebrows
  - Prominent forehead with prominent scalp veins
  - Enlargement and delayed closure of the anterior fontanelle (earliest known closure 21 months; still open at age 3 years in one child)
  - Narrow nasal bridge with convex nasal ridge
  - Prominent columella (developing in late childhood)
  - Thin vermilion of the upper lip
  - Mild micrognathia
- Eyes
  - Blue sclerae (during the first few months of life)
  - Lamellar cataracts
  - Rod-cone dystrophy
- Hearing loss (conductive, sensorineural, and mixed)
- Early developmental delay (primarily speech) with normal cognition

Laboratory findings

- Elevated hepatic transaminases
- Intermittent neutropenia

Skeletal radiographs (See Figure 2.)

- Long bones
  - Short long bones
  - Overtubulation with thin diaphyses and flared metaphyses
  - Lucency of proximal femora
  - Coxa valga

- Megaepiphyses
- Hand
  - Small hands with short metacarpals and short phalanges
  - Accessory ossification centers of the proximal metacarpals
  - Cone-shaped epiphyses of the phalanges
  - Ivory epiphyses of the distal phalanges (in late childhood)
- Spine
  - Hypoplasia of the odontoid process of C2
  - Hypoplasia of T12 or L1
  - Platyspondyly (vertebral bodies become taller with age)
  - Irregularities of the endplates of the vertebral bodies (in later life)

Establishing the Diagnosis

The diagnosis of Saul-Wilson syndrome **is established** in a proband with marked short stature, typical facial and skeletal features, and a heterozygous pathogenic (or likely pathogenic) variant in *COG4* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *COG4* variant of uncertain significance does not establish or rule out the diagnosis.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because Saul-Wilson syndrome is rare, individuals with the distinctive findings described in Suggestive Findings in whom the diagnosis is recognized are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of Saul-Wilson syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1: Single-Gene Testing

Sequence analysis of *COG4* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.

Note: (1) Since only two variants, both resulting in a p.Gly516Arg missense change, have been reported to date, **targeted analysis** for these variants could be performed first to confirm a clinical diagnosis of Saul-Wilson syndrome. (2) Since Saul-Wilson syndrome occurs through a gain-of-function mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

Option 2: Genomic Testing

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

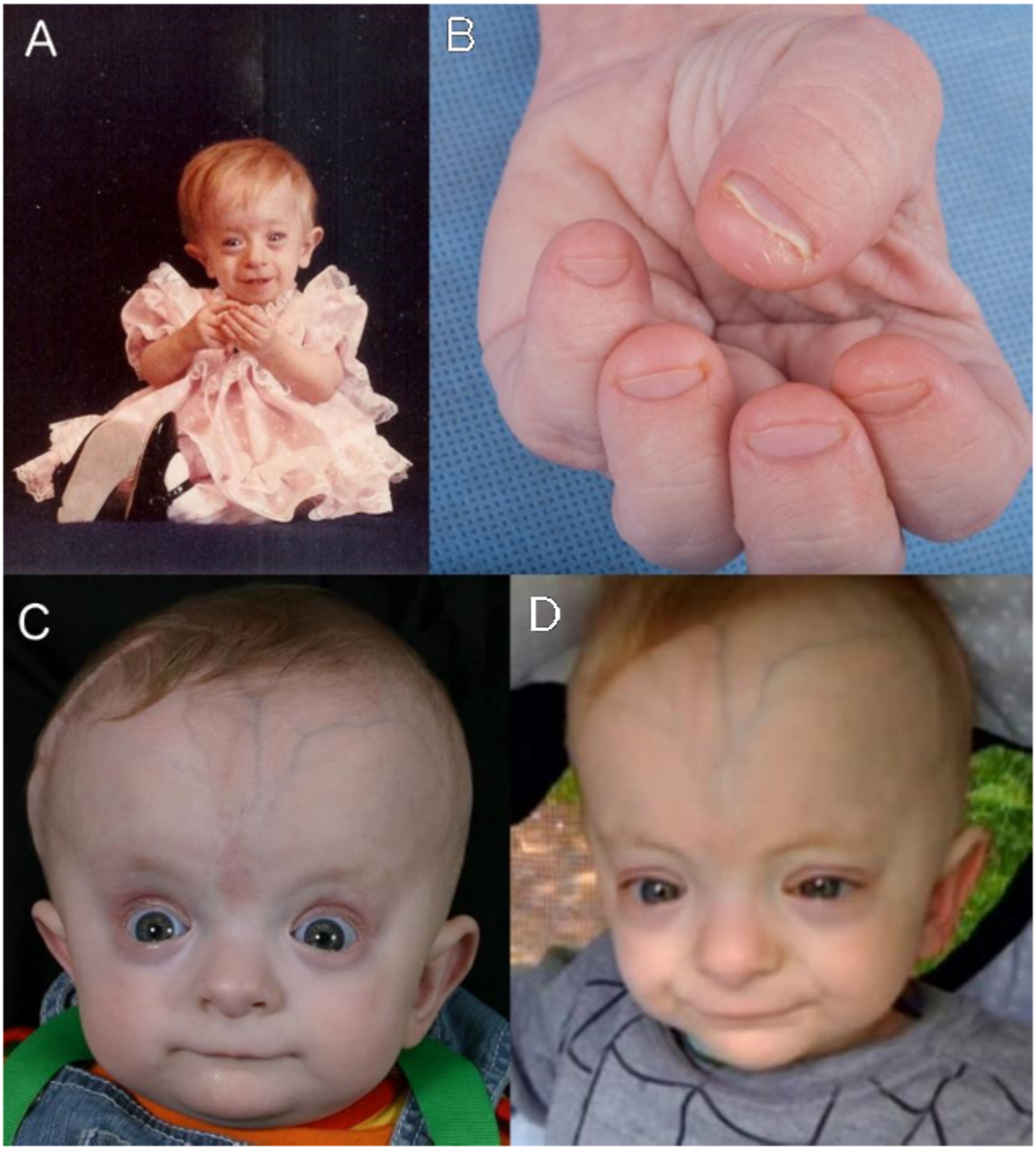

Figure 1. A, C, and D. Note prominent forehead, scalp veins, and columella, as well as thin vermilion of the upper lip.
B. Note short distal phalanges of the fingers.
Images provided by the author.

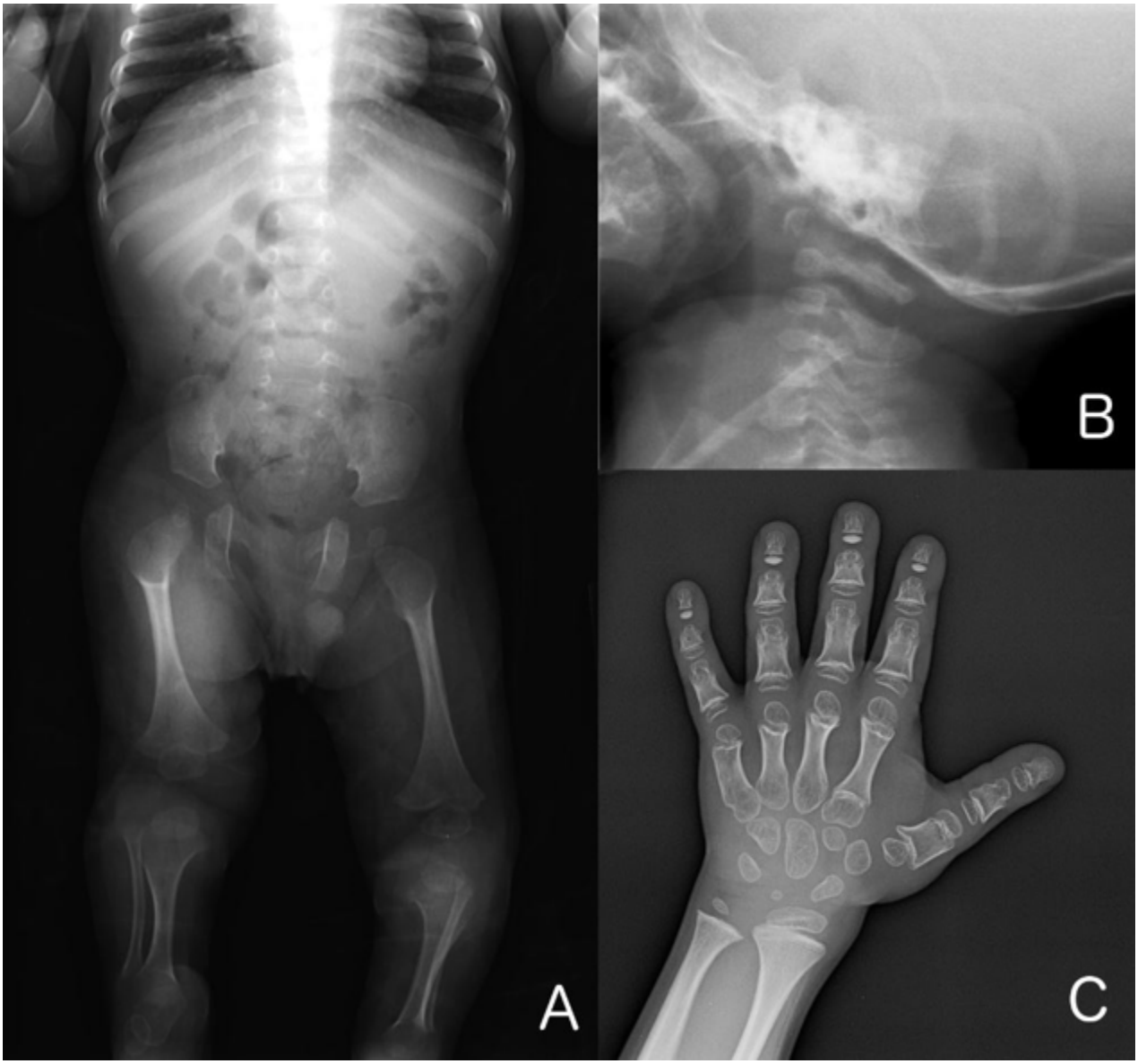

Figure 2. A. Babygram obtained at age 11 months. Note coxa valga, overtubulation of the long bones, and lucencies of the proximal femora.

B. Lateral cervical spine radiograph obtained at age eight months highlighting hypoplasia of the odontoid process

C. Left hand radiograph obtained at age six years nine months showing short metacarpals and short phalanges, cone-shaped epiphyses of phalanges, pseudoepiphysis of the second metacarpal, and ivory epiphyses of the distal phalanges.

Images provided by the author.

Table 1. Molecular Genetic Testing Used in Saul-Wilson Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
COG4	Sequence analysis [3]	14/14 [4]
	Gene-targeted deletion/duplication analysis [5]	None detected [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Ferreira et al [2018]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Since Saul-Wilson syndrome occurs through a gain-of-function mechanism and large intragenic deletions or duplication has not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

Clinical Characteristics

Clinical Description

Saul-Wilson syndrome is a skeletal dysplasia characterized by profound short stature, distinctive craniofacial features, short distal phalanges of fingers and toes, and often clubfoot. Early development (primarily speech) is delayed; cognition is normal. Other findings can include hearing loss (conductive, sensorineural, and mixed), lamellar cataracts, and/or rod-cone retinal dystrophy.

A total of 16 individuals with Saul-Wilson syndrome have been reported to date. Saul-Wilson syndrome was first described in a small-for-gestational-age infant with bulging fontanelles, clubfoot, blue sclerae, and blunted fingertips; over time, growth was delayed and the child developed bilateral cataracts, and hearing loss as the result of frequent otitis media [Saul 1982]. Three additional individuals with similar features were reported [Saul & Wilson 1990, Hersh et al 1994]. Subsequently the diagnosis of Saul-Wilson syndrome was entertained in a child without typical facial features [Chinen et al 2015], but the diagnosis could not be confirmed by molecular genetic testing. Fourteen individuals were described in 2018, including two originally reported in the 1990s [Ferreira et al 2018]. Since that publication, a few additional individuals with Saul-Wilson syndrome worldwide have been diagnosed [Author, personal observation]. The clinical findings discussed in this section are based on these reports.

Growth

Individuals with Saul-Wilson syndrome show impaired postnatal growth, and several also had intrauterine growth restriction (IUGR).

Mean length, weight, and head circumference at birth:

- Length. 44.1 cm (range: 38.0-49.0)
- Weight. 2.09 kg (range: 1.45-2.80)
- Head circumference. 31.7 cm (range: 29.0-34.0)

Z scores at birth:

- Length. -2.3 (1.5 SD; range: -0.4 to -5.1)
- Weight. -2.4 (0.7 SD; range: -1.2 to -3.8)

- Head circumference: -2.0 (0.9 SD; range: -0.8 to -3.9)

Z scores decline sharply over the first few months of life. At last examination:

- Stature. -6.3 (1.8 SD; range: -3.5 to -9.8)
- Weight. -4.0 (1.2 SD; range: -1.1 to -5.8)
- Head circumference. -1.7 (1.7 SD; range: 0.8 to -5.0)

Based on data available from three adults

- Mean height, weight, and head circumference at skeletal maturity:
  - Height. 107.6 cm
  - Weight. 30.5 kg
  - Head circumference. 50.2 cm
- Z scores at skeletal maturity:
  - Height. -8.9 (0.8 SD; range: -8.3 to -9.8)
  - Weight. -4.3 (0.6 SD; range: -3.6 to -4.8)
  - Head circumference. -3.9 (1.6 SD; range: -2.7 to -5.0)

Growth charts for clinical use are currently under development.

Despite absolute microcephaly, head circumferences exceed the height by more than 2 SD, with consequent relative macrocephaly.

Development

Speech delay (8/11) and motor delay (12/14) are common, probably related to the presence of hearing loss and skeletal deformities, respectively; cognitive development does not appear to be affected.

Ophthalmologic Features

The majority of affected individuals develop lamellar cataracts during the first few years of life (10/13), and several developed retinal involvement (6/9). Retinal pigmentary changes can be seen in the periphery as early as the toddler years. During adolescence and early adulthood, a rod-cone dystrophy (5/9) becomes evident with constricted visual fields and night blindness.

Macular cystic changes were also described (2/4). One individual had myelinated retinal nerve fibers [Ferreira et al 2020].

Skeletal Features

Shortening of the distal phalanges of fingers and toes is appreciated on physical examination (12/14). This finding, apparent at birth, did not progress over time. The majority of individuals (10/14) had clubfoot, and in some cases residual deformity even after multiple attempts at surgical repair [Ferreira et al 2020]. Pectus deformity (5/14) and cervical spinal cord compression (3/7) have also been reported.

Bone fragility has been suggested, as several individuals (4/14) developed fractures with minimal or no known trauma [Ferreira et al 2020]. One of these individuals had poor fracture healing, which was also described in the original patient [Saul & Wilson 1990]. Nonunion with pseudoarthrosis has been seen in two individuals [Saul & Wilson 1990, Ferreira et al 2020]. Although DXA scans for two individuals reported bone mineral density (BMD) <2 SD below the mean, the height-adjusted BMD [Zemel et al 2010, Zemel et al 2011] was normal in both [Author, personal observation].

Osteoarticular pain was reported by all three adults. Two had confirmed degenerative joint disease, leading to joint replacement surgeries in one individual in her 20s [Ferreira et al 2020].

The combination of megaepiphyses with coxa valga, leading to acetabulum-femoral epiphyseal incongruence, may contribute to premature osteoarthropathy of the hip.

Other

Hearing loss, seen in the majority of affected individuals over time, can be conductive, sensorineural, or mixed. In one child hearing impairment associated with inner-ear malformations was detected on newborn hearing screen.

MRI findings. Ventriculomegaly was seen in 5/9 and spinal cord syrinx in 1/4 individuals. Spinal cord compression was observed in 3/7: in one child with soft-tissue pannus surrounding the odontoid process, it was seen as early as age four years, and in another child with cervical spine instability, as late as age 14 years.

Intermittent neutropenia, though not appreciated in the first two months of life, was seen in all 12 individuals subsequently evaluated for this finding [Ferreira et al 2020]. The earliest known age of onset is three months, and it still occurred in adults. While intermittent neutropenia could be one possible explanation for the frequent (although rarely life-threatening) respiratory infections experienced in the first years of life, the neutropenia persisted into adulthood whereas the number of respiratory infections decreased over time.

Asymptomatic elevation of liver transaminases. Elevated aspartate aminotransferase was observed in 6/8 individuals and elevated alanine aminotransferase in 3/8, without abnormalities in other liver function tests, such as serum albumin, coagulation parameters, alkaline phosphatase, and bilirubin [Ferreira et al 2020].

Genotype-Phenotype Correlations

No genotype-phenotype correlation is possible because all affected individuals have the same amino acid substitution.

Penetrance

Penetrance is thought to be 100%.

Prevalence

Sixteen individuals have been reported to date. Three additional individuals are known to have the diagnosis of Saul-Wilson syndrome [Author, personal observation]. There is no known geographic predilection.

Genetically Related (Allelic) Disorders

Biallelic loss-of-function or hypomorphic variants in *COG4* are associated with COG4-CDG (see Congenital Disorders of N-Linked Glycosylation and Multiple Pathway Overview). COG4-CDG manifests with seizures, hypotonia, intellectual disability, microcephaly, elevated transaminases, and in one case recurrent infections.

Differential Diagnosis

Table 2. Disorders Interest in the Differential Diagnosis of Saul-Wilson Syndrome

DiffDx Disorder	Cause	MOI	Features of DiffDx Disorder	
			Overlapping w/SWS	Distinguishing from SWS
Silver-Russell syndrome	Chromosome 11p15.5- or chromosome 7-related	See footnote 1.	Short stature (largely prenatal onset w/no postnatal catch-up growth); relative macrocephaly w/enlarged anterior fontanelle; frontal prominence; blue sclerae; ivory epiphyses	Limb-length asymmetry, multiple café au lait spots, & hypoglycemia; no spondyloepimetaphyseal changes, ocular signs, hearing loss, neutropenia, or ↑ transaminases
Osteogenesis imperfecta (See *COL1A1/2* Osteogenesis Imperfecta.)	*COL1A1* *COL1A2* (>15 genes) [2]	AD [2]	Blue sclerae; bone fragility; hearing loss	Dentinogenesis imperfecta; no spondyloepimetaphyseal changes, cataracts, retinal degeneration, neutropenia, or ↑ transaminases
Microcephalic osteodysplastic primordial dwarfism type II	*PCNT*	AR	Profound prenatal-onset short stature; microcephaly; low-hanging columella; thin bones w/metaphyseal widening; metacarpal pseudoepiphyses; ivory epiphyses	Vascular issues; no shortening of distal phalanges or frontal prominence
Wiedemann-Rautenstrauch syndrome (OMIM 264090)	*POLR3A*	AR	Early progeroid features; poor growth; frontal prominence; delayed closure of anterior fontanelle; prominent scalp veins; convex nasal ridge; thin vermilion of upper lip	Intellectual disability [3]; no shortening of distal phalanges
Hallermann-Streiff syndrome (OMIM 234100)	Unknown	Unknown	Short stature; cataracts; micrognathia; prominent scalp veins; slender diaphyses	Distinct facial gestalt (e.g., characteristic thin nose & more pronounced micrognathia)
Floating-Harbor syndrome	*SRCAP*	AD	Profound prenatal-onset short stature; low-hanging columella; thin vermilion of upper lip; speech delay	Distinct facial gestalt (e.g., distinctive prominent nose)

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; MOI = mode of inheritance; SWS = Saul-Wilson syndrome

1. In most families, a proband with SRS represents a simplex case (a single affected family member) and has SRS as the result of an apparent *de novo* epigenetic or genetic alteration (e.g., loss of paternal methylation at the H19/IGF2 imprinting center 1 or maternal uniparental disomy for chromosome 7).

2. The majority of individuals diagnosed with osteogenesis imperfect (OI) have the disorder as the result of a pathogenic variant in *COL1A1* or *COL1A2*. *COL1A1/2*-OI is inherited in an autosomal dominant manner. OI caused by pathogenic variants in other genes (see OMIM PS166200) may be associated with autosomal recessive, autosomal dominant, or X-linked inheritance.

3. Intellectual disability is not typically observed in Saul-Wilson syndrome.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Saul-Wilson syndrome, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Saul-Wilson Syndrome

System/Concern	Evaluation	Comment
Constitutional	Measurement of HT, WT, & HC	Assess for evidence of linear growth failure using SWS-specific growth charts.
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	Avoid overfeeding.
Development	Developmental assessment	To incl motor & speech/language eval
Musculoskeletal	Refer to physiatry clinic (OT/PT, rehab specialist).	To evaluate fine & gross motor skills, mobility, & activities of daily living
	Refer to orthopedist.	• Mgmt of clubfoot • Assess osteoarticular pain.
	Obtain history of bone fractures.	
Spine	• Flexion-extension radiographs of lateral cervical spine • Flexion-extension MRI if instability & compression seen on radiographs or interpretation is limited (e.g., in young individuals w/delayed ossification of cervical vertebral bodies)	Evaluate for cervical instability & risk of spinal cord compression
Eyes	Ophthalmologic eval	To incl assessment for rod-cone dystrophy in individuals old enough to cooperate: • BCVA • Refractive error • Assessment of dark adaptation • Full-field ERG • Spectral-domain OCT Young children: assess visual acuity & refractive error as a baseline. Children & adolescents: assess for cataracts.
Hearing	Audiologic eval [1]	Assess for SNHL & conductive hearing loss.
Hematology	Complete blood count w/absolute neutrophil count	To evaluate for neutropenia
Liver	Aspartate aminotransferase, alanine aminotransferase	To evaluate for ↑ liver enzymes

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	
	Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support.

BCVA = best-corrected Snellen visual acuity; BMD = bone mineral density; ERG = electroretinography; FTT = failure to thrive; HC = head circumference; HT = height; OCT = optical coherence tomography; OT = occupational therapy; PT = physical therapy; SNHL= sensorineural hearing loss; SWS = Saul-Wilson syndrome; WT = weight
1. See Hereditary Hearing Loss and Deafness Overview for details about audiologic evaluations.

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Saul-Wilson Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Delayed development	See Developmental Delay Management Issues.	
Musculoskeletal	Skeletal dysplasia or physiatry clinic (orthopedics, OT/PT, rehab specialist)	Address mobility issues in those w/residual foot deformities (post-club foot repair), osteoarticular pain.
Cervical spine compression	Surgical mgmt for medullopathy (C1-C2 fixation) by expert familiar w/skeletal dysplasias & spine involvement	Given possibility of C1-C2 subluxation &/or spinal cord compression, follow best practices in perioperative mgmt of those w/skeletal dysplasias. [1]
Cataract / Retinal dystrophy	Standard treatment(s) as recommended by ophthalmologist	Cataracts: Consider surgery when dense to prevent amblyopia Retinal dystrophy: • Night vision scopes or selected wavelength filters [2] • Community vision services in teen yrs / young adulthood [3]
Hearing loss	Per treating otolaryngologist: • Myringotomy tubes • Hearing aids	Community hearing services through early intervention or school district [4]
Neutropenia	Per treating immunologist or infectious disease specialist	If frequent infections: consider GCSF to improve absolute neutrophil counts. [5]

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Family/ Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments.	Consider involvement in adaptive sports or Special Olympics.

GCSF = granulocyte colony-stimulating factor; OT = occupational therapist; PT = physical therapist
1. White et al [2017]. Including cervical spine imaging prior to general anesthesia.
2. See Nonsyndromic Retinitis Pigmentosa Overview for information about management.
3. In the US, publicly funded agencies at the state level provide services for the visually impaired or those with progressive eye disorders; services include vocational training, mobility training, and skills for independent living.
4. See Hereditary Hearing Loss and Deafness Overview for information about management.
5. Ferreira et al [2020]

Developmental Delay Management Issues

The following information represents typical management recommendations for individuals with developmental delay in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating,

assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Surveillance

Table 5. Recommended Surveillance for Individuals with Saul-Wilson Syndrome

System/Concern	Evaluation	Frequency
Constitutional	Measure HT, WT, & HC using growth curves standardized for SWS.	At each visit
Development	Monitor developmental progress / educational needs.	At each visit in young children
Musculoskeletal	To evaluate fine & gross motor skills, mobility, & activities of daily living	Annually
	Assess osteoarticular pain.	At each visit starting in young adulthood
	DXA scan for bone fragility	As needed based on history
	• Flexion-extension radiograph • Flexion-extension MRI if instability & compression on radiographs or limited interpretation on radiographs	Per orthopedist based on clinical findings or planned surgery
Eyes	Complete eye exam for: • Those known to have rod-cone dystrophy: BVCA, refractive error, dark adaptation, & visual field testing • Those not known to have rod-cone dystrophy (See Table 3.) • All patients: cataracts	Annually
Hearing	Audiologic eval to determine type & extent of hearing loss or success of intervention	Annually
Other	Obtain complete blood counts to assess neutrophil count.	Annually (or as needed during acute infections)

BCVA = best-corrected Snellen visual acuity; DXA = dual-energy x-ray absorptiometry; HC = head circumference; HT = height; SWS = Saul-Wilson syndrome; WT = weight

Agents/Circumstances to Avoid

Participation in gymnastics and jumping on a trampoline should be avoided until atlanto-axial instability is excluded.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnancy of an affected woman has not been documented to date, although regular menstrual cycles and a normal hormone profile in two adult females suggest no impairment of the ability to conceive [Ferreira et al 2020].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Saul-Wilson syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- No individual with Saul-Wilson syndrome reported to date has had an affected parent.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the *COG4* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is germline mosaicism in a parent. Parental germline mosaicism is presumed in one family with two affected sibs.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *COG4* pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known SWS-related *COG4* pathogenic variant that cannot be detected in the leukocyte DNA of either parent or the parents have not been tested for the *COG4* pathogenic variant but are clinically unaffected, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with SWS has a 50% chance of inheriting the SWS-related *COG4* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

Prenatal Testing and Preimplantation Genetic Testing

Once the *COG4* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Organization for Rare Disorders (NORD)**
  Phone: 800-999-6673
  RareCare® Patient Assistance Programs
- **Skeletal Dysplasia Management Consortium**
  skeletaldysplasia.org
- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Saul-Wilson Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
COG4	16q22.1	Conserved oligomeric Golgi complex subunit 4	COG4 database	COG4	COG4

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Saul-Wilson Syndrome (View All in OMIM)

606976	COMPONENT OF OLIGOMERIC GOLGI COMPLEX 4; COG4
618150	SAUL-WILSON SYNDROME; SWILS

Molecular Pathogenesis

COG4 is a subunit of the conserved oligomeric Golgi (COG) complex, a hetero-octameric protein complex that regulates vesicular trafficking between the Golgi apparatus and the endoplasmic reticulum (ER).

Mechanism of disease causation. The distinct phenotypes, recurrent nature of the p.Gly516Arg variant, and accelerated (not delayed) retrograde Golgi-to-ER transport seen in cells support Saul-Wilson syndrome occurring through a gain-of-function mechanism [Ferreira et al 2018].

Table 6. Notable *COG4* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_015386.2 NP_056201.2	c.1546G>A	p.Gly516Arg	Recurrent pathogenic variants w/evidence for gain-of-function activity [Ferreira et al 2018]
	c.1546G>C		

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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