Genomics paper

Turner syndrome

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Abstract

Turner syndrome (TS) is a sex chromosome aneuploidy with a variable spectrum of symptoms including short stature, ovarian failure and skeletal abnormalities. The etiology of TS is complex, and the mechanisms driving its pathogenesis remain unclear.

In our study, we used the online Gene Expression Omnibus (GEO) microarray expression profiling dataset GSE46687 to identify differentially expressed genes (DEGs) between monosomy X TS patients and normal female individuals. The relevant data on 26 subjects with TS (45,XO) and 10 subjects with the normal karyotype (46,XX) was investigated.

In total, 25 upregulated and 60 downregulated genes were identified in the differential expression analysis. The tissue-specific gene expression analysis of the DEGs revealed that the system with the most highly enriched tissue-specific gene expression was the hematologic/immune system, followed by the skin/skeletal muscle and neurologic systems.

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Introduction

Turner syndrome (TS) is a common genetic condition caused by abnormal sex chromosomes that affect 1 in 2500 female live births. TS was gradually recognized as a syndrome characterized by the complete absence or partial loss of an X chromosome in phenotypic females. The clinical signs of TS include short stature, gonadal dysgenesis, lymphedema webbed neck, and more than 400 types of dysmorphic features. In addition, cardiovascular disease is more prevalent in women with TS, including congenital cardiac abnormalities, aortic dilation and dissection, hypertension, and ischemic heart disease. In addition, ~30% of individuals with TS have a bicuspid aortic valve (BAV). Typically, nearly half the patients with TS have a 45,X karyotype, 20–30% of patients with TS present with

mosaicism (45,XO/46,XX), and the remainder has X chromosome structural abnormalities. Females with TS present with highly variable clinical features, which are caused by the haploinsufficiency of genes involved in multiple systems.

TS is a multiple-system disease, and the etiology is complex. However, the mechanisms underlying the pathogenesis of TS remain unclear. Previous studies indicated that haploinsufficiency of the short stature homeobox (SHOX) gene leads to the occurrence of short stature and many specific skeletal anomalies in TS individuals. However, as a mainly developmental disorder, the pathogenesis of congenital heart defects in TS stills unclear. In previous research, mutations in NKX2.5, GATA5, and NOTCH1 have been identified as the causative factor in non-syndromic patients with inherited BAV. Moreover, chromosome structural variants and potential pathogenic genes such as TIMP3 and TIMP1 may be associated with TS patients with congenital cardiac abnormalities. In addition, sex chromosome imbalance and dysregulation of certain genes on the X chromosome (such as FMR1, PDIAPH2, and BMP15, etc.) may result in accelerated oocyte atresia, leading to gonadal dysgenesis later in life. And haploinsufficiency of a lymphatic gene is related to the development of lymphedema and webbed neck. Recently, haploinsufficiency of immune-associated genes on the X chromosome was reported to result in the development of autoimmune diseases, including autoimmune thyroiditis, diabetes, and autoimmune enteritis.

Altered autosomal gene expression, as well as chrX gene expression, has been observed in females with TS (45,X monosomy) in different samples as human fibroblast cell line, peripheral blood mononuclear cells, as well as in the induced pluripotent human cell lines, with inconsistent results. However, further data analysis and data mining are still absent, especially the derivation of the X chromosome of the patients who inherited the monosomy X chromosome from their mother or father (TS with Xm and Xp). Therefore, we used statistical analysis and some data mining techniques to reveal patterns of genes responsible for TS. Here, we used the peripheral blood mononuclear cell (PBMC) microarray dataset GSE46687 created by Bondy et al. to perform a genome-wide gene expression analysis to investigate the differentially expressed genes (DEGs) between monosomy X TS patients and normal female 46,XX individuals to understand postnatal differences. Our results will contribute to our understanding of the

genetic etiology of TS and provide new insights into the clinical diagnosis and treatment of TS.