Mutational profile of rare variants in inflammasome-related genes in Behçet disease. A Next Generation Sequencing approach

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Table S1. Variants in Inflammasome-related genes identified in Behçet disease patients in the present study.

Mutations	SNP id.	Alleles nbr. N=710	Alleles (MAF) 1KG ALL pops. N=5008	Alleles (MAF) 1KG IBS pop. N=214	Reported pathology	PolyPhen2 functional prediction	SIFT functional prediction
CECR1_Arg49Trp	rs199614299 (**)	2	0 (0)	0 (0)	Unknown	Benign	Damaging
CECR1_Ala247Val	rs750868279 (**)	1	0 (0)	0 (0)	Unknown	Damaging	Tolerated
CECR1_Met309Ile	rs146597836	3	3 (0.0006)	1 (0.005)	Unknown	Benign	Tolerated
CECR1_His335Arg	rs2231495	218	1826 (0.3646)	58 (0.271)	Non-functional Polym	Benign	Tolerated
CECR1_Val349Ile	rs74317375	3	4 (0.0008)	0 (0)	Unknown	Benign	Tolerated
CECR1_Thr360Ala	rs775440641 (**)	2	0 (0)	0 (0)	Sneddon's syndrome	Damaging	Damaging
MEFV_Ala89Thr	rs104895124 (**)	1	0 (0)	0 (0)	FMF	Damaging	Damaging
MEFV_Leu110Pro	rs11466018	1	59 (0.0118)	0 (0)	FMF	Benign	Damaging
MEFV_Gly111Glu	rs751454741 (**)	1	0 (0)	0 (0)	Unknown	Benign	Tolerated
MEFV_Glu148Gln	rs3743930	5	633 (0.1264)	0 (0)	FMF, Functional Polym	Damaging	Damaging
MEFV_Arg202Gln	rs224222	156	681 (0.136)	63 (0.294)	Non-functional Polym	Benign	Tolerated
MEFV_Leu367Val	NA	1	0 (0)	0 (0)	Unknown	Benign	Tolerated
MEFV_Pro369Ser	rs11466023	3	101 (0.0202)	1 (0.005)	FMF	Damaging	Damaging
MEFV_His404Arg	rs755659290 (**)	1	0 (0)	0 (0)	Unknown	Damaging	Damaging
MEFV_Arg408Gln	rs11466024	3	86 (0.0172)	1 (0.005)	FMF	Benign	Tolerated
MEFV_Met582Leu	rs104895165 (**)	1	0 (0)	0 (0)	Recurrent Arthritis, FMF	Benign	Tolerated
MEFV_Ile591Thr	rs11466045	5	22 (0.0044)	2 (0.009)	FMF	Benign	Tolerated
MEFV_Met694Val	rs61752717	2	1 (0.0002)	0 (0)	FMF	Benign	Tolerated
MEFV_Lys695Arg	rs104895094	1	9 (0.0018)	1 (0.005)	FMF	Damaging	Tolerated
MEFV_Val726Ala	rs28940579 (**)	1	0 (0)	0 (0.000)	FMF	Benign	Tolerated
MEFV_Ala744Ser	rs61732874	5	9 (0.0018)	4 (0.019)	FMF	Benign	Tolerated
MEFV_Arg761His	rs104895097 (**)	1	0 (0)	0 (0)	FMF	Benign	Tolerated
MVK_Val5Ala	rs141765653	1	1 (0.0002)	0 (0)	HIDS	Benign	Tolerated
MVK_Ser52Asn	rs7957619	79	380 (0.0759)	33 (0.154)	Non-functional Polym	Benign	Tolerated
MVK_Val80Ile	rs76914224	1	10 (0.002)	0 (0)	HIDS	Benign	Tolerated
MVK_Thr237Ser	rs104895366 (**)	1	0 (0)	0 (0)	HIDS	Damaging	Tolerated
MVK_Val293Met	rs104895356	1	1 (0.0002)	0 (0)	HIDS	Damaging	Tolerated
MVK_Val377Ile	rs28934897 (**)	1	0 (0)	0 (0)	HIDS	Benign	Tolerated
NLRP3_Val198Met	rs121908147	5	20 (0.004)	1 (0.005)	FCAS	Benign	Tolerated
NLRP3_Ile315Val	rs180177501 (**)	1	0 (0)	0 (0)	MAGIC Syndrome	Benign	Tolerated
NLRP3_Arg488Lys	rs145268073	2	1 (0.0002)	0 (0)	FCAS	Benign	Tolerated
NLRP3_Gln703Lys	rs35829419	39	112 (0.0224)	16 (0.075)	FCAS, Functional Polym	Benign	Tolerated
NLRP3_Ser726Gly	rs147946775	1	1 (0.0002)	0 (0)	CINCA/NOMID	Damaging	Tolerated
NOD2_Leu81Val	rs34936594 (**)	1	0 (0)	0 (0)	Unknown	Benign	Damaging
NOD2_Ala140Thr	rs34684955	1	35 (0.007)	0 (0)	CD	Benign	Tolerated
NOD2_Leu248Arg	rs104895423	1	1 (0.0002)	0 (0)	CD	Damaging	Damaging
NOD2_Pro268Ser	rs2066842	61	511 (0.102)	61 (0.285)	Non-functional Polym	Benign	Tolerated
NOD2_Asn289Ser	rs5743271	13	20 (0.004)	2 (0.009)	CD	Benign	Tolerated
NOD2_Arg311Trp	rs104895427	2	4 (0.0008)	0 (0)	CD	Damaging	Damaging
NOD2_Leu349Phe	NA	2	0 (0)	0 (0)	Unknown	Benign	Damaging
NOD2_Arg702Trp	rs2066844	22	72 (0.0144)	12 (0.056)	CD	Damaging	Damaging
NOD2_Arg703Cys	rs5743277	2	5 (0.001)	0 (0)	CD	Damaging	Damaging
NOD2_Val733Leu	NA	1	0 (0)	0 (0)	Unknown	Benign	Tolerated
NOD2_Ala755Val	rs61747625	2	1 (0.0002)	0 (0)	CD	Damaging	Tolerated
NOD2_Arg791Gln	rs104895464	2	1 (0.0002)	0 (0)	Spondylarthropathy	Benign	Tolerated
NOD2_Val793Met	rs104895444	3	1 (0.0002)	0 (0)	CD	Benign	Tolerated
NOD2_Val816Ile	NA	1	0 (0)	0 (0)	Unknown	Benign	Tolerated
NOD2_Met863Val	rs104895447	1	1 (0.0002)	0 (0)	CD	Benign	Tolerated
NOD2_Gly908Arg	rs2066845	7	23 (0.0046)	2 (0.009)	CD	Damaging	Damaging
NOD2_Ala918Asp	rs104895452	1	3 (0.0006)	1 (0.005)	CD	Damaging	Tolerated
NOD2_Val955Ile	rs5743291	62	167 (0.0333)	28 (0.131)	CD, Functional Polym	Benign	Tolerated
PSTPIP1_Thr68Met	rs201872851	2	13 (0.0026)	0 (0)	Unknown	Damaging	Tolerated
PSTPIP1_Val122Ile	NA	1	0 (0)	0 (0)	Unknown	Benign	Tolerated
PSTPIP1_Glu277Asp	NA	1	0 (0)	0 (0)	PAPASH	Benign	Tolerated
PSTPIP1_Asp289His	NA	2	0 (0)	0 (0)	Unknown	Damaging	Tolerated
PSTPIP1_Arg405Cys	rs201253322	2	4 (0.0008)	1 (0.005)	Idiopathic juvenile arthritis	Benign	Tolerated
TNFRSF1A_Pro75Leu	rs4149637	3	141 (0.0282)	0 (0)	TRAPS	Damaging	Tolerated
TNFRSF1A_Arg121Gln	rs4149584	8	30 (0.006)	0 (0)	TRAPS	Benign	Tolerated
TNFRSF1A_His155Tyr	NA	1	0 (0)	0 (0)	Unknown	Benign	Tolerated
TNFRSF1A_Ile199Thr	rs104895247 (**)	2	0 (0)	0 (0)	Unknown	Benign	Tolerated
TNFRSF1A_Arg312Lys	rs200900510	1	6 (0.0012)	0 (0)	Unknown	Benign	Tolerated
TNFRSF1A_Asn336His	NA	4	0 (0)	0 (0)	Unknown	Benign	Damaging

Polym: Polymorphism. NA: not available or SNP undescribed. Unknown: Unavailable information in clinical data bases. 1KG: 1000 genomes, (**): SNP not found in 1000 Genomes Project Phase 3 but found in Exome Aggregation Consortium (ExAC) database.

Table S2. Frequency of 3 *NOD2* loss of function variants in Spanish BD patients and controls

NOD2	p.Asn289Ser		p.Arg702Trp		p.Gly908Arg	
	BD	**Controls**	**BD**	**Controls**	**BD**	**Controls**
Mutated alleles	13 (0.018)	2 (0.009)	22 (0.03)	12 (0.06)	7 (0.01)	2 (0.01)
Total tested alleles	710	214	710	214	710	214
P-values	0.36		0.09		0.95	

Controls and their genotypes from 1000 genomes IBS population.

Table S3. Clinical features of BD patients carrying rare variants.

Gene	Nr. Patients	Clinical features					
		Genital sores (60%)*	**Vascular affection (21%)***	**Digestive affection (16%)***	**Arthritis (42%)***	**SNC affection (18%)***	**Uveitis (54%)***
CECR1	11	67%	0%	33%	33%	33%	0%
MEFV	32	89%	11%	22%	44%	22%	78%
MVK	5	0%	0%	80%	80%	0%	0%
NLRP3	9	67%	33%	33%	67%	0%	33%
NOD2	40	43%	0%	14%	43%	0%	29%
PSTPIP1	8	50%	0%	17%	67%	17%	50%
TNFRSF1A	19	67%	33%	33%	33%	33%	67%

For each gene, percentage of patients with rare variants having each clinical manifestation is displayed.
*Percentage of patients with this clinical feature in the BD cohort.
No significant differences were found in any case (Pc>0.05).

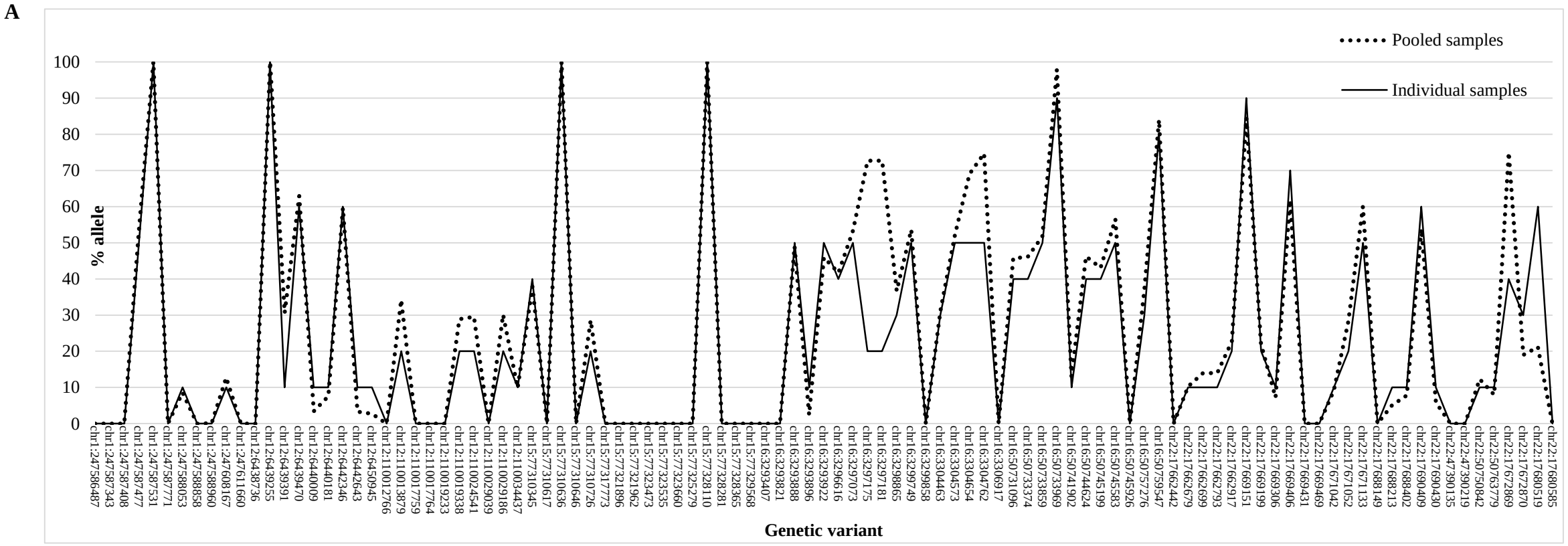

Figure S1. Validation of the method used to quantify alleles in the pooled samples. **A.** Representation of the percentage of each allele in 101 polymorphic positions (listed in the x axis) sequenced in 5 samples, in both ways, individually (continuous line) and pooled (dotted line). **B.** Coefficient of linear correlation (R^2) for the percentage of the alleles quantification in the same quality control.

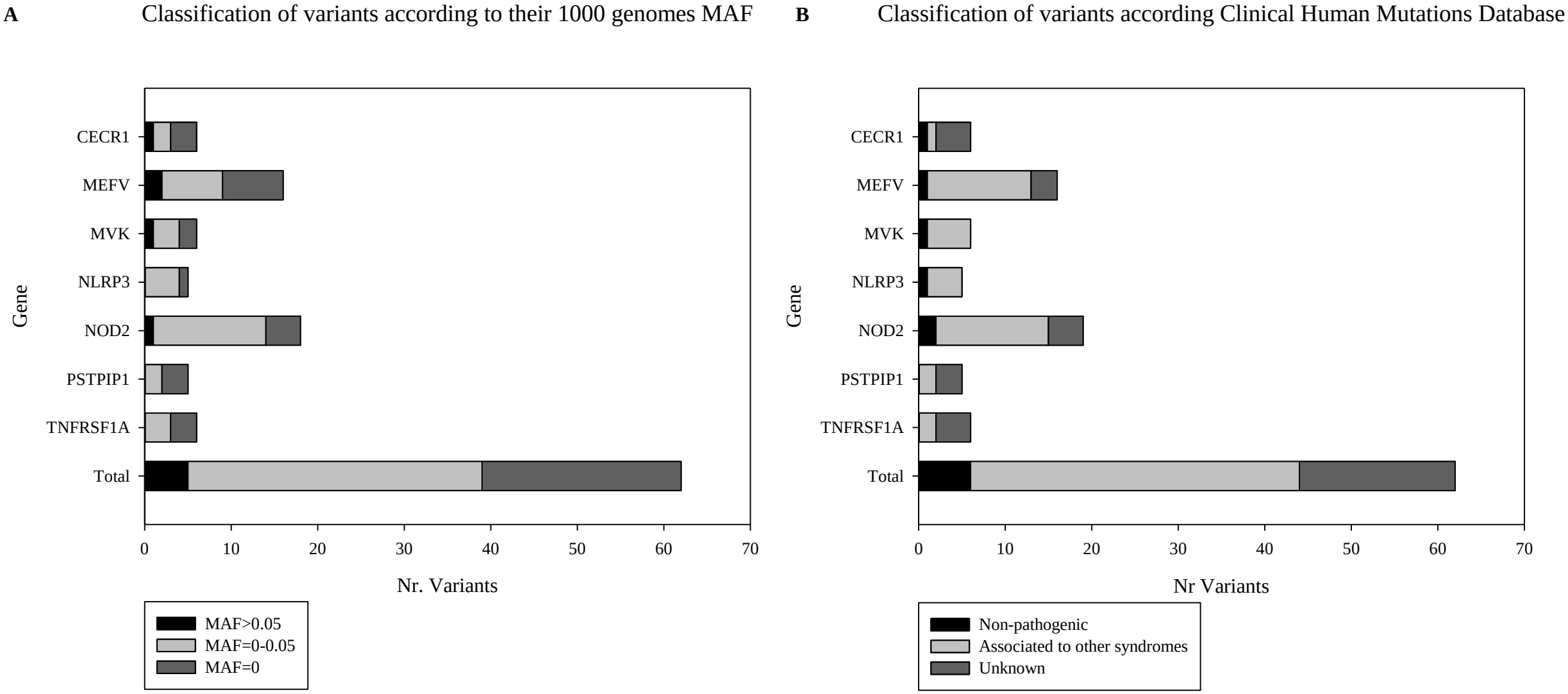

Figure S2. Graphical representation of the number of variants classified in subgroups according to (**A**) their 1000 genomes MAF and (**B**) the information available in clinical human mutation databases.