

Supplementary Information

A Prospective Cohort Study on the association of *HTRA1* and Ischemic Stroke in Chinese Han

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Methods

Reverse transcription reactions and conditions

The reverse transcription reactions were performed in a 20 μ l reaction mixture including 0.3 μ g RNA, 2 μ l 5'gDNA Eraser Buffer, 1 μ l gDNA Eraser, 4 μ l Nuclease-Free Water, 4 μ l 5 x Primescript Buffer 2, 1 μ l Enzyme Mix1 and 1 μ l RT Primer Mix. The PCR conditions were 67 $^{\circ}$ C for 15min, 85 $^{\circ}$ C for 5s.

RT-PCR reactions and conditions

According to the NCBI Nucleotide database, the human HTRA1 has only 1 transcript variant, the primer sequences were listed as follows: HTRA1, 5-GTCTGGGTTTATTGTGTCGGAA-3 (forward) and 5-CGTTCTTCAGCTCAACTTTGACC-3 (reverse); GAPDH, 5-GCACCGTCAAGGCTGAGAAC-3 (forward) and 5-TGGTGAAGACGCCAGTGGA-3 (reverse). The primers were designed using Primer Bank (<https://pga.mgh.harvard.edu/primerbank/>) or Primer Premier 3 (<http://bioinfo.ut.ee/primer3-0.4.0/>). Real-time PCR (RT-PCR) reactions performed in a 10 μ l reaction mixture including 2 μ l cDNA, 5 μ l HieffTM qPCR SYBR GEEN Master Mix, 2.6 μ l Nuclease-Free water, 0.2 μ l upstream primer and 0.2 μ l downstream primer. The RT-PCR conditions were 95 $^{\circ}$ C for 5 min, 95 $^{\circ}$ C for 10s, 60 $^{\circ}$ C for 20s and 72 $^{\circ}$ C for 20s with forty cycles. Melting curve includes 1 cycle with 95 $^{\circ}$ C for 15s, 60 $^{\circ}$ C for 1min and 95 $^{\circ}$ C for 15s. Three parallel samples were set up with a standard deviation less than 0.5, and the average value was calculated.

Supplementary Table 1 Bioinformatics of the four tagSNPs in *HTRAI*

SNP	Allele	Chr	Position	Location	MAF	HWE ^a	TFBS	RegulomeDB
rs2268350	C>T	10	124241050	intronic	0.227	0.548		2a
rs2672587	C>G	10	124225345	intronic	0.464	0.342		2b
rs3793917	C>G	10	124209265	1.8kb from 5' UTR	0.466	0.771	Yes	4
rs12413729	G>A	10	124249120	intronic	0.131	0.444		2b

SNP: single nucleotide polymorphisms; Chr: Chromosome; MAF: minor allele frequency; HWE: Hardy-Weinberg equilibrium; TFBS: Transcription Factor Binding Site.

a. χ^2 test was used to assess HWE in control.

Supplementary Table 2 Association analysis of *HTRAI* polymorphisms and IS incidence

SNP	Genotype	IS (n)	Pearson year(y)	Incident density (10 ⁴)	Model, HR (95%CI)*, P		
					Additive model	Dominant model	Recessive model
rs2268350	CC	65	8306.07	78.26	1.19(0.96-1.475)	1.117(0.821-1.52)	1.499(1.030-2.181)
	CT	88	9901.61	88.87	<i>P</i> =0.112	<i>P</i> =0.482	<i>P</i> =0.034
	TT	34	2896.86	117.37			
rs2672587	CC	44	5529.04	79.58	0.989(0.806-1.214)	1.253(0.885-1.774)	0.755(0.521-1.093)
	CG	106	10614.82	99.86	<i>P</i> =0.918	<i>P</i> =0.204	<i>P</i> =0.137
	GG	37	4965.70	74.51			
rs3793917	CC	49	6376.34	76.85	1.062(0.867-1.301)	1.341(0.962-1.868)	0.829(0.567-1.212)
	CG	104	10514.05	98.92	<i>P</i> =0.562	<i>P</i> =0.083	<i>P</i> =0.333
	GG	34	4206.72	80.82			
rs12413729	GG	148	15885.92	93.16	0.878(0.631-1.221)	0.84(0.587-1.201)	1.296(0.412-4.081)
	GA	36	4874.21	73.86	<i>P</i> =0.438	<i>P</i> =0.339	<i>P</i> =0.658
	AA	3	356.67	84.11			

*Adjusted for age, gender, TC, TG, LDL, HDL, BMI, smoking, drinking, HTN and T2DM

Supplementary Table 3 Stratification analyses for the association between four SNPs and IS incidence

SNP	Group	Genotype	IS(n)	Pearson year(y)	Incident density (10 ⁴)	Model, HR (95%CI)*, <i>P</i>		
						Additive model	Dominant model	Recessive model
rs2268350	Male	CC	30	3425.41	87.58	1.356(0.989-1.858)	1.152(0.733-1.811)	2.057(1.24-3.411)
		CT	44	4058.09	108.43	<i>P</i> =0.058	<i>P</i> =0.539	<i>P</i> =0.005
		TT	20	1156.86	172.88			
	Female	CC	35	4880.66	71.71	1.08(0.8-1.458)	1.114(0.725-1.712)	1.091(0.611-1.95)
		CT	44	5843.52	75.30	<i>P</i> =0.616	<i>P</i> =0.622	<i>P</i> =0.768
		TT	14	1740.00	80.46			
rs2268350	<55	CC	5	3029.5	16.50	1.29(0.532-3.13)	1.128(0.31-4.108)	1.97(0.425-9.129)
		CT	4	3634.7	11.01	<i>P</i> =0.573	<i>P</i> =0.855	<i>P</i> =0.386
		TT	3	1014.7	29.57			
	≥55	CC	60	5276.6	113.71	1.181(0.946-1.474)	1.128(0.82-1.551)	1.441(0.974-2.132)
		CT	84	6267.0	134.04	<i>P</i> =0.142	<i>P</i> =0.459	<i>P</i> =0.067
		TT	31	1882.2	164.70			
rs2268350	Nonsmoking	CC	51	6208.79	82.14	1.099(0.855-1.411)	1.053(0.74-1.499)	1.277(0.807-2.021)
		CT	67	7527.04	89.01	<i>P</i> =0.461	<i>P</i> =0.773	<i>P</i> =0.297
		TT	22	2155	102.09			
	Smoking	CC	14	2097.28	66.75	1.767(1.125-2.778)	1.52(0.781-2.959)	2.933(1.464-5.875)
		CT	21	2374.57	88.44	<i>P</i> =0.014	<i>P</i> =0.217	<i>P</i> =0.002
		TT	12	741.86	161.76			
rs2268350	Nondrinking	CC	56	6396.76	87.54	1.114(0.876-1.418)	0.977(0.695-1.372)	1.49(0.984-2.255)
		CT	65	7787.67	83.47	<i>P</i> =0.379	<i>P</i> =0.892	<i>P</i> =0.06
		TT	28	2256.29	124.1			
	Drinking	CC	9	1909.32	47.14	1.855(1.119-3.074)	2.942(1.235-7.007)	1.69(0.684-4.175)
		CT	23	2113.95	108.8	<i>P</i> =0.017	<i>P</i> =0.015	<i>P</i> =0.256

rs2672587	Male	TT	6	640.57	93.67			
		CC	24	2244.60	106.92	0.899(0.673-1.202)	1.15(0.706-1.874)	0.616(0.357-1.063)
		CG	53	4306.79	123.06	<i>P</i> =0.473	<i>P</i> =0.575	<i>P</i> =0.082
	Female	GG	17	2088.97	81.38			
		CC	20	3284.44	60.89	1.083(0.808-1.452)	1.357(0.822-2.238)	0.908(0.545-1.511)
		CG	54	6308.03	85.61	<i>P</i> =0.592	<i>P</i> =0.233	<i>P</i> =0.710
rs2672587	<55	GG	19	2876.73	66.05			
		CC	2	1979.3	10.10	1.131(0.458-2.791)	1.236(0.256-5.959)	1.13(0.278-4.591)
		CG	6	3803.3	15.78	<i>P</i> =0.79	<i>P</i> =0.792	<i>P</i> =0.864
	≥55	GG	4	1901.3	21.04			
		CC	42	3549.8	118.32	0.971(0.785-1.2)	1.203(0.843-1.715)	0.741(0.504-1.091)
		CG	101	6811.5	148.28	<i>P</i> =0.783	<i>P</i> =0.309	<i>P</i> =0.129
rs2672587	Nonsmoking	GG	32	3064.4	104.43			
		CC	26	4160.35	62.49	1.149(0.906-1.457)	1.662(1.076-2.569)	0.901(0.599-1.357)
		CG	84	7966.11	105.45	<i>P</i> =0.253	<i>P</i> =0.022	<i>P</i> =0.619
	Smoking	GG	30	3769.38	79.59			
		CC	18	1368.69	131.51	0.631(0.405-0.985)	0.608(0.324-1.141)	0.436(0.171-1.112)
		CG	23	2648.71	86.83	<i>P</i> =0.043	<i>P</i> =0.121	<i>P</i> =0.082
rs2672587	Nondrinking	GG	6	1196.32	50.15			
		CC	32	4274.97	74.85	1.022(0.812-1.286)	1.342(0.901-1.999)	0.778(0.516-1.174)
		CG	88	8339.87	105.52	<i>P</i> =0.855	<i>P</i> =0.148	<i>P</i> =0.232
	Drinking	GG	29	3830.88	75.7			
		CC	12	1254.07	95.69	0.854(0.529-1.377)	1.044(0.482-2.261)	0.561(0.219-1.439)
		CG	19	2274.95	83.52	<i>P</i> =0.517	<i>P</i> =0.913	<i>P</i> =0.229
rs3793917	Male	GG	7	1134.82	61.68			
		CC	28	2612.54	107.18	0.85(0.632-1.144)	1.003(0.635-1.586)	0.569(0.313-1.037)

		CG	52	4285.23	121.35	$P=0.283$	$P=0.989$	$P=0.066$
		GG	14	1735.05	80.69			
	Female	CC	21	3763.81	55.79	1.326(0.999-1.76)	1.91(1.156-3.154)	1.135(0.689-1.869)
		CG	52	6228.82	83.48	$P=0.051$	$P=0.011$	$P=0.618$
		GG	20	2471.67	80.92			
rs3793917	<55	CC	2	2349.8	8.51	1.494(0.607-3.676)	1.942(0.393-9.602)	1.531(0.369-6.346)
		CG	6	3832.9	15.65	$P=0.382$	$P=0.416$	$P=0.557$
		GG	4	1496.3	26.73			
	≥55	CC	47	4026.5	116.73	1.038(0.842-1.281)	1.297(0.923-1.822)	0.799(0.537-1.19)
		CG	98	6681.2	146.68	$P=0.725$	$P=0.134$	$P=0.269$
		GG	30	2710.4	110.68			
rs3793917	Nonsmoking	CC	28	4785.95	58.5	1.328(1.053-1.675)	2.08(1.366-3.167)	1.049(0.693-1.588)
		CG	83	7890.11	105.19	$P=0.016$	$P=0.001$	$P=0.819$
		GG	29	3207.34	90.42			
	Smoking	CC	21	1590.4	132.04	0.498(0.312-0.796)	0.452(0.244-0.837)	0.302(0.1-0.911)
		CG	21	2623.94	80.03	$P=0.004$	$P=0.011$	$P=0.033$
		GG	5	999.38	50.03			
rs3793917	Nondrinking	CC	35	4932.98	70.95	1.178(0.94-1.476)	1.647(1.12-2.42)	0.91(0.6-1.381)
		CG	86	8204.34	104.82	$P=0.154$	$P=0.011$	$P=0.657$
		GG	28	3297.3	84.92			
	Drinking	CC	14	1443.36	97	0.666(0.398-1.114)	0.671(0.322-1.399)	0.427(0.14-1.301)
		CG	18	2309.71	77.93	$P=0.121$	$P=0.287$	$P=0.134$
		GG	6	909.42	65.98			
rs12413729	Male	GG	74	6503.71	113.78	1.007(0.634-1.598)	0.944(0.569-1.567)	2.025(0.49-8.362)
		GA	18	1989.75	90.46	$P=0.977$	$P=0.825$	$P=0.330$
		AA	2	153.12	130.62			

rs12413729	Female	GG	74	9382.21	78.87	0.733(0.442-1.216)	0.706(0.41-1.218)	0.799(0.11-5.825)
		GA	18	2884.46	62.40	<i>P</i> =0.230	<i>P</i> =0.211	<i>P</i> =0.825
		AA	1	203.54	49.13			
	<55	GG	10	5760.2	17.36	1.094(0.302-3.963)	0.724(0.135-3.897)	5.613(0.414-76.146)
		GA	1	1804.6	5.54	<i>P</i> =0.891	<i>P</i> =0.707	<i>P</i> =0.195
		AA	1	125.3	79.80			
	≥55	GG	138	10125.7	136.29	0.877(0.623-1.234)	0.863(0.598-1.248)	0.906(0.223-3.678)
		GA	35	3069.6	114.02	<i>P</i> =0.451	<i>P</i> =0.434	<i>P</i> =0.891
		AA	2	231.4	86.45			
rs12413729	Nonsmoking	GG	114	12029.25	94.77	0.816(0.543-1.225)	0.811(0.526-1.25)	0.653(0.091-4.711)
		GA	25	3610.39	69.24	<i>P</i> =0.327	<i>P</i> =0.342	<i>P</i> =0.673
		AA	1	257.22	38.88			
	Smoking	GG	34	3856.66	88.16	0.989(0.539-1.814)	0.846(0.429-1.667)	3.206(0.748-13.738)
		GA	11	1263.82	87.04	<i>P</i> =0.971	<i>P</i> =0.628	<i>P</i> =0.117
		AA	2	99.45	201.11			
rs12413729	Nondrinking	GG	118	12427.4	94.95	0.86(0.592-1.248)	0.836(0.558-1.252)	1.006(0.248-4.089)
		GA	29	3745.88	77.42	<i>P</i> =0.427	<i>P</i> =0.385	<i>P</i> =0.993
		AA	2	273.46	73.14			
	Drinking	GG	30	3458.52	86.74	1.077(0.512-2.265)	0.973(0.429-2.205)	3.165(0.406-24.676)
		GA	7	1128.33	62.04	<i>P</i> =0.845	<i>P</i> =0.948	<i>P</i> =0.271
		AA	1	83.2	120.19			

Age stratification adjusted for age, gender, TCH, TG, LDL-C, LDL-C, BMI, drinking, smoking, HTN and T2DM.

Gender stratification adjusted for age, TCH, TG, LDL-C, LDL-C, BMI, drinking, smoking, HTN and T2DM.

Smoking stratification adjusted for age, gender, TCH, TG, LDL-C, LDL-C, BMI, drinking, HTN and T2DM.

Drinking stratification adjusted for age, gender, TCH, TG, LDL-C, LDL-C, BMI, smoking, HTN and T2DM.

Supplementary Table 4 Additive interaction of gender, smoking, drinking and HTRA1 polymorphisms on ischemic stroke

SNPs	Modification factor	Genotypes	Stratum	IS(n)	HR (95%CI)	P	RERI (95%CI)	AP (95%CI)	S (95%CI)
rs2268350	Gender	CC	Male	30	1.00(reference)				
		CC	Female	35	0.977(0.595-1.605)	0.928	-0.032(-0.162-0.156)	-0.003(-0.161-0.154)	0.778(0.000-1207458.066)
		CT+TT	Male	64	1.414(0.911-2.194)	0.122	<i>P</i> =0.969	<i>P</i> =0.969	<i>P</i> =0.973
		CT+TT	Female	58	1.014(0.648-1.588)	0.951			
	Smoking	CC	Nonsmoking	51	1.00(reference)				
		CC	Smoking	14	0.637(0.345-1.178)	0.150	0.183(-0.035-0.401)	0.137(0.000-0.273)	2.154(1.173-3.955)
		CT+TT	Nonsmoking	89	1.035(0.731-1.464)	0.847	<i>P</i> =0.099	<i>P</i> =0.050	<i>P</i> =0.013
		CT+TT	Smoking	33	1.212(0.782-1.880)	0.390			
	Drinking	CC	Nondrinking	56	1.00(reference)				
		CC	Drinking	9	0.365(0.172-0.773)	0.009	0.065(-0.141-0.270)	0.063(-0.123-0.248)	-0.950
		CT+TT	Nondrinking	93	0.974(0.697-1.362)	0.879	<i>P</i> =0.054	<i>P</i> =0.054	
		CT+TT	Drinking	29	1.024(0.651-1.612)	0.918			
rs2672587	Smoking	GG	Nonsmoking	26	1.00(reference)				
		GG	Smoking	18	2.024(1.107-3.699)	0.022	-0.816(-0.2-0.037)	-0.1(0.257-0.058)	1.805(0.671-4.855)
		GC+CC	Nonsmoking	114	1.605(1.047-2.460)	0.030	<i>P</i> =0.177	<i>P</i> =0.214	<i>P</i> =0.242
		GC+CC	Smoking	29	1.130(0.661-1.932)	0.656			
rs3793917	Smoking	CC	Nonsmoking	28	1.00(reference)				
		CC	Smoking	21	2.205(1.251-3.887)	0.006	-0.064(-0.194-0.067)	-0.07(-0.225-0.085)	3.355(0.078-145.355)
		CG+GG	Nonsmoking	112	1.787(1.180-2.707)	0.006	<i>P</i> =0.341	<i>P</i> =0.376	<i>P</i> =0.529
		CG+GG	Smoking	26	1.137(0.661-1.954)	0.643			
	Drinking	CC	Nondrinking	35	1.00(reference)				
		CC	Drinking	14	1.144(0.612-2.139)	0.674	-0.053(-0.17-0.064)	-0.073(-0.247-0.102)	1.241(0.815-1.891)
		CG+GG	Nondrinking	114	1.414(0.967-2.068)	0.074	<i>P</i> =0.375	<i>P</i> =0.414	<i>P</i> =0.314
		CG+GG	Drinking	24	0.890(0.524-1.510)	0.665			

Gender stratification adjusted for age, TCH, TG, LDL-C, LDL-C, BMI, drinking, smoking, HTN and T2DM.

Smoking stratification adjusted for age, gender, TCH, TG, LDL-C, LDL-C, BMI, drinking, HTN and T2DM.

Drinking stratification adjusted for age, gender, TCH, TG, LDL-C, LDL-C, BMI, smoking, HTN and T2DM.

Supplementary Table 5 Demographic and clinical characteristics for the case-control study of ischemic stroke

Characteristics	Group	Controls	IS cases	F/χ^2	P
		n=72	n=72		
Age (year)		62.6±7.9	63.14±8.6	0.392	0.696
Gender (%)	Male	48(66.7%)	48(66.7%)	0	1
	Female	24(33.3%)	24(33.3%)		
Smokers (%)	Yes	42(58.3%)	19(27.5%)	13.614	<0.001
	No	30(41.7%)	50(72.5%)		
Drinkers (%)	Yes	38(52.8%)	9(12.7%)	26.055	<0.001
	No	34(47.2%)	62(87.3%)		
SBP		152.56±21.64	155.3±21.15	0.731	0.466
DBP		83.56±10.70	89.59±12.45	2.977	<0.01
Hypertension (%)	Yes	24(33.3%)	45(72.6%)	20.554	<0.001
	No	48(66.7%)	17(27.4%)		
T2DM (%)	Yes	15(20.8%)	12(19.4%)	0.045	0.832
	No	57(79.2%)	50(80.6%)		

SBP, systolic blood pressure; DBP, diastolic blood pressure; T2DM, type 2 diabetes mellitus; IS: ischemic stroke.

* and ** indicates that the statistical difference when compared with the controls;

*, $P<0.05$; **, $P<0.001$.

Supplementary Table 6 Comparisons of *HTRAI* mRNA ($2^{-\Delta\Delta CT}$) level among different genotypes of four tagSNPs in additive model and dominant model

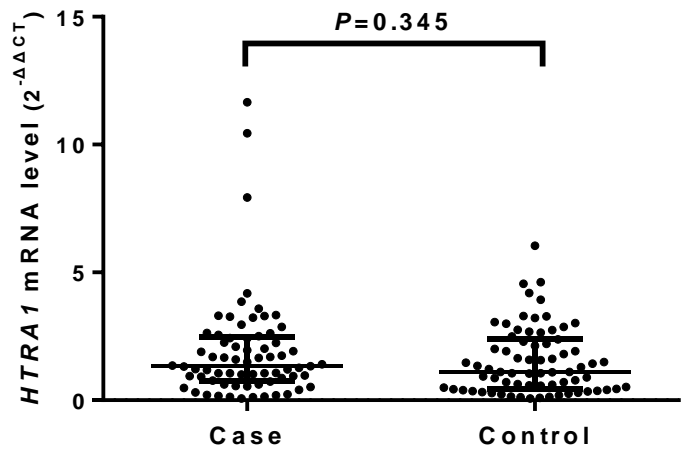
Group	SNP	Stratum	n	WT	HT	MT	P^a	P^b
Case	rs2268350 (C>T)	All cases	31/33/5	1.70(1.18-2.62)	1.05(0.51-2.10)	1.05(0.19-7.92)	0.116	0.044
		Smoking	7/11/2	1.67(1.18-2.62)	0.73(0.20-1.07)	2.16(0.14-)	0.148	0.067
		Nonsmoking	24/22/3	1.72(1.01-2.59)	1.29(0.73-2.31)	1.05(0.24-)	0.521	0.254
	rs2672587 (C>G)	All cases	15/39/15	1.07(0.52-1.89)	1.69(0.77-2.62)	1.22(0.73-2.96)	0.517	0.282
		Smoking	5/13/2	1.18(1.01-1.77)	1.02(0.17-3.58)	0.85(0.73-)	0.740	0.612
		Nonsmoking	10/26/13	0.99(0.42-2.14)	1.72(1.05-2.47)	1.33(0.78-3.12)	0.345	0.163
	rs3793917 (C>G)	All cases	22/39/8	1.62(0.90-2.54)	1.20(0.54-2.43)	1.50(1.09-2.83)	0.446	0.503
		Smoking	6/13/1	1.77(1.15-3.01)	0.73(0.17-2.16)	1.67	0.11	0.062
		Nonsmoking	16/26/7	1.48(0.68-2.44)	1.55(0.73-2.47)	1.33(1.05-2.96)	0.785	0.685
	rs12413729 (G>A)	All cases	54/12/3	1.32(0.70-2.30)	2.13(0.98-3.72)	1.07(0.21-)	0.364	0.415
		Smoking	14/4/2	0.98(0.28-1.90)	2.42(0.29-6.92)	1.48(1.07-)	0.65	0.397
		Nonsmoking	40/8/1	1.38(0.88-2.38)	2.13(1.02-3.18)	0.21	0.184	0.657
Control	rs2268350 (C>T)	All controls	30/24/15	1.27(0.42-2.81)	1.32(0.47-2.25)	0.71(0.32-2.20)	0.651	0.579
		Smoking	14/17/9	1.26(0.80-2.49)	1.29(0.51-1.88)	0.61(0.28-1.63)	0.352	0.292
		Nonsmoking	16/7/6	1.29(0.38-2.95)	1.65(0.35-2.76)	1.35(0.60-2.65)	0.946	0.948
	rs2672587 (C>G)	All controls	16/25/27	1.96(0.69-2.69)	1.09(0.45-2.03)	0.89(0.40-2.29)	0.379	0.165
		Smoking	10/16/13	1.86(0.56-2.70)	1.07(0.59-1.96)	0.71(0.42-1.59)	0.377	0.258
		Nonsmoking	6/9/14	2.44(0.86-2.83)	1.11(0.38-2.28)	1.34(0.36-3.09)	0.691	0.546
	rs3793917 (C>G)	All controls	16/35/18	1.62(0.42-2.47)	0.94(0.41-2.01)	1.48(0.59-3.00)	0.391	0.722
		Smoking	10/20/10	0.96(0.23-1.92)	0.99(0.58-2.10)	1.32(0.59-1.97)	0.663	0.414
		Nonsmoking	6/15/8	2.44(1.62-2.83)	0.49(0.34-1.65)	2.14(0.64-3.17)	0.092	0.142
	rs12413729	All controls	51/14/5	1.10(0.41-2.38)	1.28(0.64-2.28)	0.71(0.38-1.73)	0.598	0.963

(G>A)	Smoking	32/5/4	1.07(0.53-2.10)	1.34(0.75-1.91)	0.66(0.26-0.76)	0.253	0.466
	Nonsmoking	19/9/1	1.47(0.35-2.76)	1.22(0.54-2.57)	2.68	0.701	0.769

WT: wild type; HT: heterozygote; MT: mutant type.

a. *P* for additive model

b. *P* for dominant model



e-Figure 1. Comparison of *HTRA1* mRNA levels between IS case group and control group.