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REVIEW ARTICLE

Turner syndrome and genetic polymorphism: a systematic review

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KEYWORDS
Turner syndrome;
Genetic polymorphism;
Growth hormone;
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Abstract
Objective: To present the main results of the literature on genetic polymorphisms in Turner syndrome and their association with the clinical signs and the etiology of this chromosomal disorder.
Data sources: The review was conducted in the PubMed database without any time limit, using the terms *Turner syndrome* and *genetic polymorphism*. A total of 116 articles were found, and based on the established inclusion and exclusion criteria 17 were selected for the review.
Data synthesis: The polymorphisms investigated in patients with Turner syndrome were associated with growth deficit, causing short stature, low bone mineral density, autoimmunity and cardiac abnormalities, which are frequently found in patients with Turner syndrome. The role of single nucleotide polymorphisms in the etiology of Turner syndrome, i.e., in chromosomal nondisjunction, was also confirmed.
Conclusions: Genetic polymorphisms appear to be associated with Turner syndrome. However, in view of the small number of published studies and their contradictory findings, further studies in different populations are needed in order to clarify the role of genetic variants in the clinical signs and etiology of the Turner syndrome.

PALAVRAS-CHAVE
Síndrome de Turner;
Polimorfismo genético;

Síndrome de Turner e polimorfismo genético: uma revisão sistemática

Resumo
Objetivo: Apresentar os principais resultados dos estudos que investigaram polimorfismos genéticos em síndrome de Turner, bem como sua associação com alguns sinais clínicos e etiologia desse distúrbio cromossômico.

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Hormônio do crescimento;
Aneuploidia

Fontes de dados: Revisão bibliográfica feita no PubMed, sem limite de período, com os seguintes termos: *Turner syndrome* and *genetic polymorphism*. Foram identificados 116 artigos e, de acordo com os critérios de inclusão e exclusão, 17 foram selecionados para leitura.
Síntese dos dados: Os polimorfismos investigados em pacientes com síndrome de Turner estavam relacionados com déficit de crescimento, que causou baixa estatura, densidade mineral óssea baixa, autoimunidade e anomalias cardíacas, que podem estar presentes com frequências significativas nas pacientes. Também foi verificado o papel dos polimorfismos de único nucleotídeo (SNPs) na etiologia da síndrome de Turner, ou seja, na não disjunção cromossômica.
Conclusões: Os polimorfismos genéticos parecem estar associados à síndrome de Turner. Entretanto, por conta dos poucos estudos publicados e dos achados contraditórios, pesquisas em diferentes populações são necessárias para esclarecer o papel dessas variantes genéticas para os sinais clínicos e a etiologia do distúrbio cromossômico.

Introduction

The description of female patients with Turner syndrome (TS) was published in 1938 by Henry Turner[1]; however, in 1930, German pediatrician Dr. Otto Ullrich had already reported a case of an 8-year-old girl with signs suggestive of TS.[2] Therefore, this syndrome is also called Ullrich-Turner syndrome.

The disorder has an incidence of 1/2500 girls and clinical signs include lymphedema of hands and feet, short and webbed neck, low hairline at the nape of the neck, cubitus valgus, hypoplastic or hyperconvex nails, micrognathia, high-arched palate, short stature, gonadal dysgenesis, primary amenorrhea, sexual infantilism, infertility, shield chest, breast hypertelorism, cardiac (coarctation of the aorta and ventricular septal defects) and renal anomalies (horseshoe kidney, urethral duplication and unilateral kidney agenesis), multiple pigmented nevi, scoliosis, fourth/fifth metacarpal or metatarsal hypoplasia or both. The following problems may also be present: hearing impairment, arterial hypertension, osteoporosis, obesity, visual disturbances, impaired glucose tolerance, learning disabilities, psychosocial problems and thyroid diseases, among other autoimmune diseases.[3]

TS is characterized by large phenotypic variability, ranging from the classical form (girls with pubertal development and growth delay) to those with few dysmorphic signs, which are almost indistinguishable from the general population.[4] The definitive diagnosis of TS is carried out by analyzing the karyotype, which allows the identification of the individual's chromosomal constitution. TS chromosomal etiology was only elucidated in 1959, when the first patient was investigated by cytogenetics and showed the 45, X chromosomal constitution.[5] Brazilian studies in patients with TS showed that the karyotype 45, X, i.e., monosomy of the sex chromosome X, was found in 40–60% of patients with TS, but mosaicisms and karyotypes with structural alterations, mainly isochromosomes, are also found.[4,6–8] A retrospective study indicated that better-quality diagnosis has improved the quality of the cytogenetic result of TS, with modification of the proportion between the types of karyotype observed, especially the progressive decrease in the identification of 45, X patients and increased detection of karyotypes with structural aberrations.[6]

In Brazil, the mean age of TS diagnosis is around 12 years of age,[4,7,9,10] and 25.3% and 51.1% of the patients were respectively diagnosed in childhood (1–11 years) and adolescence (12–18 years), on account of the short stature.[7] Therefore, it is important to assess girls with short stature, regardless of the presence of typical dysmorphic signs and pubertal delay, by requesting the karyotype analysis to confirm or rule out TS. The authors also point out that neonatologists and pediatricians should be aware about the possibility of genetic syndromes such as TS, considering that the main signs are present at birth, but are not taken into account at that time.[7] Thus, medical training improvement aimed to recognize the spectrum of clinical manifestations of this chromosomal syndrome is necessary. In addition to the difficulty of achieving an early diagnosis of this genetic condition, other factors associated with late TS diagnosis include less severe growth retardation, presence of spontaneous pubertal signs, socioeconomic determinants and absence of obvious dysmorphic features.[4,10]

Early diagnosis of TS is vital, as it also allows the identification of congenital and acquired anomalies, as well as the detection of cases with Y chromosome sequences in the karyotype, which is associated with gonadoblastoma, a tumor with high malignant potential that can be prevented through prophylactic gonadectomy,[11] besides allowing hormonal treatments with growth hormone (GH) and oxandrolone[12] and estrogen/progestogen[12,13] to respectively increase final height and accentuate secondary sexual characteristics at the adequate chronological age, preventing further damage to patient health. Therefore, an early and accurate diagnosis is important for a successful therapeutic approach. It is noteworthy that there is no classical karyotype or phenotype associated with TS, and the diagnosis is not always evident, but should be actively sought, both from a clinical and cytogenetic point of view.[6]

Additionally, TS is a genetic disorder, and single nucleotide polymorphisms (SNPs) may be involved in its