

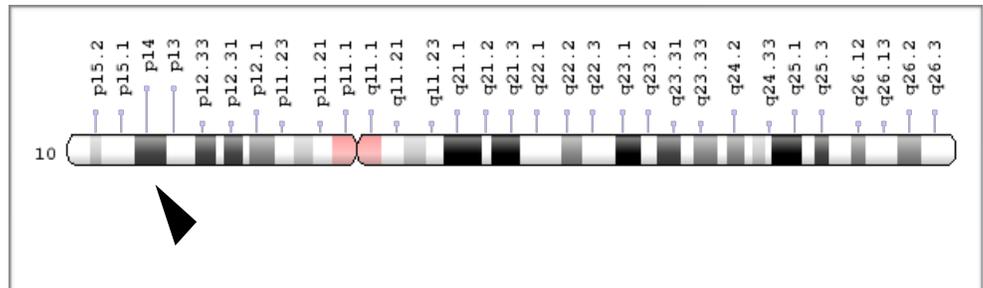


HDR SYNDROME (BARAKAT SYNDROME) INFORMATION

HDR Syndrome

The association of sensori-neural deafness, hypoparathyroidism and renal abnormalities has been known for 50 years, but the etiology of this complex became clear only recently. HDR is an abbreviation based on the first letters of the main symptoms: H (Hypoparathyroidism), D (deafness) and R (renal abnormalities). Sometimes the term “Barakat syndrome” may be used (for the name of the pediatrician who first reported this association in 1970s).

The short arm of chromosome 10 contains the GATA3 gene. This gene affects the functioning of the inner ear, thymus, kidneys, adrenals and other organs¹. HDR syndrome may be caused both by a mutation in the GATA3 gene (leading to its



haploinsufficiency)

and by a deletion of the short arm of chromosome 10 involving the 10p14 band, where this gene is located. Currently there are at least 35-40 patients with HDR syndrome caused by pure deletions of 10p14 and 15-20 more patients who have a deletion of the terminal part of 10p in association with partial trisomies of other chromosomes.

Clinical manifestations of hypoparathyroidism cause low levels of calcium in the blood that in turn cause muscular pain (myalgia) and non-febrile seizures.

Sensori-neural hearing impairment is the most obvious and frequently the first sign of the syndrome. Hearing problems are found in 97% of patients. Unfortunately, hearing impairment is known to worsen with age².

Renal abnormalities are very different. Both structural defects (unilateral aplasia, hypoplasia, dysplasia, cystic kidneys, defects of renal pelvis and ureters) and functional abnormalities (proteinuria, tubular acidosis, etc.) have been reported in affected persons. Because of the wide implementation of both prenatal ultrasonography (which shows structural defects of the kidneys) and hearing assessments of all newborns, the syndrome is recognized now much more often than before³.

The classic triad is found only in some patients. According to the literature (which includes both cases caused by mutations of the GATA3 gene and deletions involving this gene) at least 35% of patients do not have all three main findings. A combination of only two main symptoms (or only one symptom in cases with a positive family history) may be sufficient to diagnose HDR syndrome³.

Deletions involving 10p14 lead to the loss of some additional genes. As a result patients with deletions usually have additional symptoms including delay in psychomotor development, microcephaly, heart defects, pyloric stenosis, and other abnormalities.

As this deletion region is very close to another disease-causing region, some individuals with HDR syndrome may also have symptoms of a DiGeorge-like phenotype, also known as DiGeorge 2 syndrome (DGS2)⁴. DiGeorge Syndrome 2 has been found to be associated with a deletion of the critical region 10p13-14, which is adjacent to the HDR syndrome deletion region. People afflicted with both of these phenotypes may often have additional characterizations such as facial anomalies, conotruncal heart defects, T-cell immune defects, and developmental delays⁵.

The vital prognosis depends mostly on the severity of renal defects and (in patients with deletions) the presence of additional abnormalities. Treatment of patients is mostly symptomatic. Hypoparathyroidism may be controlled by parathormone. Early diagnosis of kidney disease may delay end-stage renal disease. Kidney transplantation may be necessary in some patients.

When HDR syndrome is caused by a mutation in the GATA3 gene it is inherited as an autosomal dominant condition. Deletions however are mostly sporadic. However, direct transmission of a deletion may be expected especially in persons with mild clinical manifestations. And of course a deletion in a child may be caused by a parental translocation. In this context the cytogenetic examination of the parents of any child with this deletion is necessary to determine the risk for further pregnancies.

REFERENCES

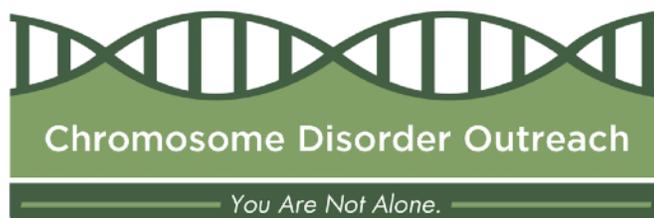
¹ Benetti E, Murer L, Bordugo A, Andretta B, Artifoni L. 10p12.1 deletion: HDR phenotype without DGS2 features. *Exp Molec Pathol* 2009, v. 86, 74-76.

² Joseph ADD, Sirisena ND, Kumanan T, Sujanitha V, Strelow V et al. Hypoparathyroidism, sensorineural deafness and renal disease (Barakat syndrome) caused by a reduced gene dosage in GATA3: a case report and review of literature. BMC Endocrine Dis 2019, v. 19:111.

³ Barakat AJ, Raygada M, Rennert OM. Barakat syndrome revisited. Am J Med Genet Part A 2018, v. 176A, 1341–1348.

⁴ MacDonald A, Martinez-Fernandez ML, Acena I et al. A new patient with deletion of 10p and revision of the literature. Study of the genotype-phenotype correlation. Bol ECEMC: Rev Dismor Epidemiol 2012, v. VI (n° 2), 57-71.

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