Characterization and genotype-phenotype correlation of patients with Fanconi anemia in a multi-ethnic population

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Novel mutations detected in patients with Fanconi anemia in Israel.

Gene	HGVS (gene)	HGVS (Coding)	HGVS (Protein)	HGMD	Highest MAF	RefSeq ID	ClinVar (Accession)	Mutation Taster	GERP (score)	splicing - dbscSNV (score)	Prediction	Ref.
FANCA; NM_000135	g.46044_46045insG	c.2172_2173 insG	p. Ser725Valfs*69	CI004868	0			Disease Causing	not conserved (-5.6)		A null (frame shift) mutation, likely pathogenic	(1)
FANCA; NM_000135	g.77948A>C (IVS43-2a>c)	c.4261-2A>C	splice site	CS042812	0.00002	rs915983602	pathogenic	Disease Causing	conserved (5.4)	damaging (0.9999)	A null (splice site) mutation, likely pathogenic	(2)
FANCA; NM_000135		ex6-31 del		CG044343							A null (large deletion) mutation, likely pathogenic	(2)
FANCA; NM_000135	g.77427_77428insT	c.4069_4070 insT	p.Ala1357Valfs*68		0			Disease Causing	conserved (5.09)		A null (frame shift) mutation, likely pathogenic	This paper
FANCA; NM_000135		ex31-37del		CG1010320							A null (large deletion) mutation, likely pathogenic	(1)
FANCA; NM_000135	g.77964_77964delT	c.4275delT	p.Asp1427Thr fs*6	CD004867	0			Disease Causing	not conserved (-4.24)		A null (frame shift) mutation, likely pathogenic	(3)
FANCA; NM_000135	g.70051C>T	c.3490C>T	p.Pro1164Ser	CM146020	0.001	rs545772434		Disease Causing	conserved (5.05)		Missense mutation, likely pathogenic	This paper
FANCA; NM_000135	g.69801C>T	c.3382C>T	p.Gln1128Ter	CM1010319	0.00001	rs1439817346	Likely pathogenic (RCV000673853)	Disease Causing	conserved (5.09)		A null (nonsense) mutation, likely pathogenic	(1)
FANCA; NM_000135		ex1-24del									A null (large deletion) mutation, likely pathogenic	This paper
FANCA; NM_000135	g.17489_17492delGCTG	c.891_893delGCTG	p.Trp298Serfs*12		0			Disease Causing			A null (frame shift & splice site) mutation, likely pathogenic	(3)
FANCA; NM_000135		ex1,2,4,5del									A null (large deletion) mutation, likely pathogenic	This paper

Gene	HGVS (gene)	HGVS (Coding)	HGVS (Protein)	HGMD	Highest MAF	RefSeq ID	ClinVar (Accession)	Mutation Taster	GERP (score)	splicing - dbscSNV (score)	Prediction	Ref.
FANCA; NM_000135	g.782G>A (IVS2+1 g>a)	c.189+1G>A	splice site		0.0001	rs891323617	Likely pathogenic (RCV000674205)	Disease Causing	conserved (5.34)	damaging (0.9999)	A null (splice site) mutation, likely pathogenic	This paper
FANCA; NM_000135	g.51770T>C (IVS28+2 T>C)	c.2778+2T>C	splice site		0.00001	rs1458001028	Likely pathogenic (RCV000671287)	Disease Causing	conserved (5.21)	damaging (0.965)	A null (splice site) mutation, likely pathogenic	This paper
FANCA; NM_000135		c.1471401_1626+395del							not conserved (-0.71)		A large deletion inc. ex16-17, likely pathogenic	This paper#
FANCC; NM_000136	g.68425C>T	c.7C>T	p. Gln3Ter		0			Disease Causing	conserved (5.13)		A null (nonsense) mutation, likely pathogenic	This paper
FANCD1/BRCA2; NM_000059	g.41098_41098delG	c.7579delG	p.Val2527Ter		0	rs1555286294	pathogenic (RCV000680273)		conserved (5.48)		A null (nonsense) mutation, likely pathogenic	This paper
FANCD1/BRCA2; NM_000059	g.82733_82733delA	c.9693delA	p.Leu3232Phefs*17		0		pathogenic (RCV000680274)		conserved (4.21)		A null (frame shift) mutation, likely pathogenic	This paper
FANCG; NM_004629	g.5628C>G	c.1742C>G	p.Ser581Ter		0			Disease Causing	conserved (5.11)		A null (nonsense) mutation, likely pathogenic	This paper
FANCG; NM_004629	g.1879A>G (IVS4+3 A>G)	c.510+3A>G	splice site		0				conserved (5.75)	damaging (0.998)	A null (Splice site) mutation, likely pathogenic	This paper
FANCJ; NM_032043	g.62255C>T	c.1126C>T	p. Gln376Ter		0.00002	rs1028347439	pathogenic (RCV000581764)	Disease Causing	conserved (5.21)		A null (nonsense) mutation, likely pathogenic	This paper

The mutations listed in this table include those published exclusively by our group. # A similar but not identical deletion of exons 16-17 was published in (4).

GERP - Genomic Evolutionary Rate Profiling; HGMD - Human Gene Mutation Database; HGVS - Human Genome Variation Society; MAF - Minor Allele Frequency; Ref. – Reference; RefSeq - Reference Sequence.

1. Tamary H, Nishri D, Yacobovich J, Zilber R, Dgany O, Krasnov T, et al. Frequency and natural history of inherited bone marrow failure syndromes: the Israeli Inherited Bone Marrow Failure Registry. Haematologica. 2010;95(8):1300-1307.
2. Tamary H, Dgany O, Toledano H, Shalev Z, Krasnov T, Shalmon L, et al. Molecular characterization of three novel Fanconi anemia mutations in Israeli Arabs. Eur J Haematol. 2004;72(5):330-335.
3. Tamary H, Bar-Yam R, Shalmon L, Rachavi G, Krostichevsky M, Elhasid R, et al. Fanconi anaemia group A (FANCA) mutations in Israeli non-Ashkenazi Jewish patients. Br J Haematol. 2000;111(1):338-343.
4. Levran O, Doggett NA, Auerbach AD. Identification of Alu-mediated deletions in the Fanconi anemia gene FAA. Hum Mutat. 1998;12(3):145-152.