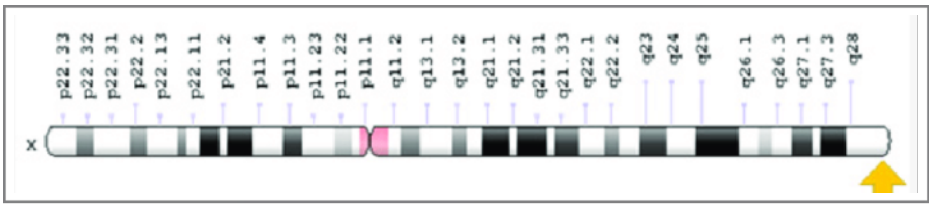
XQ28 DUPLICATION INFORMATION

Xq28 DUPLICATION SYNDROME



Xq28 duplication syndromes are a rare form of X-linked intellectual disability syndromes. These syndromes are caused by duplications within the q28 region of the X chromosome. These duplications can vary in exact size and location from person to person.

The exact prevalence of Xq28 duplications is unknown, but more than 600 cases have been reported[1]. The syndrome is usually inherited from the mother; however, cases of de novo mutations have been reported – although they are exceedingly rare.

Clinical manifestations of Xq28 duplications can be seen in both males and females. Male phenotypes tend to be more severe yet standardized due to their hemizygous karyotype (males only have one X chromosome). Females, however, can encompass a wide range of clinical manifestations, varying from mild to severe, due to their heterozygous nature and unbalanced X chromosome inactivation[2].

The most common manifestations include intellectual disability, neurobehavioral abnormalities, dysmorphic facial features, increased respiratory infections, and gastrointestinal abnormalities[2].

Some level of intellectual disability is present among all male and most female patients, mostly in the range of moderate to severe. Many patients will meet the criteria necessary for autism spectrum disorders. This is often due to their inability to use expressive language as well as having abnormal social affect and restricted/repeated behaviors[1]. At least two-thirds of patients reveal

impaired communication skills and over a half of patients have sleep disturbances, mostly as obstructive sleep apnea.

Neurologically abnormalities include seizures or epilepsy among patients, with a mean onset age around 7.4. Many of these patients, around 62%, will develop epilepsy that is drug resistant. Some patients may also develop mood disorders, like anxiety[3]. Hypotonia has also been associated with patients being delayed in reaching developmental milestones such as sitting and crawling[1].

Dysmorphic facial features occur in 93% of patients. This includes features such as midface hypoplasia, narrow and prominent ears, thick and dense hair, livedo of the limbs, tapered fingers, small feet, and vasomotor troubles[3].

Many patients will have an increased number of respiratory infections – which is a main cause of concern for reduced life-expectancy. These infections include those like pneumonia, middle ear infections, sinusitis, and bronchitis. Atopic diseases such as asthma, allergic rhinitis, and eczema are also common[2].

Gastrointestinal abnormalities are also frequent among patients. Common phenotypes include feeding difficulties due to hypotonia, gastro-esophageal reflux, swallowing dysfunction, and excessive drooling[1]. Severe constipation is also seen among 78% of patients[3].

15-20% of patients have congenital heart disease (patent ductus arteriosus or patent foramen ovale). Usually these defects do not have serious hemodynamic consequences.

The severity of clinical manifestations depends both on age and the overall duplication size. As patients age, their overall clinical manifestations as well as their motor dysfunction and functional skills significantly worsen. Parents often have concerns that include effective communication, abnormal walking/ balance, constipation, and seizures[4].

Size of the Xq28 duplications may be different, but minimally duplicated segments include the MECP2 and IRAK1 genes. Extremely rare cases with isolated duplications of the MECP2 gene show that these patients have the same manifestations. There are no cases of isolated duplications of the IRAK1 gene. That is why duplication of the MECP2 gene is considered to be the main causative factor for Xq28 duplication syndrome. In new publications, the term MECP2 duplication syndrome is used as the synonym for Xq28 duplication. Triplication of the MECP2 causes more severe clinical consequences. Involvement of genes outside the critical duplicated segment may lead to occurrence of microcephaly, cleft palate, and inguinal hernia of hypoplastic genitalia, although these defects are outside of the typical clinical spectrum of the Xq28 syndrome[5].

Vital prognosis is largely based on the amount of recurrent respiratory infections. The overall increase in clinical severity, motor dysfunction, and functional skills as patients age is also a factor in prognosis.

There are no current treatments for Xq28 duplications other than treatment of symptoms. This includes routine management of feeding difficulties as well as physical therapy and early antibiotic treatment for respiratory infections. It is important to keep a look out for delayed growth milestones, seizures, loss of speech, and progressive spasticity[6].

For a definitive diagnosis, molecular genetic testing, chromosomal microarray analyses, or an intellectual disability multigene panel can be performed. These duplications can also be determined prenatally via amniocentesis.

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