ATR-X

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ATR-X, an acronym for alpha thalassemia and mental retardation X-linked, syndrome is a congenital condition predominantly affecting males, characterized by mild to severe intellectual disability, facial, skeletal, urogenital, and hematopoietic anomalies. Less common are heart defects, eye anomalies, renal abnormalities, and gastrointestinal dysfunction. ATR-X syndrome is caused by germline variants in the ATRX gene. Until recently, the diagnosis of the ATR-X syndrome had been guided by the classical clinical manifestations and confirmed by molecular techniques. However, our new systematic analysis shows that the only clinical sign shared by all affected individuals is intellectual disability, with the other manifestations varying even within the same family. More than 190 different germline ATRX mutations in some 200 patients have been analyzed. With improved and more frequent analysis by molecular technologies, more subtle deletions and insertions have been detected recently. Moreover, emerging technologies reveal non-classic phenotypes of ATR-X syndrome as well as the description of a new clinical feature, the development of osteosarcoma which suggests an increased cancer risk in ATR-X syndrome. This review will focus on the different types of inherited ATRX mutations and their relation to clinical features in the ATR-X syndrome. We will provide an update of the frequency of clinical manifestations, the affected organs, and the genotype-phenotype correlations. Finally, we propose a shift in the diagnosis of ATR-X patients, from a clinical diagnosis to a molecular-based approach. This may assist clinicians in patient management, risk assessment and genetic counseling.