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Review paper

FANCA AND CONTRIBUTION OF STUDIES FROM ASIAN POPULATIONS TO THE UNDERSTANDING OF FANCA MEDIATED FANCONI ANEMIA

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Fanconi anemia (FA) is a recessive disorder known to cause hematological and several congenital deformities in affected individuals worldwide. Out of 22 known FA causative genes, mutations in Fanconi Anemia Complementation Group A (FANCA) accounts for 60%-70% of FA cases. FANCA is a multi-functional protein essential for genome integrity. Although many physiological roles of FANCA have been delineated but exact etiopathomechanism of FANCA in FA phenotype is yet to be elucidated. FANCA is a hypermutable and highly polymorphic gene therefore identification and interpretation of mutations implicated in recessively inherited FA can fill gaps in existing knowledge of molecular mechanisms. This review is divided into two sections. The first section described known functions of FANCA important for genomic integrity perpetuation. The second part summarized all mutations of FANCA gene reported in FA patients from Asian populations on the basis of literature published till March 2019. It provides an overview of strategies used for these mutations identification, mutation hot spots for specific Asian populations and necessitates the need of extensive global as well as regional molecular genetics research efforts mainly in less explored inbred Asian countries to formulate diagnostic and targeted therapeutic measures.

Keywords: Asian population, Fanconi anemia, FANCA, mutations

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INTRODUCTION: FANCA – A CARETAKER OF THE GENOME

Fanconi anemia (FA) is a rare genome instability disorder which occurs due to mutation/s in any one of 22 FA genes (KNIES *et al.* 2017; KIMBLE *et al.* 2018). FA proteins regulate DNA inter-strand crosslink repair hence regarded as caretakers of genome. They can be classified based on each one's role in canonical inter-strand crosslink repair pathway into three groups i.e. core complex, ID complex and downstream protein associations. Fanconi Anemia Complementation Group A (FANCA), is a member of group 1 which constitute core complex and consists of eight FANC proteins (FANCA-C, E-G, L and M) along with three Fanconi Anemia Associated Proteins (FAAP 20, 24 and 100), (MEDHURST *et al.*, 2006; LING *et al.*, 2007; ALI *et al.*, 2012; YANG *et al.*, 2013; CASTELLA *et al.*, 2015; PALOVCAK *et al.,* 2017a). FANCA is a multi-functional protein and many physiological roles have been delineated such as involvement in FA/BRCA1 pathway for repairing of inter strand cross-links (ICLs), homologous recombination (HR) and coordination with other defective DNA damage repair events like trans-lesion synthesis (TLS) and nucleotide excision repair (NER), (SRIDHARAN *et al.*, 2003; NIEDZWIEDZ *et al.*, 2004; MOLDOVAN *et al.*, 2009). FANCA gene is located at q24.3 arm of chromosome 16, contains 43 exons that encodes1455 amino acids (aa) protein with a molecular weight of 163 k Da (TEN FOE *et al.*, 1996; IANZANO *et al.*, 1997). FANCA protein contains several important domains and motifs as summarized below and shown in Figure 1. These include:

a) A bipartite Nuclear Localization Signal (NLS) consensus sequences spans 17 residues (18-34 aa) at amino terminal of protein (LIGHTFOOT *et al.*, 1999; WAISFISZ *et al.*, 1999).
b) A putative peroxidase site spans 12 residues (274-285 aa) (REN *et al.*, 2001).
c) A partial leucine zipper region is located between 1069-1090 aa (TEN FOE *et al.*, 1996).
d) Five functional Nuclear Export Sequences (NES) are spanning amino acids 54-80, 263-284, 518-534, 860-880 and 1013-1043 of FANCA protein (FERRER *et al.*, 2005).

The 1-589 amino acids region of FANCA mediates interaction with central part of BRCA1 protein (FOLIAS *et al.*, 2002) (Figure 1). Other important binding sites of FANCA protein includes a 12aa region spanning from residue 18-29 and a 105aa region spanning from residue 1095-1200 for FANCG and FAAP20 protein respectively (ALI *et al.,* 2012). A serine residue at position 1149 is a site for phosphorylation by Akt (a serine/threonine kinase) which is required for FA proteins assembly and functions (OTSUKI *et al.* 2002a). At the C-terminal, phosphorylation of FANCA on serine 1449 by ATR-CHK1 is important for formation of nuclear complex (COLLINS *et al.*, 2009).

There is a growing myriad of FANCA interacting proteins each having a role in different mechanism. For example interaction of FANCA with alpha spectrin II (αIISP) is required to act as scaffold protein in FA repair activities (MCMAHON *et al.*, 1999), with MUS81–EME1 complex for repair of DNA ICLs (BENITEZ *et al.*, 2013), with FEN1 for stabilizing the replication machinery while working on lagging strand (QIAN *et al.*, 2013a; QIAN *et al.*, 2013b; PALOVCAK *et al.*, 2017a), with HES1 for stabilizing the core complex members (TREMBLAY *et al.*, 2008), IκB Kinase-2 (IKK2) interaction for cellular stress response signaling pathway (OTSUKI *et al.*, 2002b), and with sorting nexin 5 (SNX5) for translocation between organelles (OTSUKI *et al.*, 1999). FANCA may engages with BRG1(Brahma-related gene 1) to alleviate the effects of ROS by enhancing the binding ability of BRG1 with antioxidant gene promotors (OTSUKI *et al.*, 2001), with NEK2 to preserve centromere integrity, and with CENP-E for chromosomal alignment at the spindle equator and congregation during mitosis (DU *et al.* 2009). The C-terminal of FANCA

is involved in DNA binding and may have a role in genome stability as 90% of disease causing point mutations are located in this region (YUAN *et al.*, 2012).

FANCA harbors a large number of molecular alterations and polymorphism thus considered as hypermutable and highly polymorphic gene (TEN FOE *et al.*, 1996; MORGAN *et al.*, 1999; WIJKER *et al.*, 1999a; FERRER *et al.,* 2005).To date, FANCA mutations are reported in 60%-70% of FA case (SELENTI *et al.* 2015). To evolutionarily aspect, FANCA is not conserved and it remains enigmatic how FANCA is participated in various biological events (HUANG *et al.*, 2014).

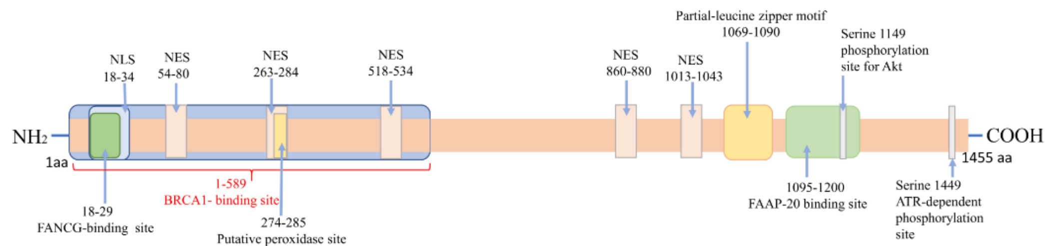

Fig. 1. Schematic diagram of all known structural and functional sites ofFANCA protein:Amino terminal of FANCA protein harbors a bipartite nuclear localization signal (NLS, 18-34 aa) with overlapped FANCG binding site (18-29 aa) and BRCA1-binding site (1-589 aa).Carboxyl terminal of FANCA polypeptide contains a putative oxidase site (274-285 aa), a partial leucine zipper motif (1069-1090 aa) followed by FAAP-binding site (1095-1200 aa), a 1149 serine phosphorylation site for Akt and 1449 serine ATR-dependent phosphorylation site. Nuclear export signals (NES) are scattered throughout the polypeptide chain.

Established functions of FANCA

Regulations of MUS81–EME1 endonuclease activity

Presence of ICLs in the DNA, halts replication and transcription that are inevitable for cell survival (AKKARI *et al.*, 2000; RÄSCHLE *et al.,* 2008). FANCA protein has the ability to recognizing ICLs and triggers the subsequent cascade of proteins to resolve the damage. In vitro study of Benitez and his colleagues have shown that on the stalled replication fork or ICL sites, FANCA recruits the heterodimer MUS81–EME1 complex that subsequently incises at the 3' side of the leading strand (BENITEZ *et al.*, 2013). Interestingly, FANCA protein acts both as activator/enhancer or inhibitor of MUS81–EME1 because various studies elucidate that upon encountering the ICL damages, MUS81- EME1 activated and recruited by FANCA for potent and delicate ICL incision (BENITEZ *et al.*, 2013). Furthermore**,** it has been demonstrated that MUS81-EME1 also resolves Holliday junction, the final step of FA pathway in damage repairing (HOLLINGSWORTH *et al.* 2004; KIM *et al.,* 2013). In addition, FANCA regulates XPF-ERCC1 activity by colocalizing with them for efficient ICL incision (KURAOKA *et al.*, 2000; FISHER *et al.,* 2008; LARIN *et al.*, 2014). Current evidences suggest that XPF–ERCC1 nuclease has a primary role in resolving ICL lesions and MUS81–EME1 has collateral role in circumstances where XPF–ERCC1 is not involved. Cumulatively, all these processes necessitate intrinsic

binding ability for DNA that resides at the C-terminal whereas affinities for other proteins are found in the N-terminal of FANCA protein.

Interaction of FANCA/XPF/Alpha II Spectrin factors

Alpha II Spectrin (αIISP) a structural protein that associates with the nuclear matrix may involve in genome preservation as it is co-immunoprecipitation with FANCA and XPF–ERCC1 (SRIDHARAN *et al.*, 2003). FANCA colocalize with XPF–ERCC1, which is essential for nucleotide excision repair (NER) pathway (KOEHLER *et al.*, 1996; BALAJEE *et al.* 1998; TORGOVNICK *et al.*, 2015). These observations points that αIISP acts as a scaffold that during the incision step of ICL repair may assists in proper assembly and recruitment of ICL resolving factors i.e., XPF–ERCC1 and FANCA. Moreover, FA proteins i.e., FANCA/B/C and D2 deficient cell lines also exhibit decreased levels of αIISP compared with normal cells (MCMAHON *et al.*, 2001). Studies have also revealed that in addition to FANCA, αIISP also makes association with FANCC and FANCG while the exact role is still unclear (MCMAHON *et al.*, 1999; LEFFERTS *et al.*, 2008). Furthermore, It has been proposed that FANCA and FANCG make association with the SH3 domain of αIISP preventing its degradation by a protease μ-calpain that cleaves αIISP at Tyr1176 with in repeat 11 (LEFFERTS *et al.,* 2008; ZHANG *et al.,* 2010). Zhang Pan and colleagues have been deciphered that FANCG and FANCA complex are also associate with μ-calpain protease, blocking its cleavage activity and allowing normal αIISP levels to persist and accomplish its roles in DNA damage repair pathways and therefore, the loss of any FA proteins would then cause over expression of μ-calpain and overactive degradation of αIISP resulting in genome instability (ZHANG *et al.*, 2010). Thus, the potent interaction between αIISP and FANCA to enhance the incision efficiency of XPF–ERCC1 suggest DNA damage repair role of αIISP.

Affection of FANCA and FEN1

DNA replication, damage repair and recombination are indispensable for preserving the integrity of genome. Flap endonuclease-1 (FEN1) is important in this regard (LIEBER, 1997; TOMLINSON *et al.*, 2010). It is a metallonuclease and belongs to Rad2 nuclease family. Structurally, FEN1 comprises two dsDNA-binding sites and a helical arch for ssDNA-binding (CHAPADOS *et al.*, 2004). Furthermore, it has been revealed that FEN1 has two other ‘minor’ activities, i.e., exonuclease (EXO) and gap-dependent endonuclease (GEN). These both activities (EXO and GEN) are required to mend secondary structures produced by (CTG)n and (GAA)n repeats (SINGH *et al.*, 2007; ZHENG *et al.*, 2010). FEN1 plays its role in processing of 5’ flapped structures during the long-patch base excision repair (BER) and Okazaki fragment maturation to rescue stalled replication forks (LIU *et al.,* 2004).

QIAN, *et al*. (2013) ascertained the important interaction of FEN1 and FANCA (QIAN *et al.*, 2013a). It has been considered that during Okazaki fragment maturation, FEN1 removes RNA primer when Polδ creates flap by displacing RNA: DNA primer (KUCHERLAPATI *et al.*, 2002; SHEN *et al.*, 2005; ZHENG *et al.*, 2007a; NAZARKINA *et al.* 2008). It has been speculated that FANCA and FEN1 may make an association with each other due to FEN1 stimulation by MUS81-EME1 in ICL repair (SHIN *et al.*, 2012; PALOVCAK *et al.*, 2017a). Recently, it has also been elaborated that FEN1 activity is stimulated by MUS81- EME1/2 which is involved in introducing nicks on inter-strand crosslinks and Holliday junction resolution (SHIN *et al.*, 2012).

Whereas MUS81- EME1 activity is regulated by FANCA thereby FANCA indirectly influence FEN1 (YUAN *et al.,* 2012; BENITEZ *et al.,* 2013). Consistent to this view, FEN1 and FANCA also accumulate at the replication bubble and manifest the same substrate specificity, i.e., 5' flap structures and single-stranded RNA (ssRNA), so FANCA may influence and enhances the FEN1 activity by recruiting or competing for its substrate (PALOVCAK *et al.*, 2017b). In support of this hypothesis, several other studies demonstrated that mutations in FEN1 impart somewhat similar phenotypes as seen in FANCA deficient predisposing to cancer and inflammation (KUCHERLAPATI *et al.*, 2002; ZHENG *et al.*, 2007b; BRIOT *et al.,* 2008; QIAN *et al.*, 2013a; DU *et al.*, 2014).

FANCA - a factor in resection mediated repair pathways

FANCA is a crucial factor for resection-mediated repair pathway. As Howard and his colleagues reported that there is a threefold reduction of GFP-positive FANCA null fibroblasts in an I-SceI based reporter assay, showing involvement of FANCA in promotion of homologous recombination (YANG *et al.*, 2005; HOWARD *et al.*, 2015). They revealed these cells restore expression of GFP at a DNA breaks sites when mended by homologous recombination. FANCA can also participate in single-strand annealing(SSA) pathway of repair under specific circumstances (YANG *et al.,* 2005). To mediate SSA, it may interact directly with two other proteins i.e., RAD52 that catalyzes the annealing step between homologous regions on resected ends at DSB and RAD59 which triggers the annealing activity of RAD52via unknown mechanism (FOLIAS *et al.*, 2002). Interestingly, various studies revealed that both FANCA and XPF/ERCC1 co-localize at ICL resolving site thereby promoting SSA when it takes place at a double ended DSBs (SRIDHARAN *et al.*, 2003; AL-MINAWI *et al.*, 2007). As in absence of FANCA the incisions ability of XPF is decreased, suggesting its stimulatory role on the XPF nuclease activity (KUMARESAN *et al.*, 2000).

Studies have ascertained that ICLs are repaired by FA factors and the FANCA have most prominent role in bypass of non-homologous end-joining mechanism (NHEJ) and promotion of alternative end-joining Alt-EJ (NAKANISHI *et al.,* 2005). Indeed, bypass of NHEJ is aptly crucial for both Alt-EJ and homologous recombination (HOWARD *et al.,* 2015). The suppression of NHEJ pathway, favors two types of HR; the conventional homology-directed repair pathway (HDR) and the non-conservative SSA pathway (PIERCE *et al.,* 2001; STARK *et al.,* 2004). Hence in the inactivation of NHEJ there is substantial increase in the rate of Alt-EJ, SSA and HDR repair pathways (BENNARDO *et al.,* 2008; HOWARD *et al.,* 2015). Finally, these findings suggested that the FA pathway is important for inhibition of NHEJ and FA-deficient cells can be salvaged by designing strategies for NHEJ disruption.

Other selective role of FANCA

Down regulation of reactive oxygen species

The most commonly found lesion produced by reactive oxygen species (ROS) is 8-hydroxydeoxy guanosine (8-oxodG)- a highly mutagenic element leading to transversion, typically, in GC-rich site of antioxidant gene's promotors, inducing lethal DNA damage if left unrepaired (GHOSH *et al.,* 1999; KLAUNIG *et al.,* 2010). Several studies have demonstrated that FA pathway in addition to DNA repair also protects from effect of ROS. Hence, ROS-induced oxidative DNA damage needs synchronization between the repair pathways. There is strong

evidence of involvement of FA proteins in oxidative DNA damage response significantly FANCA and FANCG that act as redox-sensor proteins (PARK *et al.,* 2004). Indeed, to respond oxidative stress, FANCD2 monoubiquitination and concurrently FANCA and FANCG interaction via disulphide linkage is required to form a multimeric nuclear complex suggesting their role in damage signaling pathways and DNA repair (PARK *et al.,* 2004). In addition, DNA damages by ROS in certain antioxidant genes for instance GPX1, GSTP1, GCLC and TXNRD1 leads to lethal conditions (DU *et al.,* 2012; PALOVCAK *et al.,* 2017a). It has been seen that FANCA involves in preservation of antioxidant gene promotors from ROS (DU *et al.,* 2012). Mechanistically, from FA proteins complex, FANCA engage with chromatin remolding protein BRG1(Brahma-related gene 1), enhancing the binding ability of BRG1 with antioxidant genes promotors and therefore subsequently alleviate the effects of ROS (OTSUKI *et al.,* 2001; PARK *et al.,* 2004; DU *et al.,* 2012). The BRG1-FANCA interaction depends on monoubiquitination of FANCD2 (PARK *et al.,* 2004; DE OCA *et al.,* 2005; DU *et al.,* 2012).

Regulation of the spindle assembly checkpoint

The spindle assembly checkpoint (SAC) is the tumor suppressor signaling system that mediates proper destruction of sister chromatid cohesion during mitosis to prevent aneuploidy and ensures high-fidelity chromosomal number (LARA-GONZALEZ *et al.,* 2012). As FA proteins interacts with CDK1 the key mitotic cyclin-dependent kinase which is involved in SAC (KUPFER *et al.,* 1997; D'ANGIOLELLA *et al.,* 2003; THOMPSON *et al.,* 2010). Therefore, consistent to this notion Nalepa and his colleagues using functional RNAi screens have demonstrated that FA pathway is also involved in the spindle assembly checkpoint of the mitotic apparatus in a cell cycle–dependent manner (NALEPA *et al.,* 2013). They found that several FA proteins such as FANC-A, B, E, G, L, D1, D2 and N localize to centrosomes during mitosis. Out of these FA proteins, FANCA and FANCC more specifically localize to the mitotic spindle (THOMPSON *et al.,* 2010; NALEPA *et al.,* 2013). Furthermore, Abdul-Sater, et al. (2015) revealed that FANCA mediates centrosome-associated spindle assembly and at mitotic entry translocate to the pericentriolar material to control spindle assembly (ABDUL-SATER *et al.,* 2015).

Another factor that is involved in chromosome alignment and the congregation during mitosis is CENP-E which directly interacts with N-terminus of FANCA (DU *et al.,* 2009; FOLEY *et al.,* 2009; GUDIMCHUK *et al.,* 2013). However, it is considered that alignment and assembly of chromosomes at the spindle equator are promoted by FANCA and CENP-E hence, preventing chromosomal dysfunction (PALOVCAK *et al.,* 2017b).

FANCA- a transcriptional modulator of HES1

Developmental abnormalities in FA patients not be solely due to DNA impairment while these developmental defects may be caused by deregulation of transcriptional factor such as hairy enhancer of split 1 (HES1) (TREMBLAY *et al.,* 2008; TREMBLAY *et al.,* 2009). HES1 is a Transcriptional repressor protein that involve in embryogenesis (mesoderm formation and differentiation) via Notch signaling pathway (KAGEYAMA *et al.,* 2007). Though Notch signaling mediates hematopoietic stem cell (HSC) self-renewal, while HES1 regulates integrity of progenitor cells/HSC, cell fate decisions and timing of various developmental processes (STIER *et al.,* 2002). Tremblay and his group by adopting Yeast-2-hybrid, mass spectrometry, immunofluorescence and co-immunoprecipitation technique ascertained a direct interaction of HES1 with some members of FA core complex (FANC-A, F, G and L) (TREMBLAY *et al.,* 2008).

They demonstrated that HES1-depleted cells failed to proper cellular localization of FANCA and FANCL and assembly of FA core complex (TREMBLAY *et al.,* 2009). Moreover, FA core complex precisely modulates HES1 transcriptional activity through up-regulation or repression of HES1-responsive genes i.e. by direct binding to the HES1 promotor and by preventing from binding of its co-repressor TLE (Transducin-like Enhancer of split) (GRBAVEC *et al.,* 1996; TREMBLAY *et al.* 2009). Consistent with all these observations significance of FANCA/HES1 and involvement of FA core complex in transcription regulation is elaborated. Nevertheless, deregulation of FA pathway leads several developmental defects (TREMBLAY *et al.,* 2009).

FANCA and IKK signalsome

IKK signalsome is a cellular stress response signaling pathway (DIDONATO *et al.,* 1997; MERCURIO *et al.,* 1999). Primarily IKK signalsome responds to cellular stress by regulating activity of transcriptional factor NF-κB, which also responds to reactive oxygen intermediates (ROI) signaling (H_2O_2, superoxide radicals and hydroxyl radicals) and DNA damage (MERCURIO *et al.*, 1999; OTSUKI *et al.,* 2002c). NF-κB, in turn, regulates the activity of genes for DNA repair, anti-apoptosis and redox-regulation (OTSUKI *et al,.* 2002c). Later on, OTSUKI *et al.,* (2002) proposed that IKK signalsome response to stress by two different pathways; (1) by modulating activity of transcriptional factor NF-κB and (2) by cross talking with FA pathway (OTSUKI *et al.,* 2002c). Through co-immunoprecipitation ascertained that IKK signalsome and IκB kinase-2 (IKK2), a component of multi-protein complex IKK signalsome are associated with FANCA (DIDONATO *et al.* 1997; OTSUKI *et al.,* 2002c). The C-terminal (amino acids 1090-1455) of FANCA required for interaction with IKK2 C-terminal domain (aa 50). They considered that interaction between FANCA and IKK2 may be respond to various stress signals included DNA damage, oxidative stress and pro-inflammatory cytokines (MERCURIO *et al.,* 1999; OTSUKI *et al.,* 2002c). Any disruption (mutation) in C-terminal of FANCA diminishes this interaction (OTSUKI *et al.,* 2002c). Conversely, disruption of IKK2 structure or function by mutation leads to increased hepatocyte apoptosis and ultimately death of embryo at mid-gestation (LI *et al.,* 1999).

SNX5- a Intracellular trafficking pass of FANCA

FANCA is found to be localized both in nucleus and cytoplasm of the cell (KRUYT *et al.* 1997; NÄF *et al.* 1998). Upon cellular stress, FANCA translocate from cytoplasm to nucleus for proper assembly of FA core complex. For translocation FANCA required a trafficking pass that is SNX5 (Sorting Nexin 5) (OTSUKI *et al.,* 1999). OTSUKI *et al.,* (1999) proposed that SNX5 protein factor associates with variety of receptors for intracellular trafficking (OTSUKI *et al.,* 1999). They determined that the central part (aa 451-900) of SNX5 is essential for directly interaction with C-terminal of FANCA and mediates in its intracellular translocation (OTSUKI *et al.,* 1999). Apparently, FANCA protein harbor a bipartite nuclear localization signals (NLS) at its N- terminal required for nuclear localization whereas interaction with SNX5 essential for cytoplasm localization (LIGHTFOOT *et al.,* 1999; OTSUKI *et al.,* 1999).

FANCA mutations in Asian population

To the best of our knowledge no comprehensive review has been published yet regarding FANCA mutations causing FA in Asian countries. As FANCA is reported to be responsible for about 60%-70% cases of FA (SELENTI *et al.,* 2015) and FA is inherited as autosomal recessive disorder. All autosomal recessive diseases are highly prevalent in inbred populations (FIRASAT

et al., 2017; AFZAL *et al.,* 2019) therefore Asian populations where consanguinity is customary have higher incidence FA. All the articles published till March, 2019 were assessed from www.ncbi.nlm.nih.gov/pubmed to extract data regarding mutations of FANCA gene including type of mutation, location of mutation, amino acid/protein change, population from where reported and study protocol. We identified 222 various types of FANCA mutations which are presented in Table 1 whereas Figure 2 shows frequency of each subtype of mutations in different Asian populations (Table 1 and Figure2). Country wise as well as exon wise distribution of all FANCA mutations detected in Asian countries is summarized in Figure 3 (Figure3). Some of these are concentrated in specific regions whereas some of them have been reported in various studies from different populations.

Table 1: The spectrum of FANCA mutation in Asian Population

Mutation Type	Exon/ Intron	Nucleotide change	Protein change	Detection methods	Country (References)
Missense	14	c.1273G>C	p.Asp425His	DS	India (VUNDINTI 2014a; SOLANKI et al. 2016)
	37	c.3679G>C	p.Ala1227Pro	DS	India (VUNDINTI 2014a; SOLANKI et al. 2016)
	40	c.3992 T>C	p.Leu1331Pro	DS	India (VUNDINTI 2014a; SOLANKI et al. 2016)
	41	c.4036G>A	p.Ala1346Thr	DS	India (SOLANKI et al. 2016), Netherlands (AMEZIANE et al. 2008a)
	27	c.2574C>G	p.Ser858Arg	DS	India (SOLANKI et al. 2016), Netherlands (WIJKER et al. 1999b), Israel (TAMARY et al. 2000a; TAMARY et al. 2004b)
	14	c.1303C>T	p.Arg435Cys	DS	India (SOLANKI et al. 2016), Japan(TACHIBANA et al. 1999b; ADACHI et al. 2002b; YAGASAKI et al. 2004a), Brazil (LEVRAN et al. 1997a)
	29	c.2851C>T	p.Arg951Trp	DS	India (SOLANKI et al. 2016), Netherlands (AMEZIANE et al. 2008a), USA (CHANDRA et al. 2005b; LEVRAN et al. 2005b)
	29	c.2786A>C	p.Tyr929Ser	-	India (ARTHUR et al. 2014)
	-	c.3678C>G	p.Ser1226 X	MLPA and DS	India (VUNDINTI 2014a)
	-	c.1274C > G	p.Glu425 His	MLPA and DS	India (VUNDINTI 2014a)

	40	c.4006T>G	p.Tyr1336Asp†	MLPA and NGS	Iran (NIA et al. 2016a)
	26	c.2444G>A	p.Arg815Gln	MLPA and NGS	Iran (NIA et al. 2016a)
	41	c. 4046G>C	p.Arg1349Thr	HRM and DS	Iran (MOGHADAM et al. 2016a)
	40	c. 3982A>G	p.Thr1328Ala	HRM and DS	Iran (MOGHADAM et al. 2016a), Japan (TACHIBANA et al. 1999b)
	30	c.2915G>T	p.Gly972Val+	MLPA and NGS	Iran (NIA et al. 2016a)
	42	c.4172A>G	p.Asn1391Ser	Sequencing	Pakistan (SHAHID et al. 2019a)
	42	c.4216T>G	p.Leu1406Val	Sequencing	Pakistan (SHAHID et al. 2019a)
	42	c.4226G>C	p.Arg1409Pro	Sequencing	Pakistan (SHAHID et al. 2019a)
	42	c.4239G>T	p.Lys1413Asn	Sequencing	Pakistan (SHAHID et al. 2019a)
	42	c.4252G>A	p.Val1418Met	Sequencing	Pakistan (SHAHID et al. 2019a)
	43	c.4291G>C	p.Glu1431Gln	Sequencing	Pakistan (SHAHID et al. 2019a)
	43	c.4311G>T	p.Gln1437His	Sequencing	Pakistan (SHAHID et al. 2019a)
	43	c.4321C>A	p.Gln1441Lys	Sequencing	Pakistan (SHAHID et al. 2019a)
	43	c.4328C>G	p.Ala1443Gly	Sequencing	Pakistan (SHAHID et al. 2019a)
	43	c.4348C>G	p.Gln1450Glu	Sequencing	Pakistan (SHAHID et al. 2019a)
	43	c.4316G>A	p.Arg1439Lys	Sequencing	Pakistan (SHAHID et al. 2019a)
	22	c.1927C>G	p.Pro643Ala	whole exome sequencing, DS	China (CHANG et al. 2014b) Japan (TACHIBANA et al. 1999b)
	32	c.3181A>G	p.Ser1061Gly	whole exome sequencing	China (CHANG et al. 2014b)
	32	c.3163C>T	p.Arg1055Try	SSCP, ARMS, Gene dosage assay and sequencing	China (CHANG et al. 2014b), Japan (NAKAMURA et al. 1999; ADACHI et al. 2002b; YAGASAKI et al. 2004a)
	24	c.2170A>C	p.Thr724Pro	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a)
	36	c.3581C>T	p.Pro1194Leu	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a)
	28	c.2602T>G	p.Phe868Val	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a)
	16	c.1475A>G	p.His492Arg	SSCP and ARMS	Japan (ADACHI et al. 2002b),Brazil (LEVRAN et al. 1997a)
	34	c.3350G>C	p.Arg1117Thr	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a)

	1	c.1A>G	p.Met1Val	DS	Japan (TACHIBANA et al. 1999b)
	20	c.1792G>A	p.Asp598Asn	SSCP and ARMS	Japan (ADACHI et al. 2002b)
	26	c.2450T>C	p.Leu817Pro	SSCP and ARMS	Japan (ADACHI et al. 2002b), Brazil (LEVRAN et al. 1997a)
	27	c.2534T>C	p.Leu845Pro	SSCP and ARMS	Japan (ADACHI et al. 2002b)
	32	c.3164G>T	p.Arg1055Leu	SSCP and ARMS	Japan (ADACHI et al. 2002b), Brazil (LEVRAN et al. 1997a)
	33	c.3329A>C	p.His1110Pro	SSCP and ARMS	Japan (ADACHI et al. 2002b), Europe (MORGAN et al. 1999b)
	34	c.3382C>G	p.Gln1128Glu	SSCP and ARMS	Japan (ADACHI et al. 2002b), Brazil (LEVRAN et al. 1997a)
	34	c.3391A>G	p.Thr1131Ala	SSCP and ARMS	Japan (ADACHI et al. 2002b), North European (LEVRAN et al. 1997a)
	38	c.3786C>G	p.Phe1262Leu	SSCP and ARMS	Japan (ADACHI et al. 2002b), Europe (MORGAN et al. 1999b)
	39	c.3904T>C	p.Trp1302Arg	SSCP and ARMS	Japan (ADACHI et al. 2002b), North European (LEVRAN et al. 1997a)
	40	c.3971C>T	p.Pro1324Leu	SSCP and ARMS, whole exome sequencing	Japan (ADACHI et al. 2002b) Europe (MORGAN et al. 1999b), China (ZHENG et al. 2013b)
	41	c.4075G>T	p.Asp1359Tyr	SSCP and ARMS	Japan (ADACHI et al. 2002b), Italy (SAVINO et al. 1997)
	41	c.4080G>C	p.Met1360Ile	SSCP and ARMS	Japan (ADACHI et al. 2002b), Europe (MORGAN et al. 1999b)
	42	c.4249C>G	p.His1417Asp	SSCP and ARMS	Japan (ADACHI et al. 2002b), Middle East (LEVRAN et al. 1997a)
	9	c.796A>GP	p.Thr266Ala	MLPA and DS	Japan (TACHIBANA et al. 1999b), India (VUNDINTI 2014a)
	14	c.1235C>TP	p.Ala412Val	DS	Japan (TACHIBANA et al. 1999b), China (CHANG et al. 2014b)

	26	c.2426G>A	p.Gly809Asp	MLPA and DS	Japan (TACHIBANA et al. 1999b), India (VUNDINTI 2014a)
	16	1501A>G	p.Gly501Ser	MLPA and DS	Japan (TACHIBANA et al. 1999b) India (VUNDINTI 2014a)
	25	c.2290C>T	p.Arg764Trp	WES	Japan (MORI et al. 2019a)
	27	c.2527T>G	p.Tyr843Asp	WES	Japan (MORI et al. 2019a)
	28	c.2723_2725TCT>GCC	p.LeuS908_909Arg	WES	Japan (MORI et al. 2019a)
	40	c.3965T>G	p.Val1322Gly	WES	Japan (MORI et al. 2019a)
	42	c.4198C>T	p.Arg1400Cys	WES	Japan (MORI et al. 2019a)
	42	c.4199G>C	p.Arg1400Pro	WES	Japan (MORI et al. 2019a)
	1	c.2T>C	p.Met1Thr	MLPA and DS	Turkey (ASLAN 2017a)
	8	c.1066C>T	-	MLPA and DS	Japan (MORI et al. 2019a) Korea (PARK et al. 2013b)
	8	c.755A>G	p.Asp252Gly	SSCP and ARMS	Saudi Arabia (LEVRAN et al. 1997a)
	8	c.732G>C	p.Leu244Phe	SSCP and ARMS	Saudi Arabia (LEVRAN et al. 1997a)
	43	c.4291G>C	p.E1431Q	sequencing	Pakistan (SHAHID et al. 2019a)
	1	c.24C>G	p.Asn8Lys	SSCP and ARMS	Saudi Arabia (LEVRAN et al. 1997a)
	6	c.542C>T	p.Ala181Val	SSCP and ARMS	Saudi Arabia (LEVRAN et al. 1997a)
Non-sense	24	c.2182C>T	p.Gln728Ter	DS	India (SOLANKI et al. 2016)
	28	c.2630C>G	p.Ser877Ter	MLPA and DS	India (VUNDINTI 2014a; SOLANKI et al. 2016)
	37	c.3677C>G	p.Ser1226Ter	DS	India (SOLANKI et al. 2016)
	32	c.3189G>A	p.Trp1063Ter	DS	India (SOLANKI et al. 2016)
	2	c.163C>T	p.Gln55Ter	DS	India (SOLANKI et al. 2016), Netherlands (WIJKER et al. 1999b)
	28	c.2749C>T	p.Arg917Ter	DS	India (SOLANKI et al. 2016)
	33	c.3286C>T	p.Gln1096Ter	MLPA and NGS	Iran (NIA et al. 2016a),USA (LEVRAN et al. 2005b)
	1	c.15G>A	p.Trp5X	WES	Japan (MORI et al. 2019a)
	5	c.462T>G	p.Tyr154X	WES	Japan (MORI et al.

					2019a)
	15	c.1464C>A	p.Tyr488X	WES	Japan (MORI et al. 2019a)
	29	c.2840C>G	p.Ser947X	WES	Japan (MORI et al. 2019a)
	30	c.2870G>A	p.Trp957X	WES	Japan (MORI et al. 2019a)
	33	c.3295C>T	p.Gln1099X	WES	Japan (MORI et al. 2019a)
	36	c.3568C>T	p.Gln1190X	WES	Japan (MORI et al. 2019a)
	5	c.505G>T	p.Glu169Ter	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a; MORI et al. 2019a)
Insertion/Duplication	41	c.4046_4047insT	p.Arg1349SerfsX7	HRM and DS	Iran (MOGHADAM et al. 2016a)
	41	c.4048_4049insT	p.Glu1350ValfsX7	HRM and DS	Iran (MOGHADAM et al. 2016a)
	41	c.4021_4022insA		HRM and DS	Iran (MOGHADAM et al. 2016a)
	39	c.3919_3920insT	p.Gln1307LfsX6	whole exome sequencing	Japan (MORI et al. 2019a)
	41	c.4042_4043insC	p.Ile1348TfsX77	whole exome sequencing	Japan (MORI et al. 2019a)
	39	c.3918_3919insT	p.Gln1307fsX6	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a)
	3	c.190_191insT	p.Glu65ArgfsX5	-	Japan (SEKINAKA et al. 2017; MORI et al. 2019a)
	24	c.2172_2173insG	p.Ser725ValfsTer6	SSCP and DS	Israel (TAMARY et al. 2000a)
	37	c.3708_3709 insA	p.Val1237Sfs*39	sequencing	Pakistan (SHAHID *et al.* 2019a)
	39	c.3854_3855insT	p.His1286Pfs*25	sequencing	Pakistan (SHAHID et al. 2019a)
	39	c.3872_3873insT	p.Leu1292Pfs*19	sequencing	Pakistan (SHAHID et al. 2019a)
Silent	13	c.1143G>T	p.Ter381Ter	DS	Japan (TACHIBANA et al. 1999b)
	30	c.2901C>T	p.Ser967Ser	DS	Japan (TACHIBANA et al. 1999b)
	37	c.3654A>G	p.Pro1218Pro	DS	Japan (TACHIBANA et al. 1999b), Pakistan (SHAHID et al. 2019a)
	38	c.3807G>C	p.Leu1269Leu	DS	Japan (TACHIBANA et al. 1999b)Pakistan {Shahid, 2019 #177
	43	c.4275T>A	-	sequencing	Pakistan (SHAHID et al. 2019a)
	43	c.4263G>A	-	sequencing	Pakistan (SHAHID et al. 2019a)

Splice mutation	32	c.3066+1G>T		NGS	India (SOLOMON et al. 2015b)
	3	c.190-2A>G	-	MLPA and NGS	Iran (NIA et al. 2016a)
	33	c.3348+1G>T	-	MLPA and NGS	Iran (NIA et al. 2016a)
	2	c.85-2A>T	-	MLPA and NGS	Iran (NIA et al. 2016a)
	4	c.510+1G>T	-	MLPA and NGS	Iran (NIA et al. 2016a)
	2	c.217-2A>G	-	MLPA and NGS	Iran (NIA et al. 2016a)
	33	c.3348+1G>A	-	MLPA and NGS	Iran (NIA et al. 2016a)
	Intron 9	c.827-1G>T	Aberrant splicing	Gene dosage assay and sequencing	Japan (YAGASAKI *et al.* 2004a)
	Intron 39	c.3934+2T>C	Aberrant splicing	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a)
	Intron 41	c.4168-1G>C	Aberrant splicing	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a; MORI et al. 2019a)
	Intron 27	c.2602-2A>T	p.868_869delFQ	DS, Gene dosage assay and sequencing,	Japan (TACHIBANA et al. 1999b; YAGASAKI et al. 2004a; MORI et al. 2019a)
	Intron 3	c.283+2T>C	Aberrant splicing	WES	Japan (MORI *et al.* 2019a)
	Intron 11	c.1007-2A>G	Aberrant splicing	WES	Japan (MORI et al. 2019a)
	Intron 16	c.1567-1G>A	Aberrant splicing	WES	Japan (MORI et al. 2019a)
	Intron 25	c.2316+2T>A	Aberrant splicing	WES	Japan (MORI et al. 2019a)
	Intron 41	c.4168-2A>G	Aberrant splicing	WES	Japan (MORI et al. 2019a)
	Intron 15	c.1471-1G> A	p.Val490HisfsX6	MLPA and sequencing	China(LI et al. 2018a)
	Intron 31	c.3067-4T>C	-	whole exome sequencing	China (CHANG et al. 2014b)
	Intron 41	IVS 42-2A>C	-	SSCP and DS	Israel (TAMARY et al. 2004b)
	Intron 42	c.4261-2A > C	-	MLPA and DS	Turkey (ASLAN 2017a), Iran (NIA et al. 2016a)
	Intron 28	c.2778+1G>C	Aberrant splicing	MLPA and DS	Korea (PARK et al. 2013b)
	Intron 36	c.3627-1G>A	Aberrant splicing	MLPA and DS	Korea (PARK et al. 2013b)
	Intron 2	c.190-2A>G	-	MLPA and NGS	Iran (NIA et al. 2016a)
	15	1360–1826del	p.Ala454ProfsX72	SSCP and ARMS	Japan (ADACHI *et al.* 2002b)
	37	c.3760_3761delGA		DS	India (ARTHUR et al. 2014; SOLOMON et al. 2015b; SOLANKI et al. 2016), Turkey (LEVRAN et al. 1997a)
	39	c.3926_3929delCAGA	p.Thr1309ArgfsX5	DS	India (SOLANKI et

					al. 2016), Fanconi anemia mutation database RockfellerUniversity
	26	c.2500delC	-	DS	India (SOLANKI et al. 2016)
	38	c.3791_3793delCCT	p.Ser1264del	MLPA and NGS	Iran (NIA et al. 2016a)
	40	c.3993delG	p.Pro1332Leufs*3	MLPA and NGS	Iran (NIA et al. 2016a), India (VUNDINTI 2014a)
	38	c.3781_3785delTTCTT	p.Phe1261Leufs*1	MLPA and NGS	Iran (NIA et al. 2016a)
	14	c.1772delT	p.Leu591Argfs*3	MLPA and NGS	Iran (NIA et al. 2016a)
	41	c.4124_4125delCA	p.Thr1375Serfs*4	MLPA and NGS	Iran (NIA et al. 2016a),Spain (CASTELLA et al. 2011b)
	38	c.3788_3790delTCT	p.Phe1263del	MLPA and NGS, SSCP and ARMS	Iran (NIA et al. 2016a), Spain (CASTELLA et al. 2011b), USA (CHANDRA et al. 2005b; LEVRAN et al. 2005b), Japan (ADACHI et al. 2002b), Pakistan (CASTELLA et al. 2011b)
	11	c.987-990delTCAC	p. His330Alafs*4	MLPA and NGS	Iran (NIA et al. 2016a),USA (LEVRAN et al. 2005b)
	37	c.3696delT	p.Phe1232Leufs*1	MLPA and NGS	Iran (NIA et al. 2016a), USA (CHANDRA et al. 2005b)
	11	c.989_995delCCCGACA	p.H330LfsX2	whole exome sequencing	China (ZHENG et al. 2013b), (CHANG et al. 2014b)
	11	c.969_970delCC	-	whole exome sequencing	China (CHANG et al. 2014b)
	14	c.1298delT		whole exome sequencing	China (CHANG et al. 2014b)
	1	c.44-69del	p.Pro15RfsX40	whole exome sequencing	Japan (MORI et al. 2019a)
	27	c.2593delA	p.Ile879LfsX24	whole exome sequencing	Japan (MORI et al. 2019a)
	28	c.2730_2731delCT	p.Trp911DfsX31	whole exome sequencing	Japan (MORI et al. 2019a)
	30	c.2972delT	p.Phe991SfsX35	whole exome sequencing	Japan (MORI et al. 2019a)
	37	c.3720_3724 del	p.Glu1240DfsX36	whole exome sequencing	Japan (MORI et al. 2019a)
	38	c.3781_3785delTTCTT	p.Phe1261LfsX15	whole exome sequencing	Japan (MORI et al. 2019a)
	39	c.3931-3932delAG	p.Ser1311X	whole exome sequencing	Japan (MORI et al. 2019a)
	41	c.4015_4017delCTC	p.Leu1339del	whole exome sequencing	Japan (MORI et al. 2019a)
	41	c.4124-4125delCA	p.Thr1375SfsX49	whole exome sequencing	Japan (MORI et al. 2019a)
	37	c.3720_3724delGTCAG	Aberrant splicing	Gene dosage assay	Japan

				and sequencing	(YAGASAKI et al. 2004a), Korea (PARK et al. 2013b)
	42	c.4240_4241delAG	p.S1414fsX10	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a; MORI et al. 2019a)
	27	c.2546delC	p.S849fsX40	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a; MORI et al. 2019a), Korea (PARK et al. 2013b),
	37	c.3638_3639delCT	p.P1213fsX64	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a; MORI et al. 2019a)
	11	c.978_979delGA	p.Q326fsX12	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a; MORI et al. 2019a)
	41	c.4015_4017delTCT	p.1339delL	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a)
	Intron 37	c.3765+1G>T	-	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a; MORI et al. 2019a)
	10	c.890–893delGCTG	p.Cys297SerfsX14	SSCP and DS	Israel (TAMARY et al. 2000a)
	43	c.4275delT	p.Asp1427ThrfsX6	SSCP and DS	Israel (TAMARY et al. 2000a)
	37	c.3639delT	p.Glu1214ArgfsX3	SSCP and DS	Turkey (BALTA et al. 2000)
	36	c.3520_3522delTGG	p.Trp1174del	MLPA and DS, SSCP and ARMS	Korea (PARK et al. 2013b), Japan (ADACHI et al. 2002b)
	23	c.2057delC	p.Ala686ValfsX38	MLPA and NGS	Iran (NIA et al. 2016a)
	37	c.3715–3729del15	p.Glu1239LysfsX8	SSCP and ARMS	Japan (ADACHI et al. 2002b), Italy (LEVRAN et al. 2005b)
	Intron 27	c.2602-1G>A	p.868_869delFQ	DS, Gene dosage assay and sequencing	Japan (TACHIBANA et al. 1999b; YAGASAKI et al. 2004a; MORI et al. 2019a)
	28	IVS27-1G>A	p.868-869delFQ	DS	Japan (TACHIBANA et al. 1999b)
	28	IVS27-2A>T	868-869delFQ	DS	Japan (TACHIBANA et al. 1999b)
	42	IVS41-2A>G	1390-1420del	DS	Japan (TACHIBANA et al. 1999b)

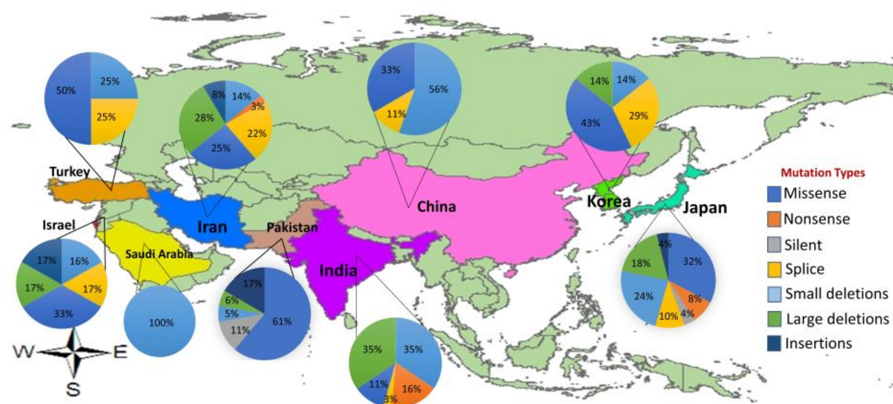

Fig.2.Frequency of reported FANCA Mutations (subtypes) in Fanconi anemia patients from different Asian countries:Pie diagrams displaying the frequency (in percentage) and localization of FANCA mutations identifiedfrom each Asian country.

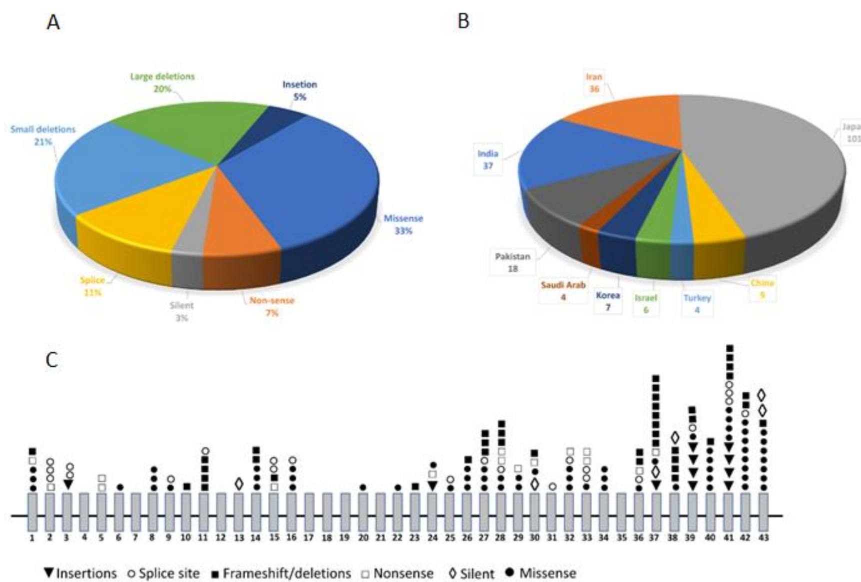

Fig.3.Pattern of FANCA exonic mutations in Asian Fanconi anemia patients: (A) Pie chartshowingtypes of various genetic mutations (in percentage) reported from Asian patients.(B) Country-wise and (C) exon-wisedistribution of FANCA mutations in Asian population.

Japan

The *FANCA* gene has been reported to be highly polymorphic and in Japanese population highest proportion of FANCA mutations were reported i.e., 36.3% (60/165) among all Asian countries. In a study conducted by Tachibana and his colleagues, 15 unclassified Japanese FA patients were screened by direct sequencing of cDNA and genomic DNA (TACHIBANA *et al.,* 1999b). They found 19 total sequence changes of FANCA, of which 11 were previously reported and remaining, were novel. Out of these alterations 10 were nonpathogenic and remaining two missense mutations, three genomic deletions, and four splicing defects were pathogenic mutations. The most common mutation was 2546delCin exon 27 which was present in six out of 15 patients (40%), resulting in a premature termination codon 40 codons downstream and formation of a truncated protein of 887 amino acids (TACHIBANA *et al.,* 1999b). Among the other base substitutions, 1303C>T pathogenic missense mutation was found in 12 out of 15 analyzed FA patients (80%) and has reported higher incidence in Indian (SOLANKI *et al.,* 2016) and Brazilian FA patients as well (LEVRAN *et al.,* 1997). Another report by Adachi and his group also described some FANCA mutations but those were previously reported by Levran et al., 2005(LEVRAN *et al.,* 2005b) (see Table 1)(ADACHI *et al.,* 2002).

YAGASAKI *et al*., (2004) used newly developed TaqMan™ quantitative PCR-based gene dosage assay and sequencing method for mutation analysis of 35 unrelated Japanese FA families of which 27 (77%) were linked to FANCA (YAGASAKI *et al.,* 2004b). They identified 48 mutant alleles and included 29 genetic alterations (21 base exchange and 8 large deletions), twenty of which were novel. They also found high frequency of c.2546delC (10/48; 21%) mutation of FANCA gene in their studied Japanese patients consistent with findings of Tachibana et al., 1999 (TACHIBANA *et al.,* 1999b). On the other hand, some recurrent mutations for instance c.1303C>T,c.2602-2A>T, c.3720-3724del and 2602-1G>A were not identified in other ethnic groups, except c.1303C>T to be found in the Brazilian population (LEVRAN *et al.,* 1997), suggesting their restricted occurrence in Japanese population. On the basis of their data they hypothesized that FANCA is rich in Alu elements which are responsible for Alu-mediated HR in production of genomic deletions (YAGASAKI *et al.,* 2004b). Surprisingly, their results revealed high prevalence of FANCA gene and its high allelic heterogeneity, in agreement with the notion that the gene is hypermutable. Recently, MORI *et al*., (2019b) analyzed 117 Japanese FA patients through Next Generation Sequencing preferably Whole Exome Sequencing (WES) whereas in some cases RNA sequencing identified pathogenic variants of FANCA genes in 68 cases. Collectively they identified 9 missense and 8 nonsense mutations. Whereas 9 splice site mutations, 16 small indels, 12 large deletions and a large duplication was also detected (MORI *et al.,* 2019b). Their findings identified a c.2546delC mutation as a hot spot mutation in Japanese ethnicity as this mutated allele had a frequency of 31.5%.

India

The spectrum of FANCA mutations among Asians covers 22.4% (37/165) in Indian population indicating it as second most influenced population for FANCA mutations. Mutational analysis of Fanconi anemia complementation group A patients from India revealed their redundancy worldwide. From Indian population SHUKLA *et al*. (2013) provided the first report of Fanconi anemia case which was a 3.5 years old male child. In their study, using Multiplex ligation-dependent probe amplification (MLPA) method they identified a novel homozygous large intragenic deletion (exons 8–27 del) in the FANCA gene (SHUKLA *et al.,* 2013b). Their

study support the previously reported mutations and suggested that FA patients exhibited high frequency defects in the FANCA gene and large deletions are the most common mutations in this gene (SHUKLA *et al.,* 2013b). VUNDINTI (2014) had first time performed a molecular study in the Indian population. In his study, using MLPA method and sequencing a total of 12 FANCA mutations were identified of which 5 were novel (c.3678 C>G, c.3993G>A, c.1274 C>G, c.2630 C>G) and remaining were previously reported (VUNDINTI, 2014).

Recently, in another study conducted by Solomon and his group using targeted next-generation sequencing for whole gene profile of FA a novel, homozygous splice site mutation, c.3066 + 1G>T, (IVS31+1G>T) in intron 31 of FANCA gene was identified which was the first report of splice site mutation in Fanconi Anemia (SOLOMON *et al.,* 2015).

Most recently Solanki, et al. (2016) studied 550-FA suspected adults and children (SOLANKI *et al.,* 2016). After chromosomal breakage test, 61 confirmed cases with FA were subjected to MLPA analysis and direct sequencing. A total of 26 FANCA variations were identified in 34 unrelated individual of which 8 were novel mutations and remaining were previously reported (SOLANKI *et al,.* 2016). Out of these 26 mutations 7 were missense of which three(3/7;43%) were novel i.e., c.3679C>G (p.Ala1227Pro), c.1273C>G (p.Asp425His), c.3992T>C (p.Leu1331Pro) and (5/7; 57%) were already reported from Netherlands (AMEZIANE *et al.,* 2008), Japan (TACHIBANA *et al.,* 1999b; ADACHI *et al.,* 2002; YAGASAKI *et al.,* 2004b), Brazil (LEVRAN *et al.,* 1997) and USA populations (CHANDRA *et al.,* 2005a; LEVRAN *et al.,* 2005b). The c.2851C>T mutation in exon 29 is highly predominant in India (SOLANKI *et al.,* 2016), Netherlands (AMEZIANE *et al.,* 2008), and USA (CHANDRA *et al.,* 2005a; LEVRAN *et al.,* 2005b). In addition, c.2574C>G mutation in exon 27 is highly prevalent in India (SOLANKI *et al.,* 2016), Netherlands (WIJKER *et al.,* 1999a), Israeli (TAMARY *et al.,* 2000; TAMARY *et al.,* 2004a) populations and c.1303C>T in exon14 is highly dominant in India (SOLANKI *et al.,* 2016), Japan (TACHIBANA *et al.,* 1999b; ADACHI *et al.,* 2002; YAGASAKI *et al.,* 2004b), and Brazil (LEVRAN *et al.,* 1997). Among 6 nonsense mutations identified in this study, 4 were new c.2182C>T, c.2630C>G, c.3189G>A and c.3677C>G in exon 24, 28, 32, 37 respectively. Also, they found 3 different small deletions, c.3760_3761delGA in exon 37, c.3926_3929delCAGA in exon 39, a novel small deletion c.2500delC in exon 26 and ten large deletions involving exon 1–8, exon 8-27, exon1-22, exon 4–7, exon 6, exon 11, exon 21, exon 30, exon 31, and exon 15–29. This was the vast study wherein most abundant nonsense mutations40% (6/40) and large deletions 38% (15/40) were found than other Asian populations so far. Their data suggested that the high prevalence of large deletions and nonsense mutation were the most vulnerable factors in FANCA patients with distinct abnormalities (SOLANKI *et al.,* 2016). Similarly, exacerbated rate of nonsense mutations causing truncated protein synthesis is responsible for lethal developmental conditions in FA patients.

Iran

Up to last decade no study was performed related to FA in Iranian population. Most recently a study regarding FANCA from Iran was performed by Moghadam and his group (MOGHADAM *et al.,* 2016b). They enrolled clinically suspected FA patients from 40 families and adopted a different strategy involving, High Resolution Melting curve (HRM), real-time RT-PCR and sequencing to identify the molecular alterations of the *FANCA* gene in Iranian population. In total, they identified 6 sequence alterations, including two frame shift mutations, two non-sense and one missense mutation and one large deletion. Sequence analysis showed two

insertions i.e., c. 4048_4049insT and c. 4046_4047insT in exon 41 whereas missense changes i.e., c. 4049G>A, c. 4046G>C in exon 41 and c. 3982A>G in exon 40 were detected. A large genomic deletion exon8 to 43 was also found in an index case. One missense alternation (c. 3982A>G) in exon 40 which led to substitution by an alanine (Ala) instead of a threonine (Thr) (p. Thr1328Ala) was previously reported in Japanese population (TACHIBANA *et al.,* 1999b; MOGHADAM *et al.,* 2016b).

In another study, 48 FA families were recruited. Almost all were having consanguineous unions and Next Generation Sequencing(NGS) and Multiple Ligation Dependent Probe Amplification(MLPA) assay were used to analyze FANCA mutations (NIA *et al.,* 2016a). Out of 48 patients 25 (25/48; 52%) had FANCA mutations. A total of 27 FANCA mutations were detected, of which 15(56%) were novel identified for the first time from Iranian population. Among single nucleotide changes they identified total 15 sequence alterations in FANCA gene of which 9 were novel and remaining were previously reported. Among novel mutations a missense (c.4006T>G),a nonsense (c.2915G>T), an in-frame deletion (c.3791_3793delCCT), 3 splice site mutations (c.190-2A>G, c.3348+1G>T and c.4261-2A>C) and 3 frame-shift deletions (c.2057delC, c.3993delG and c.3781_3785delTTCTT) were detected (NIA *et al.,* 2016a). Moreover, a broad spectrum of 12 deletions included novel and reported, ranging from single exon loss to large deletions were also ascertained (NIA *et al.,* 2016a). These studies represent 21.8% (36/165) of all FANCA mutations identified in Asian populations It was also noticeable that the large deletions 28% (10/36) are main contributors in the Iranian FA phenotype and next predominant mutations were small deletions comprising of 25% (9/36) of all mutations for this population as shown in Figure 2.

China

China has world's largest population but a little data is reported to date from this region related to FANCA mutations. Only single centered study and a few case reports are online (CHEN *et al.,* 2007; ZHENG *et al.,* 2013; CHANG *et al.,* 2014). In a study conducted by CHEN *et al.* (2007), exon 5 deletion was seen in three FA patients (CHEN *et al.,* 2007). In a case report by ZHENG *et al.* (2013) whole exome sequencing (ZHENG *et al.,* 2013) lead to identification of a recurring, non-synonymous mutation(c.3971C>T) in exon 40 and a novel frameshift mutation (c.989_995delCCCGACA) in exon11 of FANCA gene. The frameshift mutation caused protein truncation after two amino acids (p.H330LfsX2) (ZHENG *et al.,* 2013).

In another study, performed by CHANG, *et al.* (2014) using five FA patients and their parents whole exome sequencing showed that four out of five patients harbored FANCA mutations. In total eight mutations including four missense mutations, three frame shift deletions and 1 splicing error were detected. Out of these mutations, two were novel. LI *et al.* (2018) analyzed a Chinese family having two FA affected individuals using WES followed by MLPA and found that both individuals were compound heterozygote for a splice site variant i.e., c.1471-1G>A and a large deletion i.e., exons 23-30del or exons 1-18del. This study highlighted complexity of FANCA variants linked to FA phenotype (LI *et al.,* 2018b)

Israel

TAMARY, et al. (2000) enrolled thirteen Israeli Jewish (non-Ashkenazi) FA patients that were different by country of birth. They investigated the molecular alterations by single-strand conformation polymorphism (SSCP) and DNA sequencing method (TAMARY *et al.,* 2000). They

detected four ethnic-specific mutations; c.2172–2173insG in exon 24and c.4275delT in exon 43 were present in patients from Moroccan origin whereas c.890–893del in exon 10and c.2574C>G in exon 27 were present in patients with Tunisian and Indian ethnicity respectively. Out of these four mutations only missense mutation was previously reported (WIJKER *et al.,* 1999a)).They found c.2172–2173insG mutation in 10 out of 13 Moroccan patients indicating its ethnic-specific occurrence (TAMARY *et al.,* 2000). Later on, TAMARY and his co investigators (2002) recruited 3 consanguineous families having 9 FA affected individuals and screened for FANCA mutations as before. They identified 2 FANCA alternations including a gross deletion of exons 6–31 in four patients and a IVS 42-2A>C splice-site mutation in three patients. In another study, TAMARY, *et al*. (2004a) enrolled 32 unrelated Israeli patients with FA of which15 had FANCA mutations and these mutations were reported in their previous study.

Turkey

BALTA, *et al*. (2000) ascertained a novel FANCA mutation (3639delT) in a Turkish FA patient. They used SSCP) and DNA sequencing approach. This novel mutation (3639delT) was a deletion of T at position 3639 in exon 37 causing premature termination of translation (BALTA *et al.,* 2000). Recently, another case belonging to consanguineous parents was reported from Turkish population by ASLAN (2017). He performed MLPA and sequencing and detected an already reported mutations c.2T>C (p.Met1Thr) and a novel mutation c.4261-2A> C, segregating with disease in autosomal recessive manner.

Korea

PARK *et al*. (2013a) recruited 30 FA patients from Korean population and screened them by MLPA followed by direct sequencing for FANCA gene. Of total 30, six patients were sorted out as Fanconi anemia complementation group A. In these six affected individuals they identified three small deletions (c.2546delC, c.3720_3724delAAACA and c.3520_3522delTGG) of which two (c.2546delC and c.3720_3724delAAACA) were high prevalent founder mutations. All these three are already reported for Japanese population (ADACHI *et al.,* 2002; YAGASAKI *et al.,* 2004b). In addition they also reported two novel splice site mutations c.2778+1G>Cand c.3627-1G>A in Korean population (PARK *et al.,* 2013a).

FANCA mutations in Saudi Arabia and Pakistan

Regionally no study performed in Saudi Arabia whereas LEVRAN *et al*. (1997) in their study recruited FA patients that were from different backgrounds. They reported four novel missense FANCA mutations in exon 1, 6 and 8 from Saudi Arabian individuals (LEVRAN *et al.,* 1997). WIJKER *et al*. (1999a) reported a novel exon 31 deletion while CASTELLA *et al*. (2011) found a previously reported small deletion in patient with Pakistani ethnicity (ADACHI *et al.,* 2002; CASTELLA *et al.,* 2011; NIA *et al.,* 2016a). Recently, SHAHID *et al.* (2019) identified a previously reported three nucleotide deletion, three novel single nucleotide insertions and a novel missense variant linked to FA phenotype.

Table 2: Large deletions of FANCA in Asian Populations

Exon number	Detection Method	Country (References)
Exon 6	MLPA	India (SOLANKI et al. 2016), Fanconi anemiamutation database Rockfeller University
Exon 4–7	MLPA	India (SOLANKI et al. 2016), Fanconi anemiamutation database Rockfeller University
Exon 11	MLPA	India (SOLANKI et al. 2016)
Exon 31	MLPA	India (SOLANKI et al. 2016), Pakistan (WIJKER et al. 1999b) Fanconi anemia mutation database Rockfeller University
Exon 21	MLPA	India (SOLANKI et al. 2016), Netherlands (GILLE et al. 2012)
Exon 1–8	MLPA	India (SOLANKI et al. 2016), Fanconi anemiamutation database Rockfeller University
Exon 8-27	MLPA	India (SHUKLA et al. 2013a; SOLANKI et al. 2016)
Exon 30	MLPA, Gene dosage assay and sequencing	India (SOLANKI et al. 2016), Iran (NIA et al. 2016b), Japan (YAGASAKI et al. 2004a; MORI et al. 2019a), Fanconi anemiamutation
Exon 15–29	MLPA	India (SOLANKI et al. 2016), Fanconi anemiamutation database Rockfeller University
Exon 1-22	MLPA	India (SOLANKI et al. 2016), Iran (NIA et al. 2016b), Fanconi anemiamutation database Rockfeller University
Exons 1–4	-	India (ARTHUR et al. 2014)
Exons 6–14	-	India (ARTHUR et al. 2014)
Exons 10–37	-	India (ARTHUR et al. 2014)
Exons 1–44	MLPA and NGS	Iran (NIA et al. 2016b), USA(CHANDRA et al. 2005b)
Exons 8–43	HRM and DS	Iran (MOGHADAM et al. 2016a)
Exons 1–26	MLPA and NGS	Iran (NIA et al. 2016b)
Exons 18–20	MLPA and NGS	Iran (NIA et al. 2016b), Spain(CHANDRA et al. 2005b)
Exons 7	MLPA and NGS	Iran (NIA et al. 2016b)
Exons 20–22	MLPA and NGS	Iran (NIA et al. 2016b)
Exons 20–28	MLPA and NGS	Iran (NIA et al. 2016b)
Exons 16–22	MLPA and NGS	Iran (NIA et al. 2016b), IFAR USA(LEVRAN et al. 2005a)
Exon 12-26	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a)
Exon 3-6	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a)
Exon 3-3'UTR	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a)
Exon 15-21	Gene dosage assay and sequencing	Japan (YAGASAKI et al. 2004a)
Exon 24-28	DS Gene dosage assay and sequencing	Japan (TACHIBANA et al. 1999a; YAGASAKI et al. 2004a; MORI et al. 2019a)
Exon 1-3	WES	Japan (MORI et al. 2019a)
Exon 1-5	WES	Japan (MORI et al. 2019a)
Exon 1-28	WES	Japan (MORI et al. 2019a)
Exon 1-43	WES	Japan (MORI et al. 2019a)
Exon 6	WES	Japan (MORI et al. 2019a)
Exon 16-17	WES	Japan (MORI et al. 2019a)
Exon 19-29	WES	Japan (MORI et al. 2019a)
Exon 30-31	WES	Japan (MORI et al. 2019a)
Intron 37-exon 38	WES	Japan (MORI et al. 2019a)
Exon 1-18	MLPAand sequencing	Japan(LI et al. 2018a)
Exon 23-30	MLPA and sequencing	Japan(LI et al. 2018a)
Exon 38	DS	Japan (TACHIBANA et al. 1999a)
Exons 6–31	SSCP and DS	Israel (TAMARY et al. 2004b)
Exon 37	MLPA and DS	Korea (PARK *et al.* 2013b), Japan (MORI *et al.* 2019a)

CONCLUSIONS AND FUTURE PERSPECTIVES

Recent studies have identified 22 genes responsible for Fanconi anemia progression in congenital hematological abnormalities worldwide. The highly prevalent FANCA gene

participates in several biological processes owing to its clinical relevance to genetic instability, cancer, and hematopoietic differentiation defects, although not well understood. The highly elegant and remarkable function of FANCA protein is guarding genome integrity to prevent lethality of insult/s. FANCA regulates MUS81-EME1 and FEN1 endonuclease activity that introduce nicks at the stalled replication forks of ICL. It is a crucial factor for resection-mediated repair pathway by participating in the Alt-EJ DNA damage repair pathway. In addition, FANCA plays its role in chromatin remodeling and protection against ROS by interacting with BRG1. FANCA mediates centrosome-associated spindle assembly, chromosome alignment and congregation during mitosis by interacting with CENP-E. Despite all these known functions of FANCA which are discussed in detail in first section of this review, many other pathways in which FANCA is implicated are yet to be elucidated. This speculation necessitates further studies to unveil FANCA precise role in patho-physiology of congenital hematological disorders.

Here in second section of this review, we summarized all reported FANCA mutations from Asian populations. The data shown in Table 2 depicts that exon 14, 28, 32, 37, 38, 40 and 41 of FANCA are mutation hotspots for Asian ethnicity as they harbor 44% of all reported mutations (Table 2). Other remaining exons contains collectively up to 56% mutations. Furthermore, frequency of subtypes of FANCA mutations for each population is shown in Figure 2.

We summarized geographical distribution of FANCA mutations in Asia, surprisingly; Japanese population had highest number of FANCA mutations (37%) whereas Indian and Iranian populations exhibit 23% and 22% of FANCA mutations respectively. Whereas, a very low number of FANCA mutations were reported from Chinese, Turkish, Israeli, Korean, and Pakistani population. These differences could be attributed to low number of research studies conducted on genetic predisposition of FA cases from Chinese, Turkish, Israeli, Korean, and Pakistani population. The broad spectrum of FANCA mutations highlights allelic heterogeneity of FA. Thus, each mutation has different impact in the FANCA-mediated cellular processes resulting in individual differences in the FA phenotypes. Hematological disorders especially FA has very devastating impact on individuals and societies. Their consequences have significant public health issues with socioeconomic impact in the developing countries. Thus, sporadic and familial cases with inherited FA need to be actively recruited to facilitate molecular characterization in inbred Asian populations to establish molecular genetics diagnostic strategies for timely detection and treatment as well as prenatal and premarital screening to overcome disease burden on societies and health care system. Nevertheless, such studies will lead to a better understanding of disease phenotypes and precise role of FANCA in normal and mutated cells. The FANCA-null mice provide an excellent experimental model for such studies to exploit and elucidate further FANCA functions. Ideally, update of international Fanconi Anemia registries/ databases and their access to retrieve data would greatly improve our understanding about the phenotype and genotype of FA patients. This access would also facilitate clinicians to select suitable strategies for multi-site therapeutic trials on a cohort of individuals. This study emphasizes regional and global epidemiological and molecular genetic studies especially from less developed regions and formulation of standard criteria/strategies of FA diagnosis. We anticipate that data presented in this review will increase awareness and motivate further research on FANCA as well as lethal FA.

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FANCA I DOPRINOS PROUČAVANJA AZIJSKE POPULACIJE RAZUMEVANJU *FANCA* UTICAJA NA FANCONIJEVU ANEMIJU

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Izvod

Fanconijeva anemija (FA) je recesivni poremećaj za koji se zna da izaziva hematološke i nekoliko urođenih deformacija kod pogođenih ljudi širom sveta. Od 22 poznata FA uzročna gena, mutacije u *Fanconi Anemia Complementation Group A* (FANCA) čine 60% -70% slučajeva. FANCA je multifunkcionalni protein neophodan za integritet genoma. Iako su mnoge fiziološke uloge FANCA-e razgraničene, tačan etiopathomehanizam FANCA-e u fenotipu FA tek treba da se rasvetli. FANCA je hipermutabilni i visoko polimorfni gen, pa identifikacija i interpretacija mutacija umešanih u recesivno nasleđeni FA mogu da popune praznine u postojećem znanju o molekularnim mehanizmima. Ovaj pregledni rad je podeljen u dve sekcije. Prvi deo opisao je poznate funkcije FANCA važne za kontinuitet genomskog integriteta. U drugom delu su sažete sve mutacije FANCA gena prijavljene kod FA pacijenata iz azijske populacije na osnovu literature objavljene do marta 2019. Omogućuje pregled strategija koje se koriste za identifikaciju ovih mutacija, mutacijske žarišta za specifičnu azijsku populaciju i zahteva potrebu opsežnih globalnih, kao i regionalnih istraživačkih napora za molekularnu genetiku uglavnom u manje istraženim azijskim zemljama kako bi se formulisale dijagnostičke i ciljane terapijske mere.

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