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

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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.

Bloom syndrome (BSyn), first described in 1954, is a genomic instability syndrome characterized by short stature, sun-sensitive skin changes, and increased risk of cancer[1]. After the establishment of a registry for this rare disorder in 1960[2] and the accumulation of data and biological materials, striking improvements have been achieved with regard to many aspects of the disease. The comprehensive data collected from the registry were shared in the medical literature in 2007 through the publication of a significant article[3]. In that article, the latest information about the defective gene and the disease-causing mutations in this gene was presented. According to current knowledge, including this backbone study, the only known defective gene in BSyn is *BLM* (on chromosome 15; 15q26.1)[4]. *BLM* encodes a protein, a member of the RecQ family of helicases, which plays a pivotal role in DNA repair and recombination[5]. When *BLM* is mutated, along with multiple developmental abnormalities, striking DNA repair defects and genomic instability in the somatic cells occur, leading to predisposition to the development of cancers[6]. The identified mutations in *BLM* are in homozygous and compound heterozygous forms, and as single gene mutations rarely. In the published single gene-mutated cases with this autosomal recessive (AR) disorder, the possibility of additional, as-yet-unidentified mutations has been suggested. There are also reports of individuals in whom no BSyn-causing mutations of *BLM* were detected, and these cases were also suggested as having not-yet-identified mutations. In the six years since the above-mentioned publication, no new publication of the registry has been presented, and there have been no new data regarding the disease-causing gene(s). The focus of the other occasional studies published over this period has also been the known gene, namely *BLM*, and efforts are underway to develop new molecular techniques for detecting the unknown mutations in this gene [e.g., 7]. None of the publications, whether registry-originated or not, has reported information regarding any search for a novel gene in BSyn, despite the fact that the disorder has a remarkable clinical characteristic that cannot be explained by the defined gene, i.e. male dominance despite being an AR disorder (male ~53% and female ~47%, according to data from the Bloom Syndrome Registry of 2009). This clinical feature suggests the presence of a gene other than *BLM*, specifically a gene on the X chromosome. In fact, recent developments at the molecular points of the disorder suggest the possibility of BSyn development by mechanisms other than *BLM*. In this regard,

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[8]. 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 References, 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[9], 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[10]. Further, a human Xq13 gene, encoding a putative helicase, has been cloned and characterized[11].

The possibility of a new gene on the X chromosome responsible for BSyn has been suggested previously[12]. 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), FANCG (2000), FANCI (2007), FANCJ (BRIP1, 2005), FANCL (2003), FANCM (2003), FANCN (PALB2, 2007), FANCO (RADSIC, 2010)*, FANCP (2011)*, and ERCC4 (2013)*] following the addition of three new genes (identified with superscript asterisk), while the number of DC genes has reached 10 [DKC1 (1996), TERC (2004), TERT (2005), NOP10 (2007), NHP2 (2008), TINF2 (2008), USB1 (2012)*, TCAB1 (2011)*, CTC1 (2012)* and RTEL1 (2013)*] 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)[15,16]. 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[3] 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

1. Bloom D. Congenital telangiectatic erythema resembling lupus erythematosus in dwarfs; probably a syndrome entity. Am J Dis Child 1954; 88: 754-758.
2. Bloom's Syndrome Registry. http://www.rarediseases.org/rare-disease-information/organizations.
3. German J, Sanz MM, Ciocci S, et al. Syndrome-causing mutations of the BLM gene in persons in the Bloom's Syndrome Registry. Hum Mutat 2007; 28: 743-753.
4. German J, Roe AM, Leppert MF, Ellis NA. Bloom syndrome: an analysis of consanguineous families assigns the locus mutated to chromosome band 15q26.1. Proc Natl Acad Sci 1994; 91: 6669-6673.
5. Ellis NA, Groden J, Ye TZ, et al. The Bloom's syndrome gene product is homologous to RecQ helicases. Cell 1995; 83: 655-666.
6. Payne M, Hickson ID. Genomic instability and cancer: lessons from analysis of Bloom's syndrome. Biochem Soc Trans 2009; 37: 553-559.
7. Amor-Guéret M, Dubois-d'Enghien C, Laugé A, et al. Three new BLM gene mutations associated with Bloom syndrome. Genet Test 2008; 12: 257-261.
8. Deans AJ, West SC. FANCM connects the genome instability disorders Bloom's syndrome and Fanconi anemia. Mol Cell 2009; 36: 943-953.
9. X chromosome-Genetics Home Reference. http://www.ghr.nlm.nih.gov/chromosome/X. Reviewed January 2012. Published November 19, 2013.
10. Portin P. mus309 mutation, defective in DNA double-strand break repair, affects intergenic but not intragenic meiotic recombination in Drosophila melanogaster. Genet Res 2005; 86: 185-191.
11. Stayton CL, Dabovic B, Gulisano M, et al. Cloning and characterization of a new human Xq13 gene, encoding a putative helicase. Hum Mol Genet 1994; 3: 1957-1964.
12. Aslan D, Ezgu FS. The gene of Bloom's syndrome: an autosomal recessive disorder with male dominance. Genet Test Mol Biomarkers 2009; 13: 443-444.
13. GeneReviews™ [Internet]. Fanconi Anemia. Blanche P Alter, MD, MPH, FAAP and Gary Kupfer, MD. Initial Posting: February 14, 2002; Last Revision: February 7, 2013.
14. Walne AJ, Vulliamy T, Kirwan M, et al. Constitutional mutations in RTEL1 cause severe dyskeratosis congenita. Am J Hum Genet 2013; 92: 448-453.
15. Meetei AR, Levitus M, Xue Y, et al. X-linked inheritance of Fanconi anemia complementation group B. Nat Genet 2004; 36: 1219-1224.
16. Heiss NS, Knight SW, Vulliamy TJ, et al. X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions. Nat Genet 1998; 19: 32-38.