

Do we need a new look in the definition of X-linked recessive disorders?

Precisamos ter uma nova visão da definição das desordens recessivas ligadas ao X?

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The molecular revolution has changed permanently the practice of Medicine¹. Nowadays, we are frequently faced with the challenge of identifying specific gene mutations when patients are seen, in order to confirm or to clarify a suspected diagnosis². We have changed disease classification schemes to accommodate differences in their genetic bases³, and more recently we have developed therapeutic protocols based on differences in gene signature⁴. However, little has changed in the past decades regarding the complex relationship between modern molecular genetics concepts and the definition of X-linked inheritance⁵.

In fact, the concept of X-linked disorder we use today was proposed in the beginning of the 20th century and has changed very little⁶. The early concepts of dominance and recessiveness were first used for autosomal traits and, subsequently, they were somewhat adapted for the X-linked traits in order to define X-linked recessive and X-Linked dominant inheritance⁷. However, based on clinical experience with several X-linked disorders, it becomes clear that this concept needs revision⁵.

The paper written by Lourenço et al.⁸ explores this issue in the context of an X-linked recessive disorder, adrenoleukodystrophy, in which heterozygous females were previously believed to be clinically unaffected or to have a very mild phenotype⁹. This would be expected since in an X-linked recessive inheritance: males are predominantly affected; all their phenotypic healthy daughters are heterozygous; the mother of an affected male is heterozygous; among sons of heterozygous women, there is a 1:1 ratio between affected and unaffected; and one would only observe affected females if these were homozygous for the recessive allele¹⁰.

The X and Y chromosomes, which are responsible for gender determination, are unevenly distributed between men and women. Therefore, the phenotypes determined by genes located on the X chromosome have a characteristic gender distribution and a peculiar pattern of inheritance. Men have only one X chromosome, while females have two, therefore there are two possible genotypes in men and three in women with respect to an allele in the X chromosome. A man with a mutant allele in a locus on the X chromosome is hemizygous for that allele, while a woman can be homozygous for the wild type allele, homozygous the mutant allele, or heterozygous (one wild type allele and one mutant allele)¹¹. For that reason, to assure there is no gene dosage difference between men and women, a normal physiological process occurs, the X-chromosome inactivation, in which an X chromosome is inactivated in somatic cells of normal women, thereby equalizing the expression of most genes linked to the X chromosome in both sexes¹¹. In normal female cells, the choice of which X chromosome will be inactivated is random, and it is maintained in each cell line derived, thereafter¹².

Females are mosaics for two-cell lines, one with the maternal X and one with the paternal X as the active chromosome¹². The clinical relevance of X chromosome inactivation is profound, thus depending on the pattern of random inactivation of the X chromosomes, two females who are heterozygous for an X-linked disease may present very different clinical conditions, since they differ in the ratio of cells having the mutant allele on the active X chromosome.

By definition, a "dominant" or "recessive" pattern of X-linked inheritance is distinguished based on the phenotype presented by the heterozygous females; therefore, it becomes evident the type of difficulties one may face when trying to study patterns of clinical presentation in

heterozygous female patients. Women who are heterozygous for the mutant allele may present, or not, the disease phenotype depending on the random pattern of X chromosome inactivation she carries¹². This fact has prompted some authors to recommend that the use of the terms X-linked recessive and dominant be discontinued and simple replace by “X-linked” inheritance⁶.

At this point, the use of X chromosome inactivation tests is not current in clinical practice and may represent an additional diagnostic problem, since there are many variables that need to be considered in such analysis¹³. Therefore, as very well stated by Lourenço et al.⁸, extra caution should be taken when evaluating female carriers of X-linked recessive disorder.

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