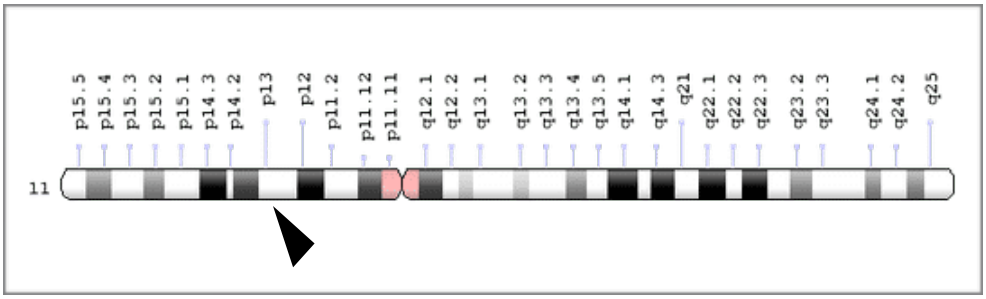
WAGR SYNDROME INFORMATION

WAGR Syndrome

WAGR is an acronym from the first letters of the mainmanifestations of this condition: Wilms tumor (W), aniridia (A), genital abnormalities (G) and retardation (R). The association of these defects has been known since the 1960s, but the chromosomal etiology of this syndrome was first reported in 1978-1979 (1). The chromosomal segment 11p13 includes two nearby genes – PAX6 and WT1, and the deletion of these genes determines the main manifestations of the syndrome. WAGR is a relatively common condition; at least 200 patients have been reported so far.



The first manifestation of the syndrome is aniridia (absence of the iris). This defect may be revealed upon the examination of a newborn baby. Aniridia may be complete or partial. Glaucoma and cataracts often develop as a consequence of aniridia. Aniridia itself is caused by a mutation in the PAX6 gene and in many families this defect is inherited in an autosomal dominant manner. If however aniridia in a newborn baby is sporadic it is a strong indication for a cytogenetic examination to exclude deletion 11p13 underlying this eye defect. At least one third of patients with sporadic aniridia may have 11p13 deletion and (as a result) other manifestations of WAGR syndrome. Molecular cytogenetic examinations show that in rare instances aniridia may be caused by deletions of the regulatory elements nearby the PAX6 gene, but the gene itself may be unaffected (2).

Genital abnormalities vary from one patient to another. Most boys reveal cryptorchidism. Hypospadias or ambiguous genitalia are relatively uncommon. Girls usually do not reveal genital abnormalities, although there are reports of streaked ovaries, hypoplastic or bicornuate (a type of congenital uterine malformation or müllerian duct anomalies in which the uterus

appears to be heart shaped) uterus, etc. However because genital abnormalities are basically mild they may escape attention of both parents and physicians.

Most patients reveal delayed psychomotor development. They start walking and talking usually later than their healthy peers. Attention deficit hyperactivity disorder or autism spectrum disorder are relatively common. However, sometimes these manifestations go unrecognized until 3-4 years of age.

Wilms tumor (nephroblastoma) is a kind of kidney cancer. It is the most serious component of the WAGR syndrome. And if this tumor is not discovered until the child has clinical manifestations the tumor may spread and achieve stages III or IV, when the chances of successful treatment are worse than when tumor is confined to the kidney. That is why the occurrence of a sporadic aniridia is a strong indication for cytogenetic examination. If this test reveals a deletion involving 11p13 the child should be periodically examined by ultrasound to exclude the development of nephroblastoma. Basically ~45% of patients with deleted 11p13 develop Wilms tumor (1). If detected, treatment of this tumor should be performed according to the existing guidelines: usually surgery [removal of the affected kidney] plus chemotherapy. Almost all patients develop Wilms tumor before the age of 5. If a child reaches age 7-8 without tumor formation further periodic ultrasound examination may be unnecessary.

Some children may develop other kidney disorders (leading to renal insufficiency) after recovery from Wilms tumor. This contrasts with children who recover from Wilms tumor unrelated to 11p13 deletion, where the chance of renal failure is only 1-2%.

Genetically, deletion of the WT1 gene is the factor leading to the development of the tumor, although this deletion does not guarantee that the child will have this pathology. Most scientists believe that genital abnormalities are also caused by deletion of the WT1 gene.

Recent research investigations believe that developmental delay and behavioral abnormalities are caused by the deletion of the PRRG4 gene located in the close proximity to WT1 gene (3).

Actually all (or almost all) deletions in patients with WAGR syndrome are different both in size and in position of the breakpoints. Most of these deletions involve additional genes from the telomeric side of the chromosome (from the side of PAX6 gene) or from its centromeric side (the side of WT1 gene). As a result many patients have deletions of other genes which may affect their neurodevelopmental status.

There are numerous reports of other defects found in the patients with WAGR syndrome. Many affected patients are obese, and some authors recommend adding an “O” to the acronym (using WAGRO instead of WAGR).

Some patients have heart defects, scoliosis, polydactyly, diaphragmatic hernia, pancreatitis etc. All these defects were reported in more than one patient. However, most likely the explanation for these defects is a deletion of other genes from both sides of the critical area of 11p13.

Life expectancy prognosis is determined by the success of the Wilms tumor treatment and renal function after it. Late discovery of the tumor and possible renal failure are the main causes of death. In the absence of these defects the vital prognosis is relatively good (4); there are several reports of adults with this syndrome.

WAGR syndrome is a contiguous deletion syndrome where the main components of the disorder are caused by deletions of several neighboring genes.

Deletions affecting 11p13 are interstitial deletions and in almost all cases they result from sporadic mutations. [This deletion differs from terminal deletions like del 4p16, where the majority of cases are caused by familial translocations]. However, several cases of insertional translocations are also known to cause WAGR syndrome. If both parents have a normal karyotype the chance of a recurrence of WAGR syndrome in the next child is almost zero.

References:

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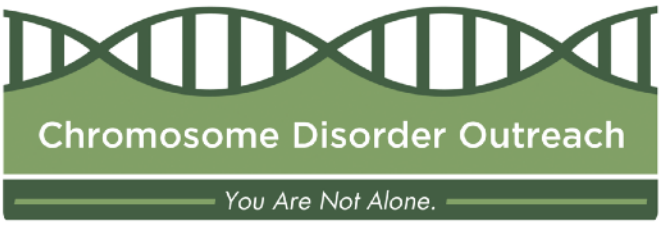
3 Yamamoto T, Togawa M, Shimada S, Sangu N, Shimojima K et al. Narrowing of the responsible region for severe developmental delay and autistic behaviors in WAGR syndrome down to 1.6 Mb including PAX6, WT1, and PRRG4. Am J Med Genet Part A 2014, v. 164A, 634-638.

4 Prasher VP, Ali M, Nasritdinova N, Routhu S, Thalitaya MD. Longevity in WAGR syndrome. Internat J Devel Disabil 2012, v. 58, 20-23.



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