Cri-du-chat syndrome is a chromosome 5p deletion syndrome first described by Lejeune et al. in 1963. The incidence is estimated to be approximately 1 in 15,000–50,000 births. The prevalence among mentally retarded individuals is approximately 1.5 in 1000.

GENETICS/BASIC DEFECTS

1. Cause
   a. Caused by deletion of short arm of chromosome 5 (5p15.2–15.3)
      i. De novo deletion (80%): paternally derived deletions in 80% of cases
      ii. Familial rearrangement (12%)
      iii. Mosaicism (3%)
      iv. Rings (2.4%)
      v. De novo translocation (3%)
   b. A high-resolution physical and transcription map generated a 3.5-Mb region of 5p15.2 that is associated with the Cri du chat syndrome region

2. Genotype–phenotype correlation
   a. Deletion of 5p15.3 results in a cat-like cry and speech delay
   b. Deletion of 5p15.2 results in the distinct facial features associated with the syndrome as well as the severe mental and developmental delay

3. Hemizygosity of δ-catenin (CTNND2, mapped to 5p15.2), reported to be associated with severe mental retardation in cri-du-chat syndrome

4. Deletion of the telomerase reverse transcriptase (TERT) gene (mapped at 5p15.33) and haploinsufficiency of telomere maintenance is probably a genetic element contributing to the phenotypic changes in cri-du-chat syndrome

CLINICAL FEATURES

1. Characteristic mewing cry
   a. A high-pitched monochromatic cry with subtle dysmorphism and neonatal complications: commonly observed in infants with this syndrome
   b. Observed in many infants with Cri-du-chat syndrome
   c. Not associated with other aneuploidies
   d. Usually considered diagnostic
   e. Loss of the characteristic cry by age 2 years in one third of children

2. Clinical findings during infancy
   a. Low birth weight
   b. Hypotonia
   c. Microcephaly
   d. Poor sucking/swallowing difficulties
   e. Need for incubator care
   f. Respiratory distress
   g. Jaundice
   h. Pneumonia
   i. Dehydration
   j. Failure to thrive/growth retardation
   k. Early ear infections
   l. Severe cognitive, speech and motor delays
   m. Facial features
      i. Round face with full cheek
      ii. Hypertelorism
      iii. Epicanthal folds
      iv. Down-slanting palpebral fissures
      v. Strabismus
      vi. Flat nasal bridge
      vii. Down-turned mouth
      viii. Micrognathia
      ix. Low-set ears
   n. Cardiac defects
      i. VSD
      ii. ASD
      iii. PDA
      iv. Tetralogy of Fallot
   o. Short fingers
   p. Single palmar creases
   q. Less frequent features
      i. Cleft lip and palate
      ii. Preauricular tags and fistulas
      iii. Thymic dysplasia
      iv. Gut malrotation
      v. Megacolon
      vi. Inguinal hernia
      vii. Dislocated hips
      viii. Cryptorchidism
     ix. Hypospadias
     x. Rare renal malformations
        a) Horseshoe kidneys
        b) Renal ectopia or agenesis
        c) Hydronephrosis
     xi. Clinodactyly of the fifth fingers
     xii. Talipes equinovarus
     xiii. Pes planus
     xiv. Syndactyly of the second and third fingers and toes
     xv. Oligosyndactyly
     xvi. Hyperextensible joints

3. Clinical findings in childhood
   a. Severe mental retardation
   b. Developmental delay
   c. Microcephaly
   d. Hypertonicity
   e. Premature graying of the hair
   f. Small, narrow and often asymmetric face
   g. Dropped-jaw
   h. Open-mouth expression secondary to facial laxity

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i. Short philtrum  
 j. Malocclusion of the teeth  
 k. Scoliosis  
 l. Short third-fifth metacarpals  
 m. Chronic medical problems  
   i. Upper respiratory tract infections  
   ii. Otitis media  
   iii. Severe constipation  
   iv. Hyperactivity  

4. Clinical findings in late childhood and adolescence  
 a. Coarsening of facial features  
 b. Prominent supraorbital ridges  
 c. Deep-set eyes  
 d. Hypoplastic nasal bridge  
 e. Affected females reaching puberty and developing secondary sex characteristics and menstruate at the usual time  
 f. Small testis and normal spermatogenesis in males  

5. Dermatoglyphics  
 a. Transverse flexion creases  
 b. Distal axial triradius  
 c. Increased whorls and arches on digits  

6. Behavioral profile  
 a. Hyperactivity  
 b. Aggression  
 c. Tantrums  
 d. Stereotypic and self-injurious behavior  
 e. Repetitive movements  
 f. Hypersensitivity to sound  
 g. Clumsiness  
 h. Obsessive attachments to objects  
 i. Able to communicate needs and interact socially with others  
 j. Autistic-like features and social withdrawal: more characteristic of individuals who have a 5p deletion as the result of an unbalanced segregation of a parental translocation  

7. Prognosis  
 a. Ability of many children to develop some language and motor skills  
 b. Ability of these children to attain developmental and social skills observed in 5- to 6-year-old children, although their linguistic abilities are seldom as advanced  
 c. Older, home-reared children  
   i. Usually ambulatory  
   ii. Able to communicate verbally or through gestural sign language  
   iii. Independent in self-care skills.  

**GENETIC COUNSELING**  
1. Recurrence risk  
   a. Patient’s sib  
     i. Recurrence risk for a de novo case is 1% or less  
     ii. Rare recurrences in chromosomally normal parents: most likely the result of gonadal mosaicism for the 5p deletion in one of the parents  
     iii. The risk is substantially high if a parent is a balanced carrier of a structural rearrangement. Risk should be assessed based on the type of structural rearrangement and its pattern of segregation  
   b. Patient’s offspring: female patients are fertile and can deliver viable affected offspring, with an estimated recurrence risk of 50%  

2. Prenatal diagnosis by amniocentesis, CVS, and PUBS for chromosome analysis to detect 5p deletion  
3. Management  
 a. Supportive care. No treatment exists for the underlying disorder  
 b. Appropriate treatment for chronic medical problems  
   i. Upper respiratory tract infections  
   ii. Otitis media  
   iii. Severe constipation  
 c. Using the relatively good receptive skills to encourage language and communicative development rather than relying on traditional verbal methods  
 d. Early intervention programs  
   i. Physical therapy  
   ii. Occupational therapy  
   iii. Speech therapy  

**DIAGNOSTIC INVESTIGATIONS**  
1. Conventional cytogenetic studies. The size of the 5p deletion may vary from the entire short arm to only 5p15. A small deletion of 5p may be missed by a conventional cytogenetic technique  
2. High-resolution cytogenetic studies are required for a smaller 5p deletion  
3. Molecular cytogenetic studies using fluorescent in situ hybridization (FISH)  
 a. Allow the diagnosis to be made in the patients with very small deletions  
 b. Use genetic markers that have been precisely localized to the area of interest  
 c. The absence of a fluorescent signal from either the maternal or paternal chromosome 5p regions: indicative of monosomy for that chromosomal region  

4. Skeletal radiographs  
 a. Microcephaly  
 b. Retromicrognathia  
 c. Cranial base malformations  
   i. Reduced cranial base angle  
   ii. Malformed sella turcica and clivus  
 d. Disproportionately short third, fourth, and fifth metacarpals and disproportionately long second, third, fourth, and fifth proximal phalanges (frequent)  

5. Echocardiography to rule out structural cardiac malformations  
6. MRI of the brain  
 a. Atrophic brainstem, middle cerebellar peduncles and cerebellar white matter  
 b. Possible hypoplasia of cerebellar vermis with enlargement of the cisterna magna and 4th ventricle  

7. Swallowing study for feeding difficulty  
8. Comprehensive evaluation for receptive and expressive language. Most children have better receptive language than expressive language  
9. Developmental testing and referral to early intervention and appropriate school placement
REFERENCES


Fig. 1. Two infants with cri-du-chat syndrome. Note a round face with full cheeks, hypertelorism, epicanthal folds, and apparently low-set ears.

Fig. 2. Cri-du-chat syndrome in an older child and a teenager showing a long and narrow face.
Fig. 3. G-banded karyotypes with 5p deletion in two children with cri-du-chat syndrome.

Fig. 4. FISH of an interphase cell and a metaphase spread with two orange signals (LSI SpectrumOrange, D5S721) and one green signal (LSI SpectrumGreen, D5S23 chromosome 5p15.2-specific probe) indicating deletion of 5p15.2.