The X chromosome: does it have a role in Bloom syndrome, a genomic instability disorder?

Deniz Aslan
Division of Hematology, Department of Pediatrics, Gazi University Faculty of Medicine, Ankara, Turkey.
E-mail: drdagutf@ttmail.com, daslan@gazi.edu.tr


The Bloom syndrome, caused by mutations in a single gene [BLM (15q26.1)], is a rare genomic instability syndrome. Despite its autosomal recessive transmission, it shows a male dominance, suggesting the possibility of a subgroup with X-linked recessive inheritance. In view of the latest molecular developments achieved in the other genomic instability syndromes, the potential functions of the X chromosome in maintaining genomic stability, and particularly, the first clues of Bloom syndrome development by mechanisms other than the BLM, we suggest herein that the X chromosome should be investigated in Bloom syndrome.

Key words: Bloom syndrome, male dominance, autosomal recessive, X chromosome, genomic stability.
new proteins have been identified (MM1 and MM2) that provide a functional connection between the pathways disturbed in BSyn and Fanconi anemia (FA), another genomic instability syndrome, and cause a disease phenotype. The gene encoding these proteins is *FANCM* (14q21.2). As another non-*BLM* mechanism, prior to the epigenetics or RNA-related causes with no gender predilection, the X chromosome may be a potential candidate in the etiology of BSyn, as suggested by the following: 1) According to the latest data from the Genetics Home Reference, although it is one of the 24 types of chromosomes (22 autosomes, X chromosome, Y chromosome), the X chromosome contains at least 10% of the total genes in the human genome, and those genes cause a broad spectrum of diseases, including genomic instability disorders, and 2) A gene located on the X chromosome (mus309) and functioning in DNA-double-strand break repair in other species (*Drosophila melanogaster*) has also been defined. Further, a human Xq13 gene, encoding a putative helicase, has been cloned and characterized.

The possibility of a new gene on the X chromosome responsible for BSyn has been suggested previously. However, there has been no prior clue for searching the X chromosome in this regard. On the other hand, over the same time frame, a number of new genes that are defective in two other major chromosomal instability syndromes, FA and dyskeratosis congenita (DC), have been defined. At present, the number of FA genes has risen to 16 [FANCA (1996), FANCB (2004), FANCC (1992), FANCD1 (BRCA2, 2002), FANCD2 (2001), FANCE (2000), FANCF (2000), FANCN (2011)*, FANCO (RADSIC, 2010)*, FANCP (2011)*, and ERCC4 (2013)*] following the addition of three new genes (identified with superscript asterisk) with the addition of four new genes (identified with superscript asterisk) [13,14]. Interestingly, in both syndromes, there are disease-causing genes on the X chromosome (FANCB- Xp22.31 and DKC1- Xq28, respectively). The proteins encoded by these genes (UniProt Q8NB91 and dyskerin, respectively) maintain genomic integrity via several mechanisms. By describing these particular genes, it became possible to explain some previously unexplained clinical features, as well as the clinical variety of each syndrome. For example, by description of FANCB, the male dominance in FA, the other AR-inherited genomic instability disorder, could be explained (~80 years after the initial description of the disease: 1927-2004), and by observation of female patients lacking X inactivation in DC, which was known as an X-linked recessive disorder, the AR and autosomal dominant (AD) forms of DC were described (~80 years after the initial description of the disease: 1910-1998). We believe that in order to provide similar developments in BSyn, the time has come to divert attention to the X chromosome. The most appropriate first step in this research might be the investigation of the X chromosome in the nine patients in the registry publication in whom no BSyn-causing mutations in *BLM* could be detected (however, as the gender of these cases was not declared, male gender is not definite). The X chromosome should be studied in all affected individuals, registered or non-registered, specifically in males, in whom no *BLM* mutation(s) were identified. This approach may help to unravel at least one unknown aspect of BSyn. It is hoped that researchers will not await the description of new cases (especially new cases with molecular confirmation) to explore this issue, since this is a very rare clinical entity and the accumulation of new cases could extend over years.

In conclusion, although a relation between BSyn and the X chromosome was suggested previously, there is nothing in the literature to indicate that an initiative on the subject has been undertaken in the past four years (i.e., there has been no study either proving or disproving this hypothesis). This raises the question of whether the target groups, namely the researchers, have been reached. With this paper, we wish to re-emphasize the subject and, through you, bring it to the attention of those researchers with large patient populations and advanced genetic laboratory facilities.

The topic of this paper is novel in that it
provides the readers an opportunity to compare the molecular developments achieved in the other genomic instability syndromes and (not) achieved in BSyn since the first publication. This comparison, along with the “potential functions of the X chromosome in maintaining genomic stability” and particularly, the “first clues of BSyn development by mechanisms other than the BLM gene”, points to the necessity of investigating the X chromosome in BSyn, i.e., an AR transmitted disorder with male dominance.

*: The genes identified by asterisk were defined after 2009. Of note, the first publication suggesting new gene(s) in BSyn was also in 2009.12

REFERENCES