# [X chromosome gene dosage as a determinant of congenital malformations and of age-related comorbidity risk in patients with Turner syndrome, from childhood to early adulthood.](https://www.ncbi.nlm.nih.gov/pubmed/30991358)

Fiot E, Zénaty D, Boizeau P, Haignere J, Dos Santos S, Léger J; French Turner Syndrome Study Group.

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**Take Home Points:**

* Turner syndrome (TS) patients with 45, X karyotype are most likely to have congenital heart disease when compared with other karyotypes
* TS mosaicism patients were less likely to develop comorbidities as they got older when compared with other karyotypes.
* Patients with a ring X chromosome were more prone to metabolic disorders.
* It is possible that X gene chromosome dosage, particularly for Xp genes, contributes to the risk of developing acquired comorbid conditions.



**Commentary by Dr. Maan Jokhadar (Atlanta), section editor of ACHD Journal Watch:** Turner syndrome (TS) as a condition in which all or part of one X-chromosome Is absent from some or all cells. TS occurs in about 1/2500 live born girls. TS is associated with congenital cardiac and renal malformations. In addition, TS is associated with increased risk of hearing loss and metabolic disease that includes obesity, dyslipidemia, hypertension, abnormal glucose metabolism, and liver dysfunction. An increased risk of autoimmune thyroid disease and celiac disease is also observed. Certain TS karyotypes may increase the associated risk of both congenital and acquired conditions.

Dr. Elodie Fiot and colleagues from France conducted a national, multi-centered, observational study that included all patients with Turner syndrome diagnosed before January 2013 and followed at participating pediatric and adult centers from the French national rare disease network (the French Turner syndrome study group). The prevalence of congenital malformations and the cumulative incidence of subsequent comorbidities was evaluated at five-year intervals, from the ages of 10 to 30 years. The median age was 9.4 years at initial evaluation and 16.8 years at last evaluation with a median follow-up of 4.1 years. This was a young cohort with only about 12% over the age of 30 years at last evaluation.

The TS karyotype associations with congenital malformations were as follows:

* 45, X (n= 549, 36%): cardiac malformations were present in 27% and renal malformations in 22%
* 45, X /46, iso-chromosome Xq (n= 280, 19%): cardiac malformations were present in 12.5% and renal malformations 18.9%
* Ring X chromosome 46, X, r(X)/ 46, XX (n= 106, 7%): cardiac malformations were present in 17% and renal malformations 20.8%.
* 45, X /46, XX Mosaic karyotype (n= 221, 15%): cardiac malformations were present in 13.1% and renal malformations 11.3%.
* Presence of Y chromosome (n= 87, 6%): cardiac malformations were present in 21.8% and renal malformations in 10.3%.
* Other (various mosaicism with triple X, variable Xp for Xq deletions, and various complex rearrangements or translocations within an X chromosome) (n= 258, 17%): cardiac malformation were present in 13.2% and renal malformations in 10.5%.

There were 35 patients with unknown karyotype who were excluded from the study.

Congenital cardiac malformations were more common with 45, X compared with other karyotypes.

As one would expect, TS patients acquired comorbid medical conditions, such as hearing loss, metabolic disease, and autoimmune disease as they got older. However, patients with TS mosaicism were less likely to develop comorbidities when compared with other karyotypes.

This study showed a lower prevalence of comorbidities in TS with 45,X/46,XX mosaicism or TS with a Y chromosome when compared with TS patients with a ring X chromosome or with a 45,X/46,isoXq or 45,X karyotype. This may underscore the role of X chromosome dosage in the occurrence of comorbidities in TS patients.

Patients with a ring X chromosome were more prone to metabolic disorders.

A plausible explanation for these findings is that X chromosome gene dosage influences TS associated conditions and results in higher risk of comorbid conditions in patients with the 45,X, 45,X/46,isoXq and 46,X,r(X)/46,XX karyotypes and a lower risk in patients with mosaic karyotypes, such as 45,X/46,XX or XY mosaic karyotypes, suggesting an important role of Xp genes.

This study adds to the understanding of the age-related increase in the incidence of acquired comorbidities and the relationship between the prevalence of congenital malformations, acquired diseases and karyotype subgroups in TS.

This was a large study but cohort was young and additional studies in older TS patients are needed.