

# Seckel syndrome

**Authors: Doctors Laurence Faivre<sup>1</sup> and Valérie Cormier-Daire**

**Creation Date: July 2001**

**Updated: May 2003**

**April 2005**

**Scientific Editor: Doctor Valérie Cormier-Daire**

<sup>1</sup>Service de génétique, CHU Hôpital d'Enfants, 10 Boulevard Maréchal de Lattre de Tassigny BP 77908, 21079 Dijon Cedex, France. [laurence.faivre@chu-dijon.fr](mailto:laurence.faivre@chu-dijon.fr)

[Abstract](#)

[Keywords](#)

[Disease name and synonyms](#)

[Prevalence](#)

[Diagnosis criteria/Definition](#)

[Clinical description](#)

[Differential diagnosis](#)

[Diagnostic methods](#)

[Etiology](#)

[Genetic counseling](#)

[Antenatal diagnosis](#)

[Management including treatment](#)

[Unresolved questions](#)

[References](#)

## Abstract

*Seckel syndrome, an autosomal recessive disorder is the most common of the microcephalic osteodysplastic dwarfisms. Seckel syndrome is characterized by a proportionate dwarfism of prenatal onset, a severe microcephaly with a bird-headed like appearance and mental retardation. Hematological abnormalities with chromosome breakage have only been found in 15 to 25% of patients. The differential diagnosis with microcephalic osteodysplastic dwarfism type II can only be made with a complete radiographic survey in the first years of life. Besides to a wide phenotypic heterogeneity between affected patients, genetic heterogeneity has also been proven, with three loci identified to date by homozygosity mapping: SCKL1 (3q22.1-q24, ataxia-telangiectasia and Rad3-related protein (ATR) gene), SCKL2 (18p11.31-q11.2, unknown gene) and SCKL3 (14q23, unknown gene). SCKL3 seems to be the predominant locus for Seckel syndrome. Approaching the function of the ATR gene, the genes with a role in DNA repair are good candidates for SCKL2 and 3. Mental retardation is usually severe and families should be helped for social problems. In case of associated hematological abnormalities (anemia, pancytopenia, acute myeloid leukaemia), medical treatment should be provided.*

## Keywords

microcephalic osteodysplastic dwarfism, proportionate dwarfism, microcephaly, mental retardation, ATR gene

## Disease name and synonyms

Seckel syndrome

Seckel dwarfism

Bird-headed dwarfism

Nanocephalic dwarfism

Microcephalic primordial dwarfism 1  
SCKL

## Prevalence

It is unknown. More than 100 cases have been reported to date.

### Diagnosis criteria/Definition

Association of:

- Proportionate dwarfism of prenatal onset
- Characteristic dysmorphic features including severe microcephaly and a bird-headed like appearance
- Mental retardation
- Autosomal recessive inheritance

### Clinical description

Seckel syndrome is characterized by:

- Intrauterine growth retardation (average birth weight 1540g);
- Severe proportionately short stature with severe microcephaly (Mean postnatal growth retardation is -7 SD with a range from -5 to -13 SD / Mean orbitofrontal cortex (OFC) is -9 SD with a range -4 to -14SD);
- A "bird-headed" profile with receding forehead, large eyes, beak-like protrusion of the nose, narrow face, receding lower jaw, micrognathia;
- Mental retardation. Half of the patients have an IQ less than 50;
- Other occasional features: premature closure of cranial sutures secondary to diminished brain growth, large eyes, antimongoloid slant of palpebral fissures, highly-arched palate, cleft palate, dysplastic ears, clinodactyly of the 5th fingers, cryptorchidism, clitoridomegaly, hirsutism, crowded teeth with malocclusion, enamel hypoplasia, agenesis of the corpus callosum, pachygyria.
- Immunodeficiency and significant predisposition to cancers have not been reported to date in Seckel syndrome.

### Differential diagnosis

A number of Seckel-like syndromes have been identified, most notably microcephalic osteodysplastic dwarfism type II and type III, and microcephalic osteodysplastic dysplasia. It has been argued that type I and III represent phenotypic variability within the same type of osteodysplastic primordial dwarfism. [Type II microcephalic osteodysplastic dwarfism](#) has been delineated as a separate entity, mainly relying on radiographic features. The main features are short limbs with preferential distal involvement, coxa vara, epiphysiolysis and metaphyseal flaring with V-shaped distal femora metaphyses. A complete radiological survey in the first year of life is necessary to make the distinction between Seckel syndrome and type II microcephalic osteodysplastic dwarfism.

### Diagnostic methods

In most cases, diagnosis depends upon recognition of clinical findings. In some cases, increased chromosomal breakage has been reported, but it was not confirmed in all cases of

Seckel syndrome and cannot be used as a tool for the diagnosis of Seckel syndrome.

X-ray features include retarded bone age, frequent hip dysplasia and dislocation of the head of the radius.

### Etiology

In 2000, a gene for Seckel syndrome was mapped to human chromosome 3q22.1-q24 (SCKL1) by homozygosity mapping in two inbred Pakistani families from the same village, with a genetic interval of 12 cM defined by loci D3S1316 and D3S3710. This gene has subsequently been identified as *ATR* (Ataxia-Telangiectasia and Rad-3 related protein) in the same families. The *ATR* mutation (A2102G in exon 9) is translationally silent but affects splicing efficiency, resulting in low levels of *ATR* in affected individuals. *ATR* is a central player in a signalling response to DNA damage that functions in concert with *ATM*. Unlike *ATM*, current evidence suggests that *ATR* responds to regions of single stranded DNA generated at stalled replication forks and bulky lesions and that *ATR* is essential, not only for development but also for somatic cell growth. The role of the *ATR* gene in DNA-damage response can explain the chromosomal instability in some Seckel patients. Cells derived from *ATR*-Seckel patients demonstrated impaired phosphorylation of a range of *ATR*-dependant substrates following exposure to UV-irradiation or hydroxyurea, but a normal *ATM*-dependant response to ionising radiation.

Another loci has been mapped in 2001 and in 2003 to chromosome 18p11.31-q11.2 (SCKL2) in one inbred Iraqi family and to chromosome 14q23 (SCKL3) in 13 Turkish families. These linkage results support the view that Seckel syndrome is a genetically heterogeneous condition and these genes remain to be identified. Analysis of Seckel syndrome cell lines suggests that defects in *ATR* signalling are common, although the defective gene is not always *ATR*, suggesting a common pathway. A recent study suggested that SCKL3 is the predominant Seckel locus, but these results remain to be confirmed in other studies.

### Genetic counseling

Multiple occurrences in sibs, increased frequency of parental consanguinity support an autosomal recessive mode of inheritance. The risk of recurrence is 25% for a couple who had a first child with Seckel syndrome. Genetic counseling for other members of the family is reassuring taking into account the low frequency of the disease, unless the couple is consanguineous.

### Antenatal diagnosis

Recurrence of the disease can be suspected by the observation of intrauterine growth retardation with microcephaly in the second trimester of pregnancy when a first child was born with Seckel syndrome. Linkage studies are difficult to use even in consanguineous families because of genetic heterogeneity of the disease. Early molecular antenatal diagnosis can be performed for a couple who has had a first child with Seckel syndrome if the familial mutations have been identified.

### Management including treatment

Hematological abnormalities have been reported in a few cases with Seckel syndrome, including anemia, pancytopenia, and acute myeloid leukemia, and medical treatment is proposed depending on the symptoms. Mental retardation is usually severe and families should be helped for social problems.

### Unresolved questions

Data are currently insufficient to determine whether genetic heterogeneity can be related to clear clinical heterogeneity. Increased chromosome instability at fragile sites following replication stress have been recently described and these findings may be related to the phenotypic findings.

### References

**Borglum AD**, Balslev T, Haagerup A, Birkebaek N, Binderup H, Kruse TA, Hertz JM. A new locus for Seckel syndrome on chromosome 18p11.31-q11.2. *Eur J Hum Genet* 2001; 9: 753-757.

**Butler MG**, Hall BD, Maclean RN, et al. Do some patients with Seckel syndrome have hematological problems and/or chromosome breakage? *Am J Med Genet* 1987; 27: 645-649.

**Casper AM**, Durkin SG, Arlt MF, Glover TW. Chromosomal instability at common fragile sites in Seckel syndrome. *Am J Hum Genet* 2004; 75: 654-60.

**Faivre L**, Le Merrer M, Lyonnet S, Plauchu H, Dagoneau N, Campos-Xavier AB, Attia-Sobol J, Verloes A, Munnich A, Cormier-Daire V. Clinical and genetic heterogeneity of Seckel syndrome. *Am J Med Genet* 2002; 112 : 379-383.

**Goodship J**, Gill H, Carter J, et al. Autozygosity mapping of a Seckel syndrome locus to chromosome 3q22.1-q24. *Am J Hum Genet* 2000; 67: 498-503.

**Kilinc MO**, Ninis VN, Ugur SA, Tuysuz B, Seven M, Balci S, Goodship J, Tolun A. Is the novel SCKL3 at 14q23 the predominant Seckel locus? *Eur J Hum Genet* 2003; 11: 851-857.

**Majewski F**, Goecke T. Studies of microcephalic primordial dwarfism. I. Approach to a delineation of the Seckel syndrome. *Am J Med Genet* 1982; 12: 7-21.

**Majewski F**, Ranke M, Schinzel A. Studies of microcephalic primordial dwarfism. II. The osteodysplastic type II of primordial dwarfism. Approach to a delineation of the Seckel syndrome. *Am J Med Genet* 1982; 12: 23-35.

**O'Driscoll M**, Ruiz-Perez VL, Woods CG, Jeggo PA, Goodship JA. A splicing mutation affecting expression of ataxia-telangiectasia and Rad3-related protein (ATR) results in Seckel syndrome. *Nat Genet* 2003; 33: 497-501.

**Shanske A**, Caride DG, Menasse-Palmer L, Bogdanow A, Marion RW. Central nervous system anomalies in Seckel syndrome: report of a new family and review of the literature. *Am J Med Genet* 1997; 70: 155-158.

**Thompson E**, Pembrey M. Seckel syndrome: an overdiagnosed syndrome. *J Med Genet* 1985; 22: 192-201.