

Cytokine gene polymorphisms associations with congenital cytomegalovirus infection and sensorineural hearing loss

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Table S1 Association analysis of individual SNPs with congenital CMV infection

Gene (SNP database ID number)	Genetic model	Genotype	Genotype frequencies; n (%)		OR (95% CI)	P-value ^a	AIC
			Congenital CMV (n = 72)	Healthy controls (n = 398)			
IL1B rs16944 (-511 T/C)	Co-D	CC	31 (43.1)	183 (46.0)	1	0.046	402.4
		CT	28 (38.9)	183 (46.0)	0.90 (0.52 - 1.57)		
		TT	13 (18.1)	32 (8.0)	2.40 (1.13 - 5.07)		
	D	CC	31 (43.1)	183 (46.0)	1	0.65	406.3
		CT/TT	41 (56.9)	215 (54.0)	1.13 (0.68 - 1.87)		
	R	CC/CT	59 (81.9)	366 (92.0)	1	0.014	400.5
		TT	13 (18.1)	32 (8.0)	2.25 (1.25 - 5.08)		
	O-D	CC/TT	44 (61.1)	215 (54.0)	1	0.26	405.3
CT		28 (38.9)	183 (46.0)	0.75 (0.45 - 1.25)			
IL1B rs1143634 (+3954 T/C)	Co-D	CC	43 (59.7)	277 (57.0)	1	0.91	408.3
		CT	24 (33.3)	141 (35.4)	0.90 (0.52 - 1.54)		
		TT	5 (6.9)	30 (7.5)	0.88 (0.32 - 2.39)		
	D	CC	43 (59.7)	227 (57.0)	1	0.67	406.3
		CT/TT	29 (40.3)	171 (43.0)	0.90 (0.54 - 1.49)		
	R	CC/CT	67 (93.1)	368 (92.5)	1	0.86	406.5
		TT	5 (6.9)	30 (7.5)	0.92 (0.34 - 2.44)		
	O-D	CC/TT	48 (66.7)	257 (64.6)	1	0.73	406.4
CT		24 (33.3)	141 (35.4)	0.91 (0.54 - 1.55)			
IL12B rs3212227 (3'UTR C/A)	Co-D	AA	49 (68.1)	255 (64.1)	1	0.53	407.2
		AC	22 (30.6)	129 (32.4)	0.89 (0.51 - 1.53)		
		CC	1 (1.4)	14 (3.5)	0.37 (0.05 - 2.89)		
	D	AA	49 (68.1)	255 (64.1)	1	0.51	406.1
		AC/CC	23 (31.9)	143 (35.9)	0.84 (0.49 - 1.43)		
	R	AA/AC	71 (98.6)	384 (96.5)	1	0.3	405.4
		CC	1 (1.4)	14 (3.5)	0.39 (0.05 - 2.98)		
	O-D	AA/CC	50 (69.4)	269 (67.6)	1	0.76	406.4

		AC	22 (30.6)	129 (32.4)	0.92 (0.53 - 1.58)		
CCL2 rs13900 ^b (+1543 T/C)	Co-D	CC	35 (48.6)	208 (52.4)	1	0.83	407.8
		CT	30 (41.7)	151 (38.0)	1.18 (0.69 - 2.01)		
		TT	7 (9.7)	38 (9.6)	1.09 (0.45 - 2.64)		
	D	CC	35 (48.6)	208 (52.4)	1	0.55	405.8
		CT/TT	37 (51.4)	189 (47.6)	1.16 (0.70 - 1.92)		
	R	CC/CT	65 (90.3)	359 (90.4)	1	0.97	406.2
TT		7 (9.7)	38 (9.6)	1.02 (0.44 - 2.38)			
O-D	CC/TT	42 (58.3)	246 (62.0)	1	0.56	405.8	
	CT	30 (41.7)	151 (38.0)	1.16 (0.70 - 1.94)			
CCL2 rs1024611 ^c (-2518 G/A)	Co-D	AA	36 (50)	219 (55.4)	1	0.7	406.8
		AG	29 (40.3)	142 (36.0)	1.24 (0.73 - 2.12)		
		GG	7 (9.7)	34 (8.6)	1.25 (0.52 - 3.04)		
	D	AA	36 (50)	219 (55.4)	1	0.39	404.8
		AG/GG	36 (50)	176 (44.6)	1.24 (0.75 - 2.06)		
	R	AA/AG	65 (90.3)	361 (91.4)	1	0.76	405.4
		GG	7 (9.7)	34 (8.6)	1.14 (0.49 - 2.69)		
	O-D	AA/GG	43 (59.7)	253 (64.0)	1	0.49	405.0
AG		29 (40.3)	142 (36.0)	1.20 (0.72 - 2.01)			
CCR5 rs333 (CCR5Δ32)	Co-D	wt wt	58 (80.6)	334 (83.9)	1	0.64	407.6
		wtΔ32	14 (19.4)	63 (15.8)	1.28 (0.67 - 2.43)		
		Δ32Δ32	0 (0)	1 (0.2)	0.00 (0.00 - NA)		
	D	wtw	58 (80.6)	334 (83.9)	1	0.49	406.0
		wtΔ32/Δ32Δ32	14 (19.4)	64 (16.1)	1.26 (0.66 - 2.39)		
	R	wtw/wtΔ32	72 (100)	397 (99.8)	1	0.56	406.2
		Δ32Δ32	0 (0)	1 (0.2)	0.00 (0.00 - NA)		
	O-D	wtw/Δ32Δ32	58 (80.6)	335 (84.2)	1	0.45	406.0
wtΔ32		14 (19.4)	63 (15.8)	1.28 (0.67 - 2.44)			
TNF rs179964 (-1031 C/T)	Co-D	TT	42 (58.3)	283 (71.1)	1	0.0092	399.1
		TC	29 (40.3)	95 (23.9)	2.06 (1.21 - 3.48)		

		CC	1 (1.4)	20 (5.0)	0.34 (0.04 - 2.58)		
	D	TT	42 (58.3)	283 (71.1)	1	0.034	402.0
		TC/CC	30 (41.7)	115 (28.9)	1.76 (1.05 - 2.95)		
	R	TT/TC	71 (98.6)	378 (95.0)	1	0.12	404.1
		CC	1 (1.4)	20 (5.0)	0.27 (0.04 - 2.02)		
	O-D	TT/CC	43 (59.7)	303 (76.1)	1	0.005	398.6
		TC	29 (40.3)	95 (23.9)	2.15 (1.27 - 3.63)		
TNF rs1800629 (-308 A/G)	Co-D	GG	52 (72.2)	283(71.1)	1	0.43	406.8
		GA	17 (23.6)	108 (27.1)	0.86 (0.47 - 1.55)		
		AA	3 (4.2)	7 (1.8)	2.33 (0.58 - 9.31)		
	D	GG	52 (72.2)	283 (71.1)	1	0.85	406.5
		GA/AA	20 (27.8)	115 (28.9)	0.95 (0.54 - 1.66)		
	R	GG/GA	69 (95.8)	391 (98.2)	1	0.24	405.1
		AA	3 (4.2)	7 (1.8)	2.43 (0.61 - 9.62)		
	O-D	GG/AA	55 (76.4)	290 (72.9)	1	0.53	406.1
		GA	17 (23.6)	108 (27.1)	0.83 (0.46 - 1.49)		
TNFRSF1A rs4149570 (-201 A/C)	Co-D	CC	29 (40.3)	173 (43.5)	1	0.55	407.3
		CA	35 (48.6)	168 (42.2)	1.24 (0.73 - 2.12)		
		AA	8 (11.1)	57 (14.3)	0.84 (0.36 - 1.94)		
	D	CC	29 (40.3)	173 (43.5)	1	0.61	406.3
		CA/CC	43 (59.7)	225 (56.5)	1.14 (0.68 - 1.90)		
	R	CC/CA	64 (88.9)	341 (85.7)	1	0.46	406.0
		AA	8 (11.1)	57 (14.3)	0.75 (0.34 - 1.64)		
	O-D	CC/AA	37 (51.4)	230 (57.8)	1	0.31	405.5
		CA	35 (48.6)	168 (42.2)	1.30 (0.78 - 2.14)		
IL10 rs1800896 (-1082 G/A)	Co-D	TT	23 (31.9)	127 (31.9)	1	0.11	404.2
		CT	42 (58.3)	196 (49.2)	1.18 (0.68 - 2.06)		
		CC	7 (9.7)	75 (18.8)	0.52 (0.21 - 1.26)		
	D	TT	23 (31.9)	127 (31.9)	1	1	406.5
		CT/CC	49 (68.1)	271 (68.1)	1.00 (0.58 - 1.71)		

	R	TT/CT	65 (90.3)	323 (81.2)	1	0.046	402.5
		CC	7 (9.7)	75 (18.8)	0.46 (0.20 - 1.05)		
	O-D	TT/CC	30 (41.7)	202 (50.8)	1	0.15	404.5
		CT	42 (58.3)	196 (49.2)	1.44 (0.87 - 2.40)		
IL10RA rs4252279 (+5964 T/C)	Co-D	CC	54 (75)	307 (77.1)	1	0.13	404.5
		CT	16 (22.2)	90 (22.6)	1.01 (0.55 - 1.85)		
		TT	2 (2.8)	1 (0.2)	11.37 (1.01 - 127.60)		
	D	CC	54 (75)	307 (77.1)	1	0.69	406.4
		CT/TT	18 (25)	91 (22.9)	1.12 (0.63 - 2.01)		
	R	CC/CT	70 (97.2)	397 (99.8)	1	0.044	402.5
		TT	2 (2.8)	1 (0.2)	11.34 (1.01 - 126.79)		
	O-D	CC/TT	56 (77.8)	308 (77.4)	1	0.97	406.5
		CT	16 (22.2)	90 (22.6)	0.98 (0.53 - 1.79)		

Abbreviations: AIC, Akaike information criterion; Co-D, Co-dominant; D, Dominant; R, Recessive; O-D, Over-dominant; IL1B. interleukin 1 beta; IL12B. interleukin 12B; 3'UTR. 3'untranslated region; CCL2. chemokine (C-C motif) ligand 2; CCR5. chemokine (C-C motif) receptor 5 gene; wt - wild type; Δ32. 32-base pair deletion; NA. not applicable; TNF. tumour necrosis factor; TNFRSF1A. tumour necrosis factor receptor superfamily member 1A. IL10. interleukin 10; IL10RA. interleukin 10 receptor alpha.

^a Significance levels were assessed using logistic regression model

^b Percentage of genotyped samples was 469/470 (99.8%)

^c Percentage of genotyped samples was 467/470 (99.4%)

Table S2 Association analysis of individual SNPs with severity of congenital CMV disease (i.e. illness score)

Gene (SNP database ID number)	Genotype	N	Mean illness score (SE)	Difference (95% CI)	P-value ^a
IL1B rs16944 (-511 T/C)	CC	31	2.58 (0.35)	0	0.15
	CT	28	3.21 (0.44)	0.63 (-0.44 - 1.70)	
	TT	13	1.85 (3.5)	-0.73 (-2.09 - 0.62)	
IL1B rs1143634 (+3954 T/C)	CC	43	2.44 (0.29)	0	0.41
	CT	24	3.17 (0.48)	0.72 (-0.34 - 1.79)	
	TT	5	2.6 (1.21)	0.16 (-1.81 - 2.21)	
IL12B rs3212227 (3'UTR C/A)	AA	49	2.69 (0.31)	0	0.12
	AC	22	2.5 (0.39)	-0.19 (-1.24 - 0.85)	
	CC	1	7 (0)	4.31 (0.18 - 8.43)	
CCL2 rs13900 (+1543 T/C)	CC	35	2.29 (0.34)	0	0.27
	CT	30	3.13 (0.37)	0.85 (-0.18 - 1.88)	
	TT	7	2.86 (1.12)	0.57 (-1.14 - 2.28)	
CCL2 rs1024611 (-2518 G/A)	AA	36	2.36 (0.34)	0	0.41
	AG	29	3.07 (0.37)	0.71 (-0.33 - 1.75)	
	GG	7	2.86 (1.12)	0.50 (-1.22 - 2.21)	
CCR5 rs333 (CCR5Δ32)	wt wt	58	2.64 (0.28)	0	0.65
	wtΔ32	14	2.93 (0.55)	0.29 (-0.95 - 1.54)	
TNF rs1799964 (-1031 C/T)	TT	42	2.69 (0.3)	0	0.44
	TC	29	2.79 (0.44)	0.10 (-0.90 - 1.11)	
	CC	1	0 (0)	-2.69 (-6.91 - 1.52)	
TNF rs1800629 (-308 A/G)	GG	52	2.52 (0.29)	0	0.14
	GA	17	2.82 (0.51)	0.30 (-0.84 - 1.45)	
	AA	3	5 (1)	2.48 (0.05 - 4.91)	
TNFRSF1A rs4149570 (-201 A/C)	CC	29	3 (0.42)	0	0.61
	CA	35	2.49 (0.32)	-0.51 (-1.57 - 0.54)	
	AA	8	2.5 (0.94)	-0.50 (-2.17 - 1.17)	
IL10 rs1800896	TT	23	3.3 (0.44)	0	0.25

(-1082 G/A)	CT	42	2.43 (0.33)	-0.88 (-1.95 - 0.20)	
	CC	7	2.29 (0.75)	-1.02 (-2.80 - 0.76)	
IL10RA rs4252279	CC	54	2.74 (0.29)	0	0.19
(+5964 T/C)	CT	16	2.88 (0.52)	0.13 (-1.04 - 1.31)	
	TT	2	0 (0)	-2.74 (-5.70 - 0.22)	

^a P-value calculated for linear regression.

Table S3 Association analysis of individual SNPs with congenital CMV-related sensorineural hearing loss (SNHL) at birth

Gene (SNP database ID number)	Genetic model	Genotype	Genotype frequencies; n (%)		OR (95% CI)	P-value ^a	AIC
			SNHL (n = 22)	Normal hearing (n = 34)			
IL1B rs16944 (-511 T/C)	Co-D	CC	9 (40.9)	14 (41.2)	1	0.94	80.9
		CT	9 (40.9)	15 (44.1)	0.93 (0.29 - 3.03)		
		TT	4 (18.2)	5 (14.7)	1.24 (0.26 - 5.92)		
	D	CC	9 (40.9)	14 (41.2)	1	0.98	79
		CT/TT	13 (59.1)	20 (58.8)	1.01 (0.34 - 3.01)		
	R	CC/CT	18 (81.8)	29 (85.3)	1	0.73	78.9
		TT	4 (18.2)	5 (14.7)	1.29 (0.31 - 5.44)		
	O-D	CC/TT	13 (59.1)	19 (55.9)	1	0.81	79
CT		9 (40.9)	15 (44.1)	0.88 (0.30 - 2.60)			
IL1B rs1143634 (+3954 T/C)	Co-D	CC	12 (54.5)	23 (67.7)	1	0.15	77.3
		CT	10 (45.5)	9 (26.5)	2.13 (0.68 - 6.65)		
		TT	0 (0)	2 (5.9)	0 (0.00 - NA)		
	D	CC	12 (54.5)	23 (67.7)	1	0.32	78.1
		CT/TT	10 (45.5)	11 (32.4)	1.74 (0.58 - 5.26)		
	R	CC/CT	22 (100)	32 (94.1)	1	0.15	77
		TT	0 (0)	2 (5.9)	0 (0.00 - NA)		
	O-D	CC/TT	12 (54.5)	25 (73.5)	1	0.14	76.9
CT		10 (45.5)	9 (26.5)	2.31 (0.75 - 7.19)			
IL12B rs3212227 (3'UTR C/A)	Co-D	AA	14 (63.6)	23 (67.7)	1	0.54	79.8
		AC	8 (36.4)	10 (29.4)	1.31 (0.42 - 4.12)		
		CC	0 (0)	1 (2.9)	0 (0.00 - NA)		
	D	AA	14 (63.6)	23 (67.7)	1	0.76	78.9
		AC/CC	8 (36.4)	11 (32.4)	1.19 (0.39 - 3.69)		
	R	AA/AC	22 (100)	33 (97.1)	1	0.32	78
CC		0 (0)	1 (2.9)	0 (0.00 - NA)			

	O-D	AA/CC	14 (63.6)	24 (70.6)	1	0.59	78.7
		AC	8 (36.4)	10 (29.4)	1.37 (0.44 - 4.29)		
CCL2 rs13900 (+1543 T/C)	Co-D	CC	6 (27.3)	19 (55.9)	1	0.1	76.5
		CT	13 (59.1)	12 (35.3)	3.43 (1.03 - 11.48)		
		TT	3 (13.6)	3 (8.8)	3.17 (0.50 - 20.04)		
	D	CC	6 (27.3)	19 (55.9)	1	0.033	74.5
		CT/TT	16 (72.7)	15 (44.1)	3.38 (1.06 - 10.74)		
	R	CC/CT	19 (86.4)	31 (91.2)	1	0.57	78.7
		TT	3 (13.6)	3 (8.8)	1.63 (0.30 - 8.92)		
	O-D	CC/TT	9 (40.9)	22 (64.7)	1	0.08	76
		CT	13 (59.1)	12 (35.3)	2.65 (0.88 - 7.98)		
CCL2 rs1024611 (-2518 G/A)	Co-D	AA	7 (31.8)	20 (58.8)	1	0.14	77.1
		AG	12 (54.5)	11 (32.4)	3.12 (0.95 - 10.22)		
		GG	3 (13.6)	3 (8.8)	2.86 (0.46 - 17.58)		
	D	AA	7 (31.8)	20 (58.8)	1	0.046	75.1
		AG/GG	15 (68.2)	14 (41.2)	3.06 (0.99 - 9.45)		
	R	AA/AG	19 (86.4)	31 (91.2)	1	0.57	78.7
		GG	3 (13.6)	3 (8.8)	1.63 (0.30 - 8.92)		
	O-D	AA/GG	23 (67.7)	10 (45.5)	1	0.099	76.3
		AG	11 (32.4)	12 (54.5)	2.51 (0.83 - 7.57)		
CCR5 rs333 (CCR5Δ32)	NA	wt wt	17 (77.3)	28 (82.3)	1	0.64	78.8
		wtΔ32	5 (22.7)	6 (17.6)	1.37 (0.36 - 5.20)		
TNF rs179964 (-1031 C/T)	Co-D	TT	12 (54.5)	19 (55.9)	1	0.59	80
		TC	10 (45.5)	14 (41.2)	1.13 (0.38 - 3.35)		
		CC	0 (0)	1 (2.9)	0 (0.00 - NA)		
	D	TT	12 (54.4)	19 (55.9)	1	0.92	79
		TC/CC	10 (45.5)	15 (44.1)	1.06 (0.36 - 3.10)		
	R	TT/TC	22 (100)	33 (97.1)	1	0.32	78
		CC	0 (0)	1 (2.9)	0 (0.00 - NA)		
	O-D	TT/CC	12 (54.4)	20 (58.8)	1	0.75	78.9

		TC	10 (45.5)	14 (41.2)	1.19 (0.40 - 3.51)		
TNF rs1800629 (-308 A/G)	Co-D	GG	16 (72.7)	26 (76.5)	1	0.93	80.9
		GA	5 (22.7)	7 (20.6)	1.16 (0.31 - 4.28)		
		AA	1 (4.5)	1 (2.9)	1.62 (0.09 - 27.84)		
	D	GG	16 (72.7)	26 (76.5)	1	0.75	78.9
		GA/AA	6 (27.3)	8 (23.5)	1.22 (0.36 - 4.16)		
	R	GG/GA	21 (95.5)	33 (97.1)	1	0.75	78.9
		AA	1 (4.5)	1 (2.9)	1.57 (0.09 - 26.50)		
	O-D	GG/AA	17 (77.3)	27 (79.4)	1	0.85	79
GA		5 (22.7)	7 (20.6)	1.13 (0.31 - 4.16)			
TNFRSF1A rs4149570 (-201 A/C)	Co-D	CC	11 (50)	12 (35.3)	1	0.53	79.8
		CA	9 (40.9)	17 (50)	0.58 (0.18 - 1.82)		
		AA	2 (9.1)	5 (14.7)	0.44 (0.07 - 2.73)		
	D	CC	11 (50)	12 (35.3)	1	0.28	77.9
		CA/CC	11 (50)	22 (64.7)	0.55 (0.18 - 1.63)		
	R	CC/CA	20 (90.9)	29 (85.3)	1	0.53	78.6
		AA	2 (9.1)	5 (14.7)	0.58 (0.10 - 3.29)		
	O-D	CC/AA	13 (59.1)	17 (50)	1	0.5	78.6
CA		9 (40.9)	17 (50)	0.69 (0.23 - 2.05)			
IL10 rs1800896 (-1082 G/A)	Co-D	TT	9 (40.9)	13 (38.2)	1	0.57	79.9
		CT	11 (50)	20 (58.8)	0.79 (0.26 - 2.44)		
		CC	2 (9.1)	1 (2.9)	2.89 (0.23 - 36.87)		
	D	TT	9 (40.9)	13 (38.2)	1	0.84	79
		CT/CC	13 (59.1)	21 (61.8)	0.89 (0.30 - 2.68)		
	R	TT/CT	20 (90.9)	33 (97.1)	1	0.32	78.1
		CC	2 (9.1)	1 (2.9)	3.30 (0.28 - 38.78)		
	O-D	TT/CC	11 (50)	14 (41.2)	1	0.52	78.6
CT		11 (50)	20 (58.8)	0.70 (0.24 - 2.06)			
IL10RA rs4252279 (+5964 T/C)	Co-D	CC	17 (77.3)	23 (67.7)	1	0.33	78.8
		CT	5 (22.7)	9 (26.5)	0.75 (0.21 - 2.65)		

	TT	0 (0)	2 (5.9)	0 (0.00 - NA)		
D	CC	17 (77.3)	23 (67.7)	1	0.43	78.4
	CT/TT	5 (22.7)	11 (32.4)	0.61 (0.18 - 2.10)		
R	CC/CT	22 (100)	32 (94.1)	1	0.15	77
	TT	0 (0)	2 (5.9)	0 (0.00 - NA)		
O-D	CC/TT	17 (77.3)	25 (73.5)	1	0.75	78.9
	CT	5 (22.7)	9 (26.5)	0.82 (0.23 - 2.87)		

^a Significance levels were assessed using logistic regression model