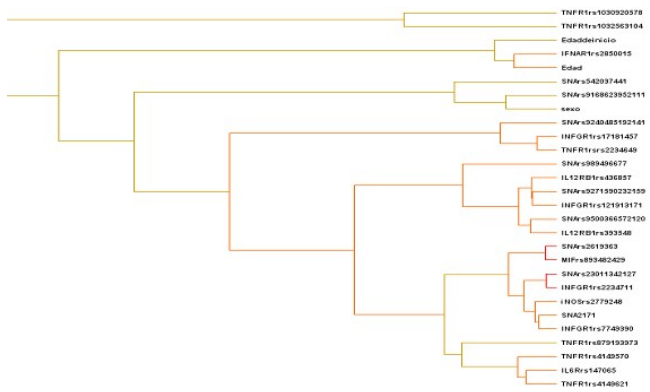

Fig. 1S. Dendogram of interactions of selected gene markers and environmental attributes with the highest percentage.of interaction in the population with problematic alcohol use.

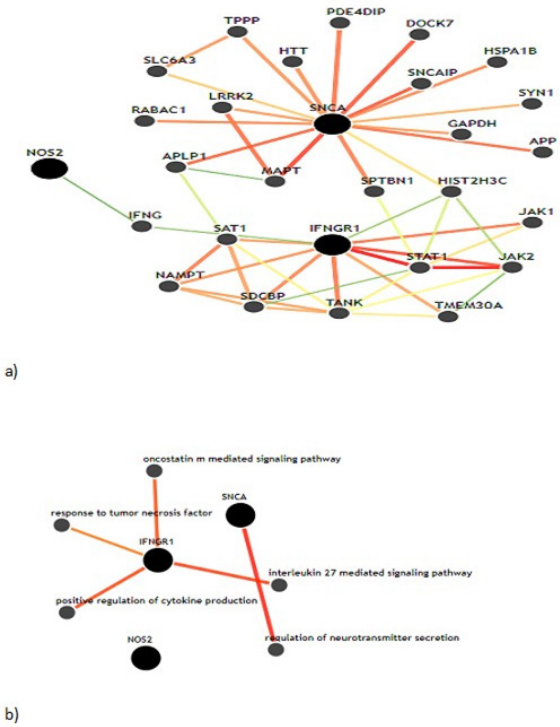

Fig. S2. Fonctional genetic network for the SNCA, IFNGR1, MIF and iNOS2 proteins. Only genes (A) and participating pathway (B).

Table S1. Characteristics of the primers used for conventional PCR to determine selected genetic variants (SNVs and STR).

Gene	PCR primers	Sequence 5'--3'	Primer length	Hybridization temperature (°C)	Length Amplicon (bp)
IL6R	Forward	CACAGCGTAATCCCGTTCAC	20	53	517
	Reverse	AGAGGCGGACAGGCTAATG	19		
iNOS2	Forward	CCCAGATGCTGAAAGTGAGG	20	55	495
	Reverse	CAGTCAAACCAGGAAGAGACCT	22		
IFNGR1	Forward	GTCAGGCTCCAAGACAACCA	20	55	696
	Reverse	GAGAAAGGCAACCGACGAG	19		
IFNAR1	Forward	GGTGTGTGTGTCAGAAGAGGC	21	55	152
	Reverse	GCAGATCCCACCAGTTACATG	21		
IL12RB1	Forward	AGAACCCCCTAGAACCCTGAC	21	55	415
	Reverse	CCCACAGCTCTCCACACATAC	21		
HMGB1	Forward	AGCTCTGCTTTCCCGTAGC	19	55	263
	Reverse	AGCCTCCTCACTCTCTCCG	19		
MIF	Forward	CCAAGTGGAGAACAGGTTGG	20	58	281
	Reverse	GCAGAAGGACCAGGAGACC	19		
RELA	Forward	TGACATCACCAAACTCCGCC	20	56,8	348
	Reverse	TGCACTACAGACGAGCCATT	20		
TNFR1	Forward	AACAAATCCTTACAGGAACCCCA	23	55	571
	Reverse	GGGTGACAGTTGAGGGTTGA	20		
α-SNCA SNV	Forward	CCGCTTGTTTTAGACGGCTG	20	51	561
	Reverse	GTCACGAGCACTCTTGTGGA	20		
α-SCNA STR-Rep1	Forward	CCTGGCATATTTGATTGCAA	20	57	269-277 (variable)
	Reverse	GACTGGCCCAAGATTAACCA	20		

Table S2. Frequency of genotypes and alleles of different SNVs of the promoter region of candidate genes is related to the inflammatory response in controls and individuals with problematic alcohol consumption.

Gene SNVs	Group	N	Genotype frequencies n (%)			Alleles frequencies n (%)	
			1/1	1/2	2/2	1	2
SNCA rs2619363 [-2229] n=85 1=T, 2=G	Controls	48	1(2)	15(31)	32(67)	17(18)	79(82)
	Problematic use of alcohol	37	4(10)	11(30)	22(59)	19(26)	55(74)
	Chi squared (p value)		2,892 (0,235)			1,589 (0,207)	
SNCA rs542037441 [-2195] n=93 1=G, 2=T	Controls	54	53(98)	1(2)	0(0)	107(99)	1(1)
	Problematic use of alcohol	39	39(100)	0(0)	0(0)	78(100)	0(0)
	Chi squared (p value)		0,730 (1,00)			0,049 (0,823)	
SNCA rs989496677 [-2185] n=93 1=C, 2=T	Controls	54	54(100)	0(0)	0(0)	108(100)	0(0)
	Problematic use of alcohol	39	39(100)	0(0)	0(0)	78(100)	0(0)
	Chi squared (p value)		Monomorphic			Monomorphic	
SNCA [-2171] n=93 1=T,2=A	Controls	51	24(47)	27(53)	0(0)	75(74)	27(26)
	Problematic use of alcohol	42	15(36)	27(64)	0(0)	57(68)	27(32)
	Chi squared (p value)		0,270 (0,298)			0,7193 (0,39639)	
SNCA rs927159023 [-2159] n=91 1=G,2=C	Controls	54	54(100)	0(0)	0(0)	108(100)	0(0)
	Problematic use of alcohol	37	37(100)	0(0)	0(0)	74(100)	0(0)
	Chi squared (p value)		Monomorphic			Monomorphic	
SNCA rs924048579 [-2141] n=93 1=C, 2=T	Controls	54	54(100)	0(0)	0(0)	108(100)	0(0)
	Problematic use of alcohol	39	38(97)	1(3)	0(0)	77(99)	1(1)
	Chi squared (p value)		0,237 (0,419)			0,0571 (0,8116)	
SNCA rs2301134 [-2127] N=93 1=G, 2=A	Controls	54	15(28)	31(57)	8(15)	61(56)	47(44)
	Alcohol Dependientes	39	10(26)	18(46)	11(28)	38(48)	40(52)
	Chi squared (p value)		2,570 (0,277)			1,096 (0,295)	
SNCA rs950036657 [-2120] n=96 1= G, 2=A	Controls	54	54(100)	0(0)	0(0)	108(100)	0(0)
	Problematic use of alcohol	42	42(100)	0(0)	0(0)	84(100)	0(0)
	Chi squared (p value)		Monomorphic			Monomorphic	
SNCA rs916862395 [-2111] n=96 1=G, 2=C	Controls	54	54(100)	0(0)	0(0)	108(100)	0(0)
	Problematic use of alcohol	42	42(100)	0(0)	0(0)	84(100)	0(0)
	Chi squared (p value)		Monomorphic			Monomorphic	
IL6R rs4845617 n=68 1=G, 2=A	Controls	32	8(25)	20(63)	4(13)	36(56)	28(44)
	Problematic use of alcohol	36	10(28)	24(67)	2(5)	44(61)	28(39)
	Chi squared (p value)		1,020 (0,600)			0,3606 (0,5636)	
IL6R rs1470654147 n=70 1=C, 2=T	Controls	34	28(82)	6(18)	0(0)	62(91)	6(9)
	Problematic use of alcohol	36	22(61)	12(33)	2(6)	56(78)	16(22)
	Chi squared (p value)		3,039 (0,218)			4,7401 (0,0294)*	
iNOS rs2779248 n=59 1=T, 2=C	Controls	24	12(50)	8(33)	4(17)	32(67)	16(33)
	Problematic use of alcohol	35	15(43)	15(43)	5(14)	45(64)	25(36)
	Chi squared (p value)		0,543 (0,762)			0,0712 (0,789)	
IFNGR1 rs121913171 n=77 1=G, 2=A	Controls	38	36(95)	2(5)	0(0)	74(97)	2(3)
	Problematic use of alcohol	39	37(95)	2(5)	0(0)	76(97)	2(3)
	Chi squared (p value)		0,001 (0,979)			0,0007 (0,979)	

IFNGR1 rs17181457 n=80 1=G, 2=A	Controls	40	35(88)	5(12)	0(0)	75(94)	5(6)
	Problematic use of alcohol	40	31(78)	6(15)	3(7)	68(92)	6(8)
	Chi squared		3,333			0,2001	
	(p value)		(0,189)			(0,6546)	
IFNGR1 rs2234711 n=66 1=A, 2=G	Controls	36	14(39)	16(44)	6(17)	44(61)	28(39)
	Problematic use of alcohol	30	10(33)	17(57)	3(10)	37(62)	23(38)
	Chi squared		1,161			0,0043	
	(p value)		(0,560)			(0,9479)	
IFNGR1 rs7749390 n=75 1=G, 2=A	Controls	39	6(15)	17(44)	16(41)	29(47)	49(63)
	Problematic use of alcohol	36	5(14)	20(55)	11(31)	30(42)	42(58)
	Chi squared		0,632			0,366	
	(p value)		(0,729)			(0,5451)	
IFNAR1 rs2850015 n=72 1=C, 2=T	Controls	40	8(20)	28(70)	4(10)	44(55)	36(45)
	Problematic use of alcohol	32	8(25)	18(56)	6(19)	34(53)	30(47)
	Chi squared		1.706			0.050	
	(p value)		(0,4261)			(0,8224)	
IL12RB1 rs436857 n=70 1=G, 2=A	Controls	30	27(90)	3(10)	0(0)	57(95)	3(5)
	Problematic use of alcohol	40	31(78)	9(22)	0(0)	71(89)	9(11)
	Chi squared		1,886			1,709+	
	(p value)		(0,212)			(0,1911)	
IL12RB1 rs393548 n=70 1=T, 2=A	Controls	30	24(80)	6(20)	0(0)	54(90)	6(10)
	Problematic use of alcohol	40	29(73)	11(27)	0(9)	69(86)	11(14)
	Chi squared		0,524			0,1668+	
	(p value)		(0,469)			(0,6811)	
TNFR1 rs1030920578 n=78 1=G, 2=A	Controls	54	54(100)	0(0)	0(0)	108(100)	0(0)
	Problematic use of alcohol	24	24(100)	0(0)	0(0)	48(100)	0(0)
	Chi squared		Monomorphic			Monomorphic	
	(p value)						
TNFR1 rs1032563104 n=78 1=G, 2=T	Controls	42	42(100)	0(0)	0(0)	84(100)	0(0)
	Problematic use of alcohol	36	36(100)	0(0)	0(0)	72(100)	0(0)
	Chi squared		Monomorphic			Monomorphic	
	(p value)						
TNFR1 rs4149621 n=74 1=T, 2=C	Controls	38	32(84)	0(0)	6(16)	64(84)	12(16)
	Problematic use of alcohol	36	26(72)	4(11)	6(17)	56(78)	16(22)
	Chi squared		2,304			1,4839	
	(p value)		(0,315)			(0,2231)	
TNFR1 rs4149570 n=62 1=C, 2=A	Controls	36	28(78)	4(11)	4(11)	60(83)	12(17)
	Problematic use of alcohol	26	24(92)	0(0)	2(8)	48(92)	4(8)
	Chi squared		1,519			2,1638	
	(p value)		(0,467)			(0,1412)	
TNFR1 rs2234649 n=46 1=T, 2=G	Controls	22	17(77)	5(23)	0(0)	39(89)	5(11)
	Problematic use of alcohol	24	23(96)	1(4)	0(0)	47(98)	1(2)
	Chi squared		3,486			1,8994	
	(p value)		(0,090)			(0,1681)+	
MIF rs893482429 n=56 1=G, 2=C	Controls	24	21(88)	2(8)	1(4)	43(91)	4(9)
	Problematic use of alcohol	32	30(94)	2(6)	0(0)	61(97)	2(3)
	Chi squared		1,475			0,6316	
	(p value)		(0,478)			(0,4217)+	
RELA rs1039347100 n=74 1=T, 2=A	Controls	38	38(100)	0(0)	0(0)	76(100)	0(0)
	Problematic use of alcohol	36	36(100)	0(0)	0(0)	72(100)	0(0)
	Chi squared		Monomorphic			Monomorphic	
	(p value)						
RELA rs1394889070 n=70 1=G, 2=T	Controls	35	35(100)	0(0)	0(0)	70(100)	0(0)
	Problematic use of alcohol	35	35(100)	0(0)	0(0)	70(100)	0(0)
	Chi squared		Monomorphic			Monomorphic	
	(p value)						
HMGB1 rs41477046 n=70 1=G, 2=A	Controls	35	35(100)	0(0)	0(0)	70(50)	0(0)
	Problematic use of alcohol	35	35(100)	0(0)	0(0)	70(50)	0(0)
	Chi squared		Monomorphic			Monomorphic	
	(p value)						

*Statistically significant differences with P<0.05, +Yates Correction.

Table S3. Association between some selected SNVs and the risk of susceptibility to alcohol dependence with their inheritance models and their genotype odds ratios and confidence intervals.

Gene and SNV´s	Dominant Model			Recessive Model			Additive Model		
	OR	95 % CI	Value p	OR	95 % CI	Value p	OR	95 % CI	Value p
SNCA rs2619363	0,73	0,30-1,78	0,49	0,18	0,02-1,64	0,085	0,64	0,31-1,32	0,23
SNCA rs230113	0,90	0,35-2,28	0,82	0,44	0,16-1,23	0,12	0,72	0,39-1,32	0,28
IL6R rs147065	0,34	0,07-1,61	0,16	0,00	0.00-NA	0,24	0.,4	0,08-1,45	0,12
iNOS rs2779248	0,75	0,26-2,13	0,59	1,20	0,29-5,02	0,8	0,91	0,44-1,88	0,8
IFNGR1 rs17181457	0,49	0,15-1,63	0,24	0,00	0.00-NA	0,039	0,46	0,17-1,25	0,1
IFNGR1 rs2234711	0,79	0,29-2,16	0,64	1,80	0,41-7,91	0,43	1,03	0,50-2,11	0,95
IFNGR1 rs7749390	0,68	0,26-1,79	0,43	0,94	0,21-4,09	0,93	0,80	0,39-1,63	0,53
IFNAR1 rs2850015	4,67	0,83-26,34	0,059	0,85	0,08-9,30	0,89	2,06	0,68-6,23	0,2
TNFR1 rs4149621	0,49	0,10-2,43	0,37	0,94	0,16-5,39	0,94	0,79	0,33-1,90	0,6
TNFR1 rs4149570	3,43	0,34-34,99	0,26	1,50	0,12-18,54	0,75	1,68	0,45-6,23	0,41

Table S4. Genotype frequencies in individuals with problematic alcohol use and controls and their risk of susceptibility (codominant genetic model).

Gene SNV´s	Genotype	Problematic use of alcohol (%)	Control (%)	Chi² (valor p)	OR (95% CI)	Fisher's exact test (p value)⁺
SNCA	GG	22(59)	32(67)			0.133 (0,8939)
rs2619363	GT	11(30)	15(31)	0,018(0,894)	1,06 (0,41-2,75)	1.529 (0,1263)
n=85	TT	4(10)	1(2)	1,49(0,222)	5.82(0,61-5,62)	
SNCA	TT	15(36)	24(47)			1,10 (0,2711)
-2171	TA	27(64)	27(53)	0,796(0,372)	1,60 (0,69-3,69)	0,226
n=93	AA	0(0)	0(0)		1,58(0,029-83,85)	(0,8212)
SNCA	GG	10(26)	15(28)			0,274 (0,7842)
rs2301134	GA	18(46)	31(57)	0,0004(0,983)	0,87 (0.32-2,34)	1.170
[-2127]	AA	11(28)	8(15)	0,029 (0 ,865)	2.06 (0,61-6,93)	(0,2418)
N=93						
IL6R	GG	10(28)	8(25)			0,073 (0,9422)
rs4845617	GA	24(67)	20(63)	0,043 (0,835)	0,96 (0,31-2,89)	0,928 (0,3534)
n=68	AA	2(5)	4(13)	0,222(0,638)	0,40(0,057-2,77)	
IL6R	CC	22(61)	28(82)			1,624 (0,1045)
rs1470654147	CT	12(33)	6(18)	1,89 (0,16932)	2,54 (0,82-7,86)	1,172
n=70	TT	2(6)	0(0)		6,33 (0,29-138,6)	(0,2411)
iNOS	TT	15(43)	12(50)			0,694 (0,487)
rs2779248	TC	15(43)	8(33)	0,164 (0,6851)	1,50 (0,47-4,71)	0,000
n=59	CC	5(14)	4(17)	0,150 (0,6985)	1,00 (0,22-4,56)	(1,000)
IFNGR1	GG	37(95)	36(95)			0,027 (0,9787)
rs121913171	GA	2(5)	2(5)	0,24 (0,6263)	0,97 (0,13-7,28)	0,013
n=77	AA	0(0)	0(0)		0,97(0,018-50,4)	(0,9893)
IFNGR1	GG	31(78)	35(88)			0,464 (0,6423)
rs17181457	GA	6(15)	5(12)	0.019 (0,89)	1,35 (0.,37-4,88)	1,349
n=80	AA	3(7)	0(0)		7,89 (0,39-158,7)	(0,1775)
IFNGR1	AA	10(33)	14(39)	0,217(0,64)		0,734 (0,4630)
rs2234711	AG	17(57)	16(44)	0,0013(0,97)	1,49 (0,51-4,29)	0435
n=66	GG	3(10)	6(17)		0,70 (0,14-3,48)	(0,6634)
IFNGR1	GG	5(14)	6(15)			0.789 (0.4299)
rs7749390	GA	20(55)	17(44)	0,29(0,59)	1 , 5 0 (0 , 5 5 - 4 , 1 0)	0.358
n=75	AA	11(31)	16(41)	0.002 (0,96)	1,33(0,28 -6.44)	(0.7204)
IFNAR1	CC	8(25)	8(20)			0,756 (0,4495)
rs2850015	CT	18(56)	28(70)	0,576 (0,45)	1.56 (0,49-4,89)	0,497 (0,6195)
n=72	TT	6(19)	4(10)	3,6 (0,058)	0,67 (0,13-3.30)	

IL12RB1	GG	31(78)	27(90)			1,340 (0,1802)
rs436857	GA	9(22)	3(10)	1.11(0,29)	2,61 (0,64-10,64)	0,067 (0,9463)
n=70	AA	0(0)	0(0)		0,87 (0,02-45,49)	
IL12RB1	TT	29(73)	24(80)			0,722 (0,4705)
rs393548	TA	11(27)	6(20)	0.20(0,66)	1,52 (0,49-4,71)	0,092 (0,9267)
n=70	AA	0(0)	0(0)		0.83 (0,016-43,4)	
TNFR1	TT	26(72)	32(84)			1,587 (0,1126)
rs4149621	TC	4(11)	0(0)	0.0001(0,99)	11,0 (0,57-214,4)	0,327 (0,436)
n=74	CC	6(17)	6(16)		1,23 (0,35-4,27)	
TNFR1	CC	24(92)	28(78)			1,549 (0,1213)
rs4149570	CA	0(0)	4(11)	0.027 (0,87)	0,096 (0,005-1,9)	0,932 (0,3516)
n=62	AA	2(8)	4(11)		0,43 (0,072- 2,55)	
TNFR1	TT	23(96)	17(77)			1,675 (0,0939)
rs2234649	TG	1(4)	5(23)	2,04 (0,15)	0,15 (0,016-1,38)	0,146 (0,8842)
n=46	GG	0(0)	0(0)		0,74 (0,014-39,4)	
MIF	GG	30(94)	21(88)			0,343 (0,7316)
rs893482429	GC	2(6)	2(8)	0,033 (0,86)	0,70 (0,091-5,37)	0,874 (0,3821)
n=56	CC	0(0)	1(4)		0,24 (0,0091-6,1)	

[+]Yates Correction.

Table S5. Interaction analysis of genotypes with covariate sex by means of logistic regression comparing controls and individuals with problematic alcohol consumption.

Gene and SNV	Genotype	Parameters			Sex
		OR	95% CI	P Value	
SNCA	G/G	0.24	(0.08-0.78)		
rs2619363	G/T	0.27	(0.08-0.94)	0.4	Men
n=85	T/T	0.11	(0.01-1.25)		
SNCA rs542037441 n=93	G/G	0.24	(0.10-0.60)	NA	Men
SNCA -2171 n=93	A/T	0.17	(0.05-0.67)	0.68	Men
SNCA rs924048579 n=93	C/C	0.26	(0.11-0.65)	NA	Men
SNCA rs2301134 n=93	A/A	0.20	(0.04-0.97)	0,9	Men
TNFR1 rs4149621 n=62	T/T	0.10	(0.02-0.56)	0.048*	Men
TNFR1 rs2234649 n=46	T/T	0.24	(0.06-0.91)	0.15	Men

*Statistically significant differences with P<0.05.

Table S6. List of genes, genetic variants studied, minimum allele frequency (MAF) and Hardy Weinberg equilibrium for both controls and cases (problematic alcohol use).

Gene	Variant	Location in it Chromosome	Alleles	MAF (control)	HWE Control (p value)	HWE Cases (p value)
SNCA	rs2619363	4q22.1	T/G	0,18	0,552	0,136
SNCA	rs542037441	4q22.1	G/T	0,01	0,947	Mono
SNCA	rs989496677	4q22.1	C/T	----	Mono	Mono
SNCA	-2171	4q22.1	T/A	0,26	0,019	0,003*
SNCA	rs927159023	4q22.1	G/C	---	Mono	Mono
SNCA	rs924048579	4q22.1	C/T	---	Mono	0,933
SNCA	rs2301134	4q22.1	G/A	0,44	0,321	0,742
SNCA	rs950036657	4q22.1	G/A	---	Mono	Mono
SNCA	rs916862395	4q22.1	G/C	---	Mono	Mono
SNCA STR-Rep1	D4S3481	4q22.1	263-277	0,02	0,000*	0,000*
IL6R	rs4845617	1q21.3	G/A	0,44	0,094	0,258
IL6R	rs1470654147	1q21.3	C/T	0,09	0,619	0,791
iNOS	rs2779248	17q11.2	C/T	0.33	0,186	0,765
IFNGR1	rs121913171	6q23.3	G/A	0,03	0,874	0,862
IFNGR1	rs17181457	6q23.3	G/A	0,06	0,627	0,005*
IFNGR1	rs2234711	6q23.3	A/G	0,39	0,876	0,380
IFNGR1	rs7749390	6q23.3	G/A	0,42	0,934	0,512
IFNAR1	rs2850015	21q22.11	C/T	0,45	0,009*	0,4641
IL12RB1	rs436857	19p13.11	G/A	0,05	0,711	0,461
IL12RB1	rs393548	19p13.11	T/A	0,10	0,496	0,342
TNFR1	rs1030920578	12p13.31	G/A	---	Mono	Mono
TNFR1	rs1032563104	12p13.31	G/T	---	Mono	Mono
TNFR1	rs4149621	12p13.31	T/C	0,16	0,000*	0,004*
TNFR1	rs4149570	12p13.31	C/A	0,17	0,011*	0,000*
TNFR1	rs2234649	12p13.31	T/G	0,11	0,548	0,917
MIF	rs893482429	22q11.23	G/C	0,09	0,078	0,925
RELA	rs1039347100	11q13.1	T/A	---	Mono	Mono
RELA	rs1394889070	11q13.1	G/T	---	Mono	Mono
HMGB1	rs41477046	13q12.3	G/A/T	---	Mono	Mono

*Statistically significant differences with P<0.05, MAF: Minimum allele frequency, HWE: Hardy Weinberg Equilibrium.

Table S7. World allele frequencies and those reported in this work.

Gene	SNV´s	Variant	Europeans	Africans	Latin americans	Colombians (reported by our group)
SNCA	rs2619363	T	0,28	0,06	0,14	0,21
		G	0,72	0,94	0,86	0,79
SNCA	rs989496677	C	1	1	NA	1
		T	0	0	NA	0
SNCA	-2171	T	NA	NA	NA	0,71
		A	NA	NA	NA	0,29
SNCA	rs927159023	G	1	1	NA	1
		C	0	0	NA	0
SNCA	rs924048519	C	NA	NA	NA	0,99
		T	NA	NA	NA	0,01
SNCA	rs2301134	G	0,51	0,33	0,59	0,53
		A	0,49	0,67	0,41	0,47
SNCA	rs950036657	G	1	1	NA	1
		A	0	0	NA	0
SNCA	rs916862395	G	1	1	NA	1
		C	0	0	NA	0
IL6R	rs4845617	G	0,6	0,67	0,52	0,59
		A	0,4	0,33	0,48	0,41
IL6R	rs1470654147	C	1	1	NA	0,84
		T	0	0	NA	0,16
iNOS	rs2779248	T	0,61	0,55	0,70	0,65
		C	0,39	0,45	0,30	0,35
IFNGR1	rs121913171	G	1	1	1	0,97
		A	0	0	0	0,03
IFNGR1	rs17181457	G	0,92	0,98	NA	0,93
		A	0,08	0,02	NA	0,07
IFNGR1	rs2234711	A	0,60	0,5	NA	0,61
		G	0,40	0,5	NA	0,39
IFNGR1	rs7749390	G	0,40	0,50	0,38	0,39
		A	0,60	0,50	0,62	0,61
IFNAR1	rs2850015	C	0,72	0,95	0,68	0,54
		T	0,28	0,05	0,32	0,46
IL12RB1	rs436857	G	0,80	0,85	0,88	0,91
		A	0,20	0,15	0,12	0,09
IL12RB1	rs393548	T	0,79	0,80	NA	0,88
		A	0,21	0,20	NA	0,12
TNFR1	rs1030920578	G	1	1	NA	1
		A	0	0	NA	0
TNFR1	rs1032563104	G	NA	NA	NA	1
		T	NA	NA	NA	0
TNFR1	rs4149621	T	0,99	0,52	0,90	0,81
		C	0,01	0,48	0,10	0,19
TNFR1	rs4149570	C	0,60	0,89	0,72	0,87
		A	0,40	0,11	0,28	0,13
TNFR1	rs2234649	T	0,99	0,91	NA	0,98
		G	0,01	0,09	NA	0,02
MIF	rs893482429	G	0	0	NA	0,05
		C	1	1	NA	0,95
RELA	rs1039347100	T	1	1	1	1
		A	0	0	0	0
RELA	rs1394889070	G	1	1	1	1
		T	0	0	0	0
HMGB1	rs41477046	G	0.99930	1	1	1
		A	0	0	0	0
		T	0.0007	0	0	0

NA Data not available.

Table S8. Statistics of analysis of multiple SNVs (by pairs) of linkage disequilibrium and haplotypes.

Hapltype of a pair of snvs		D	D´	R	Chi² (p value)
TNFR1	**TNFR1**				
rs4149621	rs4149570	0,020	0,191	0,152	1,30 (0,2546)
rs4149621	**rs2234649**	**0,026**	**0,490**	**0,268**	**4,59 (0,032) ***
rs4149570	rs2234649	0,022	0,389	0,267	3,56 (0,059)
SNCA	**SNCA**				
rs924048579	rs2301134	$2,79x10^{-3}$	0,975	0,0765	1,088 (0,297)
-2171	rs924048579	$-1,4x10^{-3}$	0,952	-0,0430	0,340 (0,560)
-2171	rs2301134	$3x10^{-3}$	0,021	0,0135	0,0335 (0,855)
rs542037441	-2171	$1,4x10^{-3}$	0,952	-0,043	0,341 (0,560)
rs542037441	rs924048579	$4,18x10^{-5}$	0,008	0,0078	0,0114 (0,915)
rs542037441	rs2301134	$-2,44x10^{-3}$	0.972	-0,0670	0,835 (0,361)
rs2619363	rs542037441	$-1,07x10^{-3}$	0,934	-0,0357	0,217 (0,641)
rs2619363	-2171	$1,78x10^{-2}$	0,116	0,098	1,60 (0,206)
rs2619363	rs924048579	$4,17x10^{-3}$	0,983	0,139	3,30 (0,069)
rs2619363	**rs2301134**	**$8,79x10^{-2}$**	**0,780**	**0,431**	**31,61 ($1,87x10^{-8}$)**
IFNGR1	**IFNGR1**				
rs2234711	**rs7749390**	**0,194**	**0,887**	**0,883**	**84,72 ($2x10^{-16}$)***
rs17181457	rs2234711	0,023	0,360	0,157	3,23 (0,072)
rs17181457	**rs7749390**	**0,040**	**0,587**	**0,272**	**10,33 (0,001)***
rs121913171	rs17181457	-0,003	0,971	-0,055	0,46 (0,498)
rs121913171	**rs2234711**	**0,016**	**0,995**	**0,205**	**5,37 (0,020)***
rs121913171	rs7749390	0,007	0,431	0,095	1,23 (0,267)
IL12RB1	**IL12RB1**				
rs436857	rs393548	0.0569	0.756	0.6226	0

*Statistically significant differences with P<0.05.

Table S9. Results with statistically significant differences in the interaction analysis of haplotypes with covariate sex by means of logistic regression. Adjusted for sex, age, and age of initiation of use.

Gene and SNV	Haplotype	Frequency	Parameters			Sex
			OR	95% CI	P vlaue	
TNFR1 **rs1030920578** **rs1032563104** **rs4149621** **rs4149570** **rs2234649**	GGTCT	0,72	0,08	0,01 -0,54	0,014*	Men
IFNGR1 **rs121913171** **rs17181457** **rs2234711** **rs7749390**	GGGA	0,03	18593193,7	18593189.9 - 18593197.3	<0.0001	Men

*Statistically significant differences with P<0.05

Table S10. Characteristics of the model of gene-gene, gene-environment interactions associated with susceptibility to alcohol-dependence, adjusted for sex, age and age of onset of consumption that presented statistically significant differences.

Model (one, two and three factors)	Training Balance Accuracy	Balance Accuracy Test	Sensitivity	Specificity	Cross Validation Consistency	OR, CI		P value
Adjusted for gender								
iNOS rs2779248	0,6485	0,6142	0,6176	0,6786	9/10	3,4103	(1,9425-5,987)	0,0001
SNCA rs2619363, MIF rs893482429	0,7608	0,6704	0,6765	0,8304	6/10	10,2344	(5,3715-19,5001)	< 0,0001
SNCA rs2301134 iNOS rs2779248, INFGR1 rs2234711	0,8186	0,6605	0,6765	0,9464	6/10	36,9394	(14,7035-92,8023)	< 0,0001
Age adjusted								
iNOS rs2779248	0,6553	0,6359	0,6226	0,687	10/10	3,6208	(2,0757-6,3161)	< 0,0001
SNCA rs2301134, IFNGR1 rs2234711	0,7622	0,6692	0,7075	0,800	5/10	9,6774	(5,2079-17,9828)	< 0,0001
SNCA rs2301134, iNOS rs2779248, IFNGR1 rs2234711	0,8198	0,6997	0,7925	0,8248	7/10	19,2919	(9,7725-38,0842)	< 0,0001
Adjusted for age of onset of use								
iNOS rs2779248	0,6522	0,6332	0,6111	0,6923	10/10	3,5357	(2,0375-6,1356)	< 0,0001
SNCA rs2619363, MIF rs893482429	0,7619	0,6887	0,6852	0,8291	6/10	10,5559	(5,6234-19,8149)	< 0,0001
SNCA rs2301134, iNOS rs2779248, INFGR1 rs2234711	0,8174	0,7108	0,787	0,8376	7/10	19,0618	(9,7199-37,3821)	< 0,0001