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Commentary

Understanding complexity of Fanconi anaemia

Fanconi anaemia (FA) is a clinically heterogeneous disorder with incidence of 1 in 350,000 births and is characterized by bone marrow failure (aplastic anaemia), developmental delay, physical abnormalities and increased incidence of solid tumours and leukaemias[1,2]. It shows either autosomal or X-linked recessive mode of inheritance. The older patients are at increased risk for squamous cell carcinoma of the head and neck and genitourinary tract. Although an exact mechanism for the FA pathway has yet to be elucidated, it seems to function in sensing DNA damage and repair. The role of FA pathway in cell signaling in response to stress stimuli and in apoptosis is well known[2]. So far, 16 genes (*FANCA*, *B*, *C*, *DI/BRACA2*, *FANCD2*, *E*, *F*, *G*, *I*, *J*, *L*, *M*, *N/PALPB2*, *FANCO/RAD51C*, *FANCP/SLX4* and *FANCQ*) have been identified that can be mutated in FA[3]. When DNA damage occurs, the eight FA proteins, A,B,C,E, F, G, L and M that form nuclear core complex at upstream of the pathway monoubiquitinate two other FA proteins FANCD2 and FANCI, resulting in targeting of FANCD2 protein in nuclear foci[4]. FANCD2 (Fanconi anaemia complementation group 2) then interacts with BRCAI and other DNA damage response proteins downstream of the FA pathway such as BRCA2, RAD51 and NBA and repairs the damage[5]. Mutation in the genes at upstream of the FA/BRCA pathway disrupts the pathway and results in non-ubiquitinated FANCD2 protein in the Western blot[6].

The diagnosis of FA can be done by cytogenetic testing for the increased chromosomal breakages or rearrangements in presence of DNA inter-stand cross-linking agents such as diepoxybutane (DEB) or mitomycin C (MMC) in bone marrow or blood cells. However, molecular analysis is still required for characterization of FA patients and demonstrating pathogenic mutations in the FA genes. Various molecular techniques like multiplex ligation-dependent probe amplification (MLPA) for detection of large deletions, for detection of common point mutations and polymorphisms, high resolution melt (HRM) technique with compatible real-time detection machine followed by confirmatory direct sequencing, direct sequencing for amplified gene regions of genomic DNA or cDNA made from RNA can be used for FANC gene molecular changes. More important is to understand the role of different proteins in Fanconi anaemia pathway. Molecular diagnosis of FA is challenging because of genetic heterogeneity associated with the disease.

In this issue, Moghadam and colleagues from Iran[7] have claimed that HRM (high resolution melting curve) analysis is simpler and more cost-effective than the MLPA procedure. But, the drawback in their investigation is that they have not complemented their 27 patients. In total, six sequence alterations in their study were identified which included two stop codons, two frame-shift mutations, one large deletion and one amino acid exchange. Therefore, their data are not sufficient to pin point the precise defect in FA pathway. Elucidation of the intricacies of the FA pathway will ultimately allow more individualized and efficacious treatment of FA patients and may provide insights into other cancer susceptibility disorders. The interesting findings of this study[7] like absence of congenital abnormality of the kidneys in Iranian patients is worth investigating in FA patients at molecular level.

FA proteins are known to play an important role in DNA damage repair. The phenotype-genotype correlation is the ultimate end for individualistic treatment in these cases. It has become clear from the previous research work that FA-D1 patients are at significant and early risk of progression to AML[8,9].

This is also important from the point of view of stem cell transplant[10]. Among all complementation groups, FAA accounts for the majority of FA patients (60-65%) followed by FAC (10%) and FAG (9%)[11].

Literature available from Asia Continent suggests *FANCA* to be most frequently affected gene among Indian origin Fanconi anaemia patients[11,12]. First reported FA case from India was with novel large intragenic deletion (exons 8-27 del) in the *FANCA* gene using MLPA[11-13]. Moreover, some unpublished data from India (personal communication) also support the prevalence of FAA complementation group. However, reports from eastern Asian countries like Korea and Japan suggest different scenario for FANC genes in Fanconi anaemia. Genotyping study has suggested that mutations in *FANCA* and *FANCG* are common in Korean FA patients[14]. They also proved existence of four common founder mutations in an East Asian FA population, two *FANCA* mutations (c.2546delC and c.3720_3724delAAACA) and two *FANCG* mutation (c.307+1G>C and c.1066C>T), which had previously been commonly observed in a Japanese FA population[15]. The same authors detected four novel deleterious mutations observed in a Japanese FA population, c.2778+1G>C, c.3627-1G>A, c.1589_1591delATA and c.1761-1G>A of *FANCG*. In Japanese population most commonly affected FANC genes are *FANCA* and *FANCG*, as reported earlier[15].

Hence, molecular screening in Fanconi anaemia should be prioritized as per frequency of mutated FANC genes amongst specific population under study and suitable molecular technique should be employed to find nature of molecular changes. This can help expand our knowledge towards genotype-phenotype relationship in Fanconi anaemia disorder, where heterogeneity makes the cause obscure.

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