

Table S1. Search strategies elaborated for Systematic Review.

Databases	Search strategy
PubMed / Medline	(diabetic retinopath*) AND ((Polymorphism*, Genetic) OR ('Genetic Polymorphism') OR ('Genetic Polymorphisms') OR ('Gene Polymorphism') OR ('Gene Polymorphisms') OR (Polymorphism*, Gene) OR (Polymorphism* (Genetics)) OR ('Genetic Susceptibility') OR ('Genetic Susceptibilities') OR (Susceptibilit*, Genetic) OR ('Genetic Predisposition') OR ('Genetic Predispositions') OR (Predisposition*, Genetic)) AND (("Polymorphism, Genetic" OR polymorphism*) AND ("Vascular Endothelial Growth Factor A" OR "VEGF-A" OR "VEGF" OR "Vascular Endothelial Growth Factor")))
Web of Science	TS=(((("Diabetic Nephropath*") AND ((Polymorphism*, Genetic) OR ("Genetic Polymorphism\$") OR ("Gene Polymorphism\$") OR (Polymorphism\$, Gene) OR (Polymorphism\$ (Genetics)) OR ("Genetic Susceptibilit*") OR (Susceptibilit*, Genetic) OR ("Genetic Predisposition\$") OR (Predisposition\$, Genetic)) AND ((VEGFA) OR (VEGF) OR ("vascular endothelial growth factor a") OR ("vascular endothelial growth factor")))))
Biblioteca Virtual em Saúde	(diabetic retinopathy*) AND (polymorphism* OR genetic polymorphism* OR gene polymorphism* OR genetic susceptibility OR genetic predisposition) AND ('VEGFA' OR 'VEGF' OR 'vascular endothelial growth factor a' OR 'vascular endothelial growth factor')
Embase	('diabetic nephropath*') AND (polymorphism*, AND genetic OR 'genetic polymorphism' OR 'genetic polymorphisms' OR 'gene polymorphism' OR 'gene polymorphisms' OR (polymorphism*, AND gene) OR (polymorphism* AND genetics) OR 'genetic susceptibility' OR 'genetic susceptibilities' OR (susceptibilit*, AND genetic) OR 'genetic predisposition' OR 'genetic predispositions' OR

(predisposition*, AND genetic)) AND ('polymorphism, genetic' OR polymorphism*) AND ('vascular endothelial growth factor a' OR 'vegf-a' OR 'vegf' OR 'vascular endothelial growth factor')

Scopus	TITLE-ABS-KEY ("Diabetic retinopath*") AND TITLE-ABS-KEY (Polymorphism*, Genetic) OR TITLE-ABS-KEY ("Genetic Polymorphism*") OR TITLE-ABS-KEY ("Gene Polymorphism*") OR TITLE-ABS-KEY ("Polymorphism, Gene") OR TITLE-ABS-KEY ("Polymorphism (Genetics)") OR TITLE-ABS-KEY ("Genetic Susceptibilit*") OR TITLE-ABS-KEY (Susceptibilit*, Genetic) OR TITLE-ABS-KEY ("Genetic Predisposition*") OR TITLE-ABS-KEY ("Predisposition, Genetic") AND TITLE-ABS-KEY("vascular endothelial growth factor a") OR TITLE-ABS-KEY("VEGFA") OR TITLE-ABS-KEY("VEGF")
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Table S2 - Values of the accuracy, precision and recall parameters by supervised machine learning, of the SNVs T-460C (rs833061) and I/D -2549, in the random forest (RF) model.

Parameters	Test	Genetic model	SNV	Reference
Accuracy	0,554	Codominant	rs833061	Paine <i>et al.</i> , 2012
Precision	0,531	Codominant	rs833061	Paine <i>et al.</i> , 2012
Recall	0,722	Codominant	rs833061	Paine <i>et al.</i> , 2012
Accuracy	0,514	Dominant	rs833061	Paine <i>et al.</i> , 2012
Precision	0,500	Dominant	rs833061	Paine <i>et al.</i> , 2012
Recall	0,986	Dominant	rs833061	Paine <i>et al.</i> , 2012
Accuracy	0,561	recessive	rs833061	Paine <i>et al.</i> , 2012
Precision	0,537	recessive	rs833061	Paine <i>et al.</i> , 2012
Recall	0,708	recessive	rs833061	Paine <i>et al.</i> , 2012
Accuracy	0,486	Overdominant	rs833061	Paine <i>et al.</i> , 2012
Precision	0,481	Overdominant	rs833061	Paine <i>et al.</i> , 2012
Recall	0,694	Overdominant	rs833061	Paine <i>et al.</i> , 2012
Accuracy	0,738	Codominant	rs833061	Ray <i>et al.</i> , 2004

Precision	0,738	Codominant	rs833061	Ray <i>et al.</i> , 2004
Recall	1,000	Codominant	rs833061	Ray <i>et al.</i> , 2004
Accuracy	0,738	Dominant	rs833061	Ray <i>et al.</i> , 2004
Precision	0,738	Dominant	rs833061	Ray <i>et al.</i> , 2004
Recall	1,000	Dominant	rs833061	Ray <i>et al.</i> , 2004
Accuracy	0,738	recessive	rs833061	Ray <i>et al.</i> , 2004
Precision	0,738	recessive	rs833061	Ray <i>et al.</i> , 2004
Recall	1,000	recessive	rs833061	Ray <i>et al.</i> , 2004
Accuracy	0,738	Overdominant	rs833061	Ray <i>et al.</i> , 2004
Precision	0,738	Overdominant	rs833061	Ray <i>et al.</i> , 2004
Recall	1,000	Overdominant	rs833061	Ray <i>et al.</i> , 2004
Accuracy	0,846	Codominant	-2549 I/D	Buraczynska et al., 2007
Precision	0,846	Codominant	-2549 I/D	Buraczynska et al., 2007
Recall	1,000	Codominant	-2549 I/D	Buraczynska et al., 2007
Accuracy	0,846	Dominant	-2549 I/D	Buraczynska et al., 2007
Precision	0,846	Dominant	-2549 I/D	Buraczynska et al., 2007
Recall	1,000	Dominant	-2549 I/D	Buraczynska et al., 2007
Accuracy	0,846	recessive	-2549 I/D	Buraczynska et al., 2007
Precision	0,846	recessive	-2549 I/D	Buraczynska et al., 2007
Recall	1,000	recessive	-2549 I/D	Buraczynska et al., 2007
Accuracy	0,846	Overdominant	-2549 I/D	Buraczynska et al., 2007
Precision	0,846	Overdominant	-2549 I/D	Buraczynska et al., 2007
Recall	1,000	Overdominant	-2549 I/D	Buraczynska et al., 2007
Accuracy	0,500	Codominant	-2549 I/D	Singh <i>et al.</i> , 2021
Precision	0,500	Codominant	-2549 I/D	Singh <i>et al.</i> , 2021
Recall	0,467	Codominant	-2549 I/D	Singh <i>et al.</i> , 2021
Accuracy	0,367	Dominant	-2549 I/D	Singh <i>et al.</i> , 2021
Precision	0,389	Dominant	-2549 I/D	Singh <i>et al.</i> , 2021
Recall	0,467	Dominant	-2549 I/D	Singh <i>et al.</i> , 2021
Accuracy	0,500	recessive	-2549 I/D	Singh <i>et al.</i> , 2021
Precision	0,500	recessive	-2549 I/D	Singh <i>et al.</i> , 2021
Recall	0,733	recessive	-2549 I/D	Singh <i>et al.</i> , 2021
Accuracy	0,567	Overdominant	-2549 I/D	Singh <i>et al.</i> , 2021
Precision	0,562	Overdominant	-2549 I/D	Singh <i>et al.</i> , 2021
Recall	0,600	Overdominant	-2549 I/D	Singh <i>et al.</i> , 2021

Table S3. Evaluation of the stereochemical quality of the obtained model.

Procheck	4zpk	4zpk.1
Residues in most favored regions	83.1%	83.9%
Residues in additional allowed regions	15.7%	13.8%
Waste in generously allowed regions	0.8%	1.4%
Waste in disallowed regions	0.4%	0.9%
Errat	81.56%	88.01%

Table S4. Results obtained after molecular docking analysis of wild and mutant models.

	HIF1-460T	HIF1-460C
HADDOCK score	-122.83(-109.4 +/- 8.3)	-124.83 (-113.1 +/- 10.3)
Van der Waals energy	-69.96(-57.8 +/- 8.5)	-78.50(-73.2 +/- 4.7)
electrostatic energy	-370.99(-371.0 +/- 11.9)	-369.31(-336.0 +/- 34.4)
Desolvation energy	21.6(21.6 +/- 2.2)	26.98(27.0 +/- 3.8)
Restraints violation energy	2.8(10.3 +/- 11.8)	2.62(2.6 +/- 0.8)

Frame S1. Characteristics of studies included in systematic review and meta-analysis

Study and year of publication	Type of study	Population	Ethnicity	Disease/stage	Sample size	Sex of the population (M/F)	Average age of the population	Genotyping method	Genetic variant analyzed
Churchill <i>et al.</i> , 2008	case-control	Europa	European	DR/PDR	case: 45 control: 61	case: 60%/40% control: 52,5%/47,5	case: 59,6 ± control: 55,3 ± 52,5	PCR-RLFP	C-460T (rs833061) T-417C (rs833062) C-160T G-152A (rs13207351) A-141C (rs28357093) G-116A (rs1570360)
Porojan <i>et al.</i> , 2015	case-control	Romania	Caucasian	T2DM	case:200 control: 208	case: 50.5%/49.5% control: 44.71%/ 55.29%	case: 63,84±12,59 control: 54,78±15	PCR-RLFP	C936 T (rs3025039)
Yuan <i>et al.</i> , 2014	case-control	China	Chinese	NPDR /PDR	case:108 control: 144	case: 40/68 control: 70/74	case:60.66 ± 8.54 control:60.95 ± 9.96	PCR-LDR	G-634 C (rs2010963)
Choudhuri <i>et al.</i> , 2015	case-control	Indian	Indian	NPDR /PDR	case:102 control: 105	case: 53.4 ± 8.15 control: 53.1 ± 7.86	case:57/48 control: 55/47	qPCR	rs2010963 em 5' UTR rs3025039 em 3' UTR rs1570360
Nakamura <i>et al.</i> , 2008	case-control	Japan	Japaneses	PDR	case:177 control: 292	case: 97/80 control: 168:124	case: 34.1 ± 13.6 control: 45.2 ± 13.0	PCR-RFLP	C-2578 A (rs699947)

Singh <i>et al.</i> , 2021	case-control	India	Indian	T2DM/DR	case:105 control: 51	case:79/26 control: 25/26	case: 58.4 ± 9.4 control: 57.5 ± 8.3/56.9 ± 7.7	PCR-RFLP	C-2578 A (rs699947) -2549 I/D (rs35569394)
Suganthalakshmi <i>et al.</i> , 2006	case-control	India	_____	T2DM/DR	case:120 control: 90	case: 56.6/43.4 control: 77.7/22.3	case: 63 ± 7.2 control: 59 ± 8.7	PCR-RFLP	C (-7) T C (-634) G UTR 5' T (-1498) C
Paine <i>et al.</i> , 2012	case-control	India	Indian	T2DM/PDR	case:253 control: 240	case: 133 (52.56%)/ 120 (47.44%) control: 128(53.33%) / 112 (46.67%)	case:52±15.0 control: 54±12.0	qPCR	T-460C (rs833061) A+874T (rs2430561)
Chun <i>et al.</i> , 2010	case-control	Korea	_____	T2DM/ NPDR/PDR	case:134 control: 260	_____	_____	qPCR	C-2578A (rs699947)
Yang <i>et al.</i> , 2010	case-control	China	Chinese	T2DM/DR	case:285 control: 96	case: 137/148 control: 48/48	case: 58.98 ±1.14 control: 52.01±1.06	qPCR	C-634G (rs2010963)
Buraczynska <i>et al.</i> , 2007	case-control	Poland	Caucasian	T2DM/DR	case: DM - 426, RD-195 control: 493	case:DM- 221/205; RD- 103/92 control: 248/245	case: 57.4±11.2/58.6 ±9.4 control: 51.4 ± 11.7**	PCR-RFLP	-2549 I/D (rs35569394)
Awata <i>et al.</i> , 2002	case-control	Japan	Japanese	T2DM/DR/ NPDR/PDR	case:118 control: 150	case:74:76 control: 61:57	case: 58.4 / 11.7 control: 54.0±15.1	PCR-RFLP	C-634 G 5' UTR
Wijaya <i>et al.</i> , 2021	case-control	Indonesia	Javanese	T2DM/DR/ NPDR	case: 33 control: 35	case: 50.15 ± 7.02	case: 21/12 control: 19/16	PCR-RFLP	C-2578A (rs699947)

						control: 50.15 ± 7.02			
El-Shazly <i>et al.</i> , 2014	cohort	Egypt	Egyptians	T2DM/DR/ NPDR	case:212 control: 180	case :108/104 control: 96/84	case: 60.53 (±5.36) control: 59.85 (±3.58)	PCR-RFLP	C-634G (rs2010963)
Fegghi <i>et al.</i> , 2011	cohort	Iran	Caucasian	T2DM/ NPDR/PDR	RDP:119 RDNP: 279	case: RDP 60/59 RDNP 135/144 control: not available	case: RDP 58.6±8.3; RDNP 56.9±6 9.7 control: not available	PCR-RFLP	G+405C (rs2010963)
Yang <i>et al.</i> , 2011	cohort	China	Chinese	T2DM/DR	case:129 control:139	case: 57/72 control: 58/81	case: 48.68±9.58 control: 50.45±8.00	Sequenom MassARRA Y technology	C-2578A (rs699947) C-460T (rs833061) A- 152G(rs13207351)
Chehadeh <i>et al.</i> , 2022	cohort	United Arab Emirates/ Europe/Asia /Africa/ Americans/ Ashkenazi Jews	—————	T2DM/DR	rs833061 Arab case: 157 European control: 7454 rs833068 Arab case: 157 European control: 4481 rs3024997 Arab case- 158 European control: 4438	case: 6/29 control: 12/20	case: 57.94± 1.55 control: 52.21± 2.00	Infinium Omni5Exom eHuman chip (Illumina Inc., San Diego, USA	T-460C (rs833061) (rs833068) (rs3024997)

Awata <i>et al.</i> , 2005	cohort	Japan	Japanese	T2DM/ NPDR/PDR	case: 175 control: 203	case: 87/88 control:93/110	case: 58±11* control:55±15	PCR-RFLP	C-634G (rs2010963)
Ray <i>et al.</i> , 2004	cohort	United Kingdom	Caucasian	PDR/ NPDR	case: 69 control: 198	case : 1/0.76 controls: 1/1	case: 51.1±15.3 controls: 52.6±16.1	qPCR	T-460C (rs833061)
Wagih <i>et al.</i> , 2022	cohort	Egypt	Egyptians	DM/PDR/ NPDR	case: 200 (100 NPDR e 100 PDR) control: 100	case: RDNP 55/45 RDP 66/34 control: 53/47	case: RDNP56.4±8.3 /RDP 54.4±10.2 control: 45.6±11.3	PCR-RFLP	G-152 A (rs13207351)

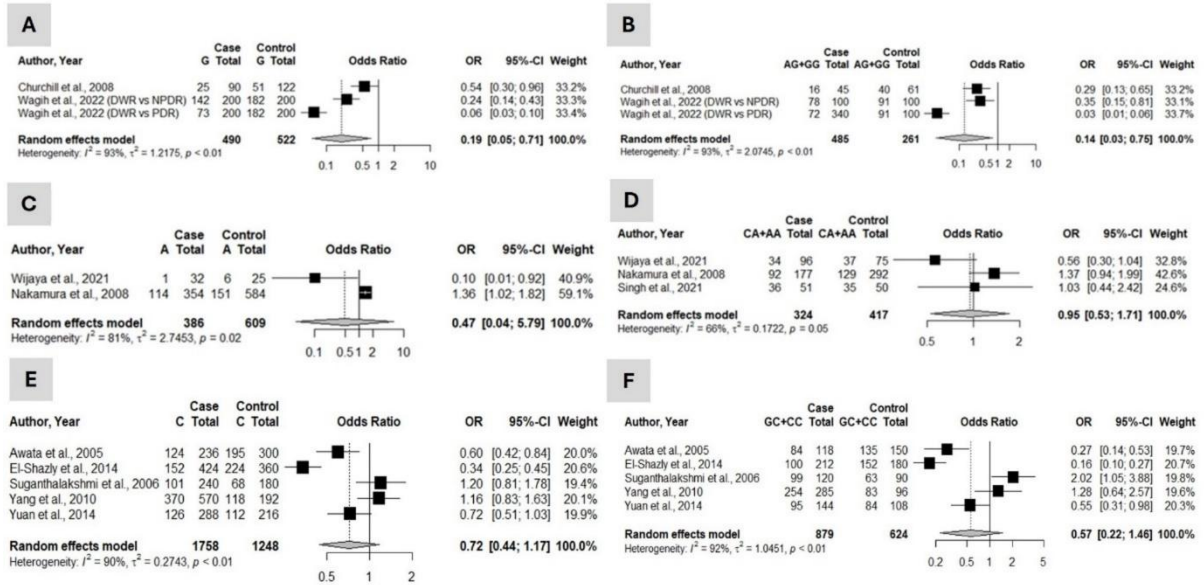


Figure S1 – Compiled from forest plots for genotypic and allelic comparisons of SNVs that did not demonstrate significant association. Allele frequency and genotype frequency, respectively: A and B - (SNP A-152G); C and D - (SNP C-2578A); E and F - (SNP G-634C).

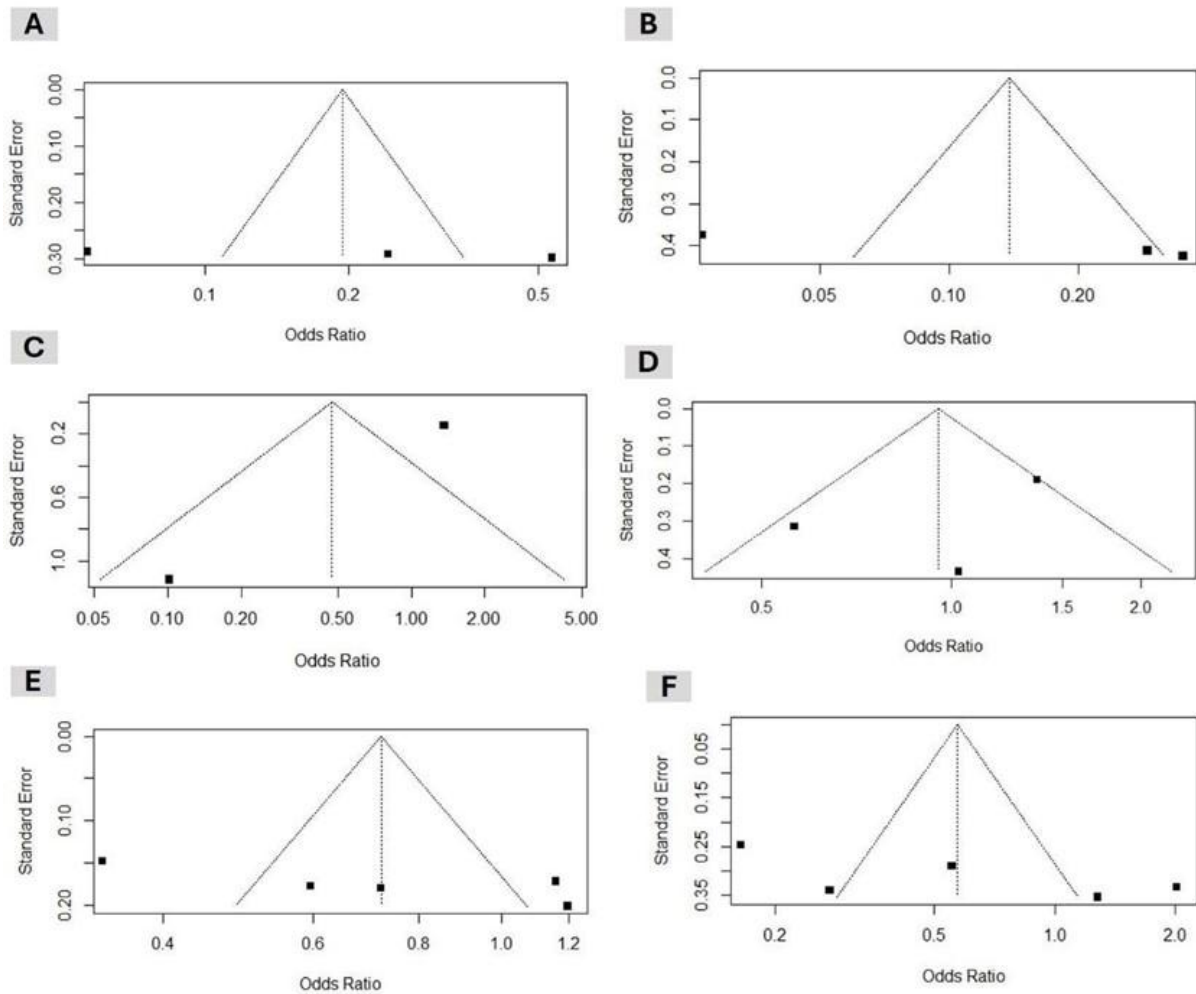


Figure S2. Funnel plots to analyze the risk of bias, using allelic and genotypic comparisons. A) Allelic funnel plot and B) Genotypic funnel plot (A-152G); C) Allelic funnel plot and D) Genotypic funnel plot (C-2578A); E) Allelic funnel plot and F) Genotypic funnel plot (G-634C).

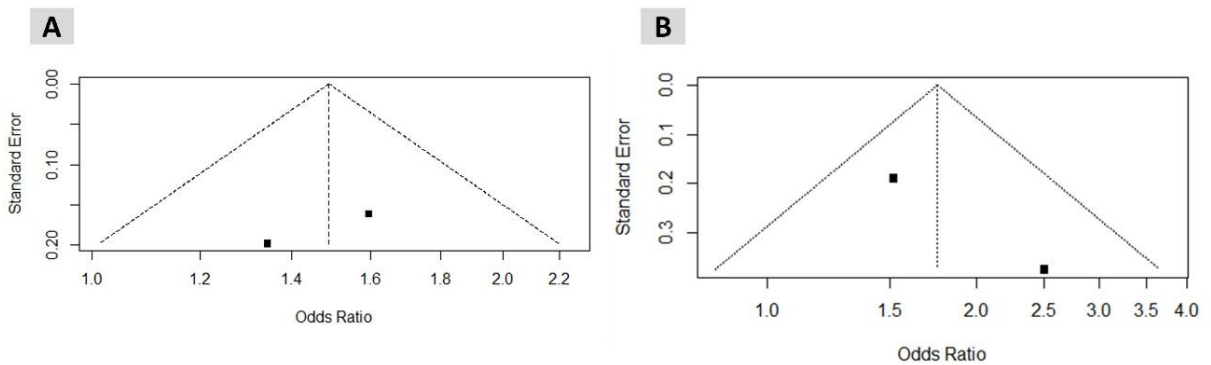


Figure S3. Funnel chart to analyze the risk of bias, using allelic and genotypic comparisons. A) T-460C allelic funnel plot and in B) T-460C genotypic funnel plot.

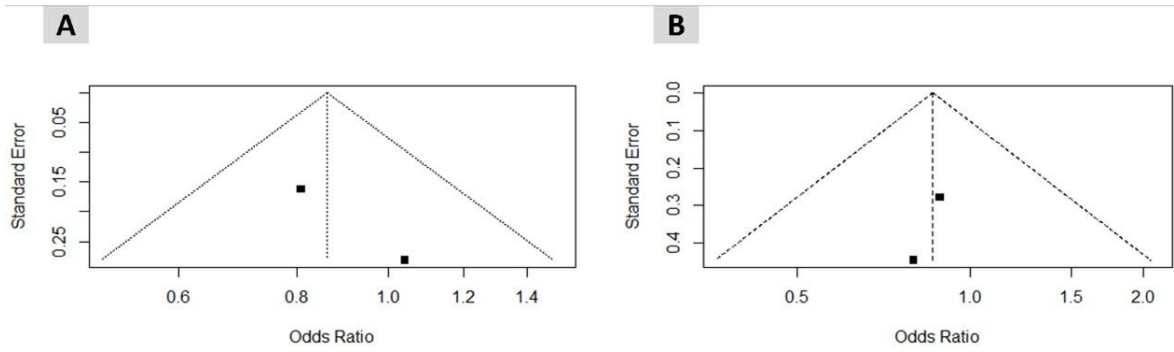


Figure S4. Funnel plot to analyze the risk of bias, using allelic and genotypic comparisons. A) Allelic funnel plot I-2549D and in B) Genotypic funnel plot I-2549D.

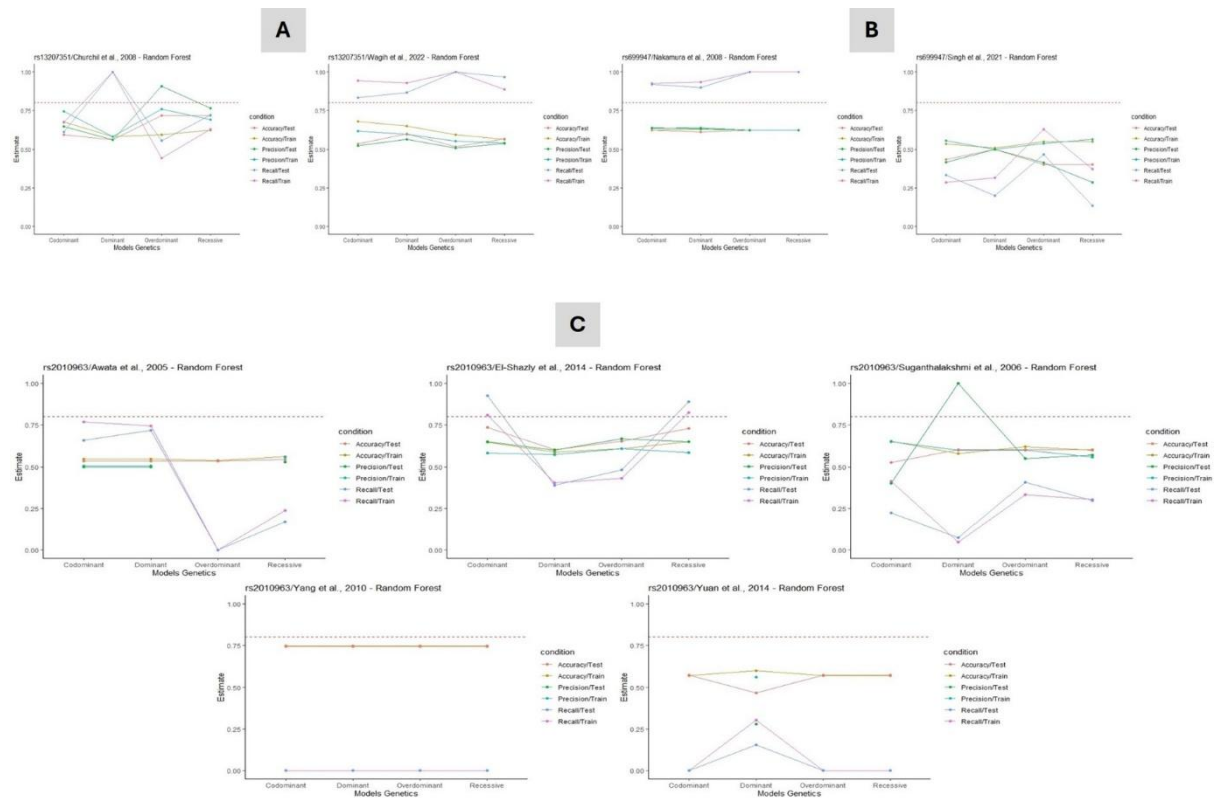


Figure S5 - Graph with machine learning parameters of SNVs: A) A-152G (rs13207351), B) C-2578A (rs699947) and C) G-634C (rs2010963).