

# X-Linked Dominant Chondrodysplasia Punctata

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## Abstract

*X-linked dominant chondrodysplasia punctata, (CDPX2 – MIM 302960) also known as Conradi-Hünemann-Happle syndrome, is a rare form of skeletal dysplasia that affects the skeleton producing short stature, asymmetric shortening of the limbs and scoliosis, as well as affecting the skin, hair and eyes.*

*Frequency is unknown. The disorder is caused by mutations in the emopamil binding protein gene, EBP, the encoded protein of which normally functions as a  $\Delta(8)$ - $\Delta(7)$  sterol isomerase in the cholesterol biosynthesis pathway catalysing the conversion of 8(9)-cholestenol to lathosterol. To date, over 50 separate familial and recurrent mutations have been reported with no obvious correlation between the molecular defects and the severity of the clinical phenotype. There is significant intrafamilial and interfamilial phenotypic variability in patients with EBP mutations.*

*Affected patients require dermatological care, as regular emollient application improves skin scaliness. Scoliosis and limb asymmetry lead to premature arthritis, requiring orthopaedic input. Genetic counselling, diagnostic DNA and biochemical tests and possible prenatal diagnosis should be offered to all families.*

## Keywords

X-linked dominant chondrodysplasia punctata, Conradi-Hünemann-Happle, cholesterol metabolism, EBP, skeletal dysplasia

## Disease name and synonyms

X-linked dominant chondrodysplasia punctata (CDPX2, CDPXD, CPXD)

Conradi-Hünemann-Happle syndrome (CHH)

Conradi-Hünemann syndrome

Conradi disease

Happle syndrome

Calcinosis universalis

Chondrodystrophia calcificans congenita

## Definition/Diagnosis criteria

Chondrodysplasia punctata is a name given to a heterogeneous collection of skeletal dysplasias characterized by punctate epiphyses. As well as the X-linked recessive (CDPX1 MIM 302950) and X-linked dominant forms (CDPX2 MIM 302960), this group includes tibia-metacarpal (MIM 118651), brachytelephalangic (MIM 602497), and rhizomelic forms (MIM 215100), as well as Zellweger syndrome (MIM 214100). CDPX2, also known as Conradi-Hünemann-

Happle (CHH) syndrome, is characterized by skeletal abnormalities including short stature, asymmetric rhizomelic shortening of the limbs, epiphyseal stippling, and craniofacial defects (Happle, 1979). In addition, there are skin defects including striated hyperkeratosis and pigmentary defects in patterns following the lines of Blaschko. Cataracts can also be present and the hair is coarse and lusterless with areas of alopecia. The clinical phenotype of CDPX2 is variable, ranging from stillborn or lethal forms, to mild, almost clinically undetectable forms.

### Differential diagnosis

Chondrodysplasia punctata is seen in many other conditions (Poznanski, 1994), including autosomal dominant chondrodysplasia punctata (MIM 118650), X-linked recessive chondrodysplasia punctata (MIM 302950), autosomal dominant tibia-metacarpal type (MIM 118651), autosomal recessive rhizomelic form (MIM 215100), brachytelephalangic form (MIM 602497), warfarin embryopathy, Zellweger syndrome (MIM 214100), CHILD syndrome (MIM 308050), Smith-Lemli-Optiz syndrome (MIM 270400), Trisomy 21 (MIM 190685), and congenital hypothyroidism (MIM 218700). Cutaneous changes and chondrodysplasia punctata occur in the X-linked dominant, X-linked recessive and autosomal recessive forms. However, the cutaneous changes in the X-linked dominant form are usually characteristic and striking. Many other skeletal dysplasias including Greenberg dysplasia (MIM 215140) can result in short stature and hydrops in utero (Offiah *et al*, 2003). Sterol analysis may help in the differential diagnosis.

### Etiology

Biochemical studies on CDPX2 patients demonstrated increased amounts of 8-dehydrocholesterol and 8(9)-cholestenol in the plasma and tissues (Kelley *et al*, 1999), and subsequent molecular studies demonstrated that CDPX2 was caused by mutations in the human emopamil binding protein gene, *EBP* (Braverman *et al*, 1999; Derry *et al*, 1999). The *EBP* gene is located on Xp11.23-p11.22 (Hanner *et al*, 1995; Schindelbauer *et al*, 1996) and comprises 5 exons. The gene encodes a 230 amino acid, 4 transmembrane domain protein that functions as a  $\Delta 8$ - $\Delta 7$  sterol isomerase with a predicted molecular weight of 27 kDa (Hanner *et al*, 1995; Silve *et al*, 1996). Further screening of *EBP* has identified over 50 mutations in females with CDPX2 (Has *et al*, 2000; Ikegawa *et al*, 2000; Becker *et al*, 2001; Herman *et al*, 2002; Offiah *et al*, 2003; Whittock *et al*, 2003a; Whittock *et al*, 2003b) and males with CDPX2

(Diaz *et al*, 2002; Aughton *et al*, 2003; Milunsky *et al*, 2003), as well as a female case of CDPX2 erroneously classified as CHILD syndrome (Grange *et al*, 2000). Of the mutations described to date, approximately 75% are nonsense, frameshift or splice site mutations that lead to a truncated protein, and 25% are missense mutations affecting essential amino acids involved in ligand binding or the insertion of the protein into the membrane. The arginine to histidine missense mutation (R147H) appears to be a frequent mutation as it has been described in patients originating from America (Braverman *et al*, 1999; Herman *et al*, 2002), Japan (Ikegawa *et al*, 2000; Shirahama *et al*, 2003), and Europe (Has *et al*, 2002; Whittock *et al*, 2003a), whereas the nonsense mutation R63X has been detected in America (Braverman *et al*, 1999; Derry *et al*, 1999; Herman *et al*, 2002) and Europe (Has *et al*, 2000; Whittock *et al*, 2003a). Inter and intrafamilial phenotypic variability is a major characteristic of individuals with *EBP* mutations and a recent study has demonstrated that intrafamilial phenotypic variation of an *EBP* mutation can be caused by skewed X-chromosome inactivation (Shirahama *et al*, 2003).

At least 11 cases of males with clinical features of CDPX2 have been reported (Croavato *et al*, 1985; Hochman *et al*, 1987; Sillevis Smitt *et al*, 1987; De Raeve *et al*, 1989; Tronnier *et al*, 1992; Omobono *et al*, 1993; Happle, 1995; Sutphen *et al*, 1995; Diaz *et al*, 2002; Aughton *et al*, 2003; Milunsky *et al*, 2003). Genetically, there are several mechanisms by which a viable male could arise. Firstly, gonosomal aneuploidy that gives rise to two X chromosomes [47,XXY] would result in the rescue of a lethal mutation via the resultant X-inactivation. Secondly, postzygotic or gonadal mosaicism of the gene would result in a male with an identical phenotype as females with CDPX2. Indeed, both of these mechanisms have now been characterized and reported in surviving males with CDPX2 (Sutphen *et al*, 1995; Aughton *et al*, 2003). A third possible mechanism is the presence of a leaky or hypomorphic mutation. This less severe mutation would of course lead to a less severe phenotype than that seen in females with CDPX2. Very recently a case of a hemizygous male with atypical CDPX2 has been reported (Milunsky *et al*, 2003). However, due to the absence of signs of chondrodysplasia punctata it has been proposed that this male has an entirely novel clinicogenetic entity and not an atypical form of CDPX2 (Happle, 2003). The majority of male CDPX2 cases are yet to be characterised at the genetic level so the

incidence of gonadal mosaicism against hypomorphic mutations remains to be deduced.

### Clinical description

X-linked dominant chondrodysplasia punctata is a distinctive skin disorder which is usually associated with skeletal defects and ocular abnormalities. Affected female fetuses have been detected prenatally with hydrops and may be stillborn. Babies may be born prematurely and there may be a collodion membrane or a generalised ichthyosiform erythroderma. Within the first year linear and swirling patterns of erythroderma and scaling develop following the lines of Blaschko. The ichthyosis continues to improve with age and the adult appearance may be so subtle as to be overlooked. The hair is coarse and lusterless with patches of cicatricial alopecia. Occasionally the nails are involved with flattening and/or splitting, but the teeth are normal. Craniofacial defects include frontal bossing, epicanthic folds, down slanting palpebral fissures and a flat nasal bridge. Skeletal defects include rhizomelic shortening of the limbs, limb asymmetry, short stature, vertebral defects, scoliosis, clinodactyly and polydactyly. There may be dysplastic hips, flexion deformities of the hips, joint stiffness and talipes equinovarus (Happle, 1979). Approximately two-thirds of cases have unilateral or bilateral congenital cataracts which may be accompanied by microphthalmia and/or microcornea (Happle, 1981). In addition there may be optic atrophy and sensorineural deafness. Life expectancy and Intelligence are normal in affected females. As CDPX2 is inherited in a X-linked dominant manner, it is expected to be lethal in hemizygous males (Wettke-Schafer *et al*, 1983). However, although rare, at least 11 cases of males with clinical features of CDPX2 have been reported (Crovato *et al*, 1985; Hochman *et al*, 1987; Sillevs Smitt *et al*, 1987; De Raeve *et al*, 1989; Tronnier *et al*, 1992; Omobono *et al*, 1993; Happle, 1995; Sutphen *et al*, 1995; Diaz *et al*, 2002; Aughton *et al*, 2003; Milunsky *et al*, 2003). Characteristic features present in these males include epiphyseal and periepiphyseal stippling, skeletal asymmetry, patchy alopecia of the scalp, brow and eyelashes, linear arrays of hypotrophic changes of the skin, structural vertebral anomalies and scoliosis. In addition, most males have developmental delay (Diaz *et al*, 2002; Milunsky *et al*, 2003).

### Diagnostic methods

Diagnosis is based on radiographic, ophthalmic, dermatological, biochemical and molecular investigations. The epiphyseal stippling seen in this condition affects the enchondral bone and

may be more widespread than in other forms of chondrodysplasia punctata, also affecting the larynx and vertebrae. The stippling often resolves in infancy. Clinical examination of the eyes, hair, nails and skin should help to confirm the distinctive clinical features of this condition. Dystrophic calcification in the keratotic follicular plug is a distinctive histopathologic feature of CDPX2 in newborns and is not seen in any other form of ichthyosis (Hoang *et al*, 2004). The clinical diagnosis should be confirmed by a sterol analysis of plasma or tissue in which elevated levels of 8-dehydrocholesterol and 8(9)-cholestenol are characteristic. However, where possible direct sequencing of the *EBP* gene should also be performed to confirm the diagnosis as sterol profiling can occasionally be misleading (Whitlock *et al*, 2003a). Neither sterol profiles, nor mutations can give an indication of the severity of the clinical phenotype, although it has been suggested that truncating mutations lead to typical CDPX2 whereas missense mutations lead to atypical CDPX2 (Ikegawa *et al*, 2000).

Gonosomal aneuploidy [47,XXY] as described in one male (Sutphen *et al*, 1995) can be determined using chromosomal analysis or FISH.

### Epidemiology

Accurate incidence and prevalence data are not available for this rare disease.

### Genetic counselling

As this disease is X-linked dominant then the expected offspring risk in an affected female is 50 %. Although the disease is embryonically lethal in the majority of male pregnancies, a very small number of affected males survive. An excess of miscarriages or male stillbirths have been reported in affected families. Gonadal mosaicism is common in patients with this disease (Has *et al*, 2000; Aughton *et al*, 2003) and this factor will have consequences on the genetic counselling of female sporadic cases. Clinicians should indicate that a sporadic incidence in this syndrome does not automatically mean a *de novo* mutation. Therefore, in calculating a recurrence risk for further pregnancies gonadal mosaicism must be considered even when dealing with a sporadic case. Genetic counselling can also prove difficult as there can be a stepwise increase in disease expression from one generation to the next (anticipation) in some families (Traupe *et al*, 1992; Sutphen *et al*, 1995). Factors that contribute to the phenomenon of anticipation may include gonadal mosaicism, random differences in X-inactivation and the reproductive

fitness of those women who are affected (Traupe *et al*, 2000).

### Antenatal diagnosis

Antenatal diagnosis has been reported in severely affected fetuses with this condition, by detecting growth retardation, skeletal asymmetry and polyhydramnios in the late 2<sup>nd</sup> and 3<sup>rd</sup> trimesters (Kelley *et al*, 1999).

However, molecular antenatal diagnosis is available through identification of the syndrome-causing *EBP* mutation using CVS (chorionic villus sample) or amniocentesis.

### Management including treatment

Affected patients require dermatological care, as regular emollient application improves skin scaliness. Scoliosis and limb asymmetry lead to premature arthritis, requiring orthopaedic input. Some patients require wigs to cover extensive alopecia. Eye defects may limit visual acuity, and some patients are registered blind or partially sighted. Genetic counselling, diagnostic DNA and biochemical tests and possible prenatal diagnosis should be offered to all families.

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