

# The IVIC Syndrome

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## Abstract

*The IVIC syndrome is a very rare malformation syndrome caused by an autosomal dominant gene with complete penetrance, variable expressivity and wide pleiotropy. The most constant feature is a radial ray defect of variable degree, with thumb hypoplasia or aplasia, triphalangism or distal placement. Carpal bones may be hypoplastic and radius and ulna proximally fused. Most affected individuals also present strabismus and hearing loss. Mild thrombocytopenia, leukocytosis and imperforate anus may occur in some patients. Frequency is unknown since only four families with this syndrome have been reported. Diagnosis is based on clinical examination. There is no specific treatment for the IVIC syndrome. A surgical correction is required for imperforate anus; deafness can be treated with a cochlear implant.*

## Key words

Radial ray defect, hypoplastic thumb, triphalangeal thumb, hearing loss, strabismus, imperforate anus, thrombocytopenia.

## Disease name and synonyms

IVIC syndrome , Oculo-oto-radial syndrome (Neri and Sammito, 1989).

unknown and no specific laboratory tests are available.

## Definition and diagnostic criteria

The IVIC syndrome is an autosomal dominant condition with radial ray hypoplasia, hearing impairment, external ophthalmoplegia and thrombocytopenia. Its name is an acronym for Instituto Venezolano de Investigaciones Científicas, where Arias *et al.* (1980) described the first case. The diagnosis is based on clinical manifestations, since the gene is

## Differential diagnosis

The syndrome must be distinguished from other conditions presenting also radial ray defects and other common features, such as: [Holt-Oram syndrome](#), [thalidomide embryopathy](#), [TAR syndrome](#), Fanconi panmyelopathy, [Aase-Smith syndrome](#), [Holmes-Borden syndrome](#), [lacrimo-auriculo-dento-digital syndrome](#), [Townes-Brocks syndrome](#). The differential diagnosis is

especially necessary in sporadic and atypical cases.

### Etiology

This syndrome is caused by a dominant mutation of an as yet unidentified autosomal gene. Penetrance is complete for the radial ray defect, while it is about 80% for hearing impairment, external ophthalmoplegia and a high *a-b* ridge count. Expressivity is quite variable, especially for the upper limb defects, varying from an almost normal thumb to a severely malformed limb. The report of monozygotic twins discordant for the syndrome (Elcioglu and Berry, 1997) suggests that the expression of the mutant gene is likely modified by epigenetic and/or environmental factors.

Although the pathogenesis is unknown, a mesenchymal defect has been postulated (Arias *et al.*, 1980).

### Clinical description:

**Limbs:** The thumb is usually hypoplastic, triphalangeal and attached to the radial border of the index finger. Preaxial polydactyly has been reported in one patient. Carpal bones may be hypoplastic and fused. The forearm may also be affected, with radius and ulna proximally fused. The metacarpophalangeal pattern profile is abnormal, characterized by a long 1<sup>st</sup> metacarpal and 5<sup>th</sup> proximal phalanx and a short 1<sup>st</sup> distal phalanx.

Limitation of movement at elbows, wrists and interphalangeal joints is present in most affected individuals. There is a delayed growth of forearms, clavicles and femora during adolescence and permanently in the spine. The lower limbs, including the feet, are normal. Affected persons present a shorter than average stature.

**Dermatoglyphics:** The most important findings are: a high *a-b* ridge count; distal placement of the axial triradius, with a radial shift only when there is a triphalangeal thumb; absence of axial triradius when thumb hypoplasia is severe; a high frequency of patterns in the second interdigital space and of a *W* pattern in the hypothenar area.

**Extraocular muscles:** Strabismus, caused by extraocular muscle weakness, is present in most affected individuals. All the extraocular muscles may be involved, with the medial and lateral recti being most commonly and severely affected. Asymmetry of involvement is frequent.

**Hearing loss:** It can be mixed or sensorineural, usually bilateral and asymmetrical, with greater loss at higher frequencies.

**Other features:** The spine may present scoliosis, frequently of left convexity. The cardiovascular system is not affected, with the occasional finding of a mild incomplete bundle branch block. Imperforate anus and defects of the urorectal septum may occur in about 10% of the patients. Mild thrombocytopenia and leukocytosis may be present in young patients.

An intravenous pyelogram, performed in a woman with imperforate anus and rectovaginal fistula, demonstrated kidneys of normal size and function, but the left one was ectopic and malrotated counter-clockwise. This suggests the possibility of renal involvement in the syndrome.

Intellectual development is not impaired and life span is generally normal.

### Diagnostic method

Diagnosis is based on clinical examination, X-ray of the affected skeletal segments, audiologic, ophthalmologic and haematological tests.

### Epidemiology

Frequency is unknown. Only three families in addition to the original one reported by Arias *et al.* (1980) have been described (Sammito *et al.*, 1988; Czeizel *et al.*, 1989; Elcioglu and Berry, 1997). Nevertheless, mild sporadic cases might not be recognized because of the widely variable expressivity of this condition.

### Genetic counselling

In accordance with autosomal dominant inheritance, recurrence risk for this condition is 50%. Genetic counselling should be offered in familial and sporadic cases, emphasising the wide expressivity of the syndrome.

### Prenatal diagnosis

Detailed ultrasound scanning at 18 weeks of gestation could demonstrate limb abnormalities, at least the most severe ones.

### Management

There is no specific treatment for the IVIC syndrome. A surgical correction is required for imperforate anus; deafness can be treated with a cochlear implant.

### Unresolved questions

The phenotypic similarity between the thalidomide embryopathy and IVIC syndrome is impressive, suggesting that similar phenotypes can be caused by either a mutant gene or a teratogenic agent. Furthermore, radial ray defects and thrombocytopenia are present not only in the IVIC syndrome, but also in [Fanconi anemia](#) and TAR. This association

suggests a common mesenchymal defect (Arias *et al.*, 1980).

Finally, the different expression of the mutant gene in genetically identical individuals, such as monozygotic twins, is interesting and gives the opportunity to speculate on some factors affecting the control of gene expression (Elcioglu and Berry, 1997).

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