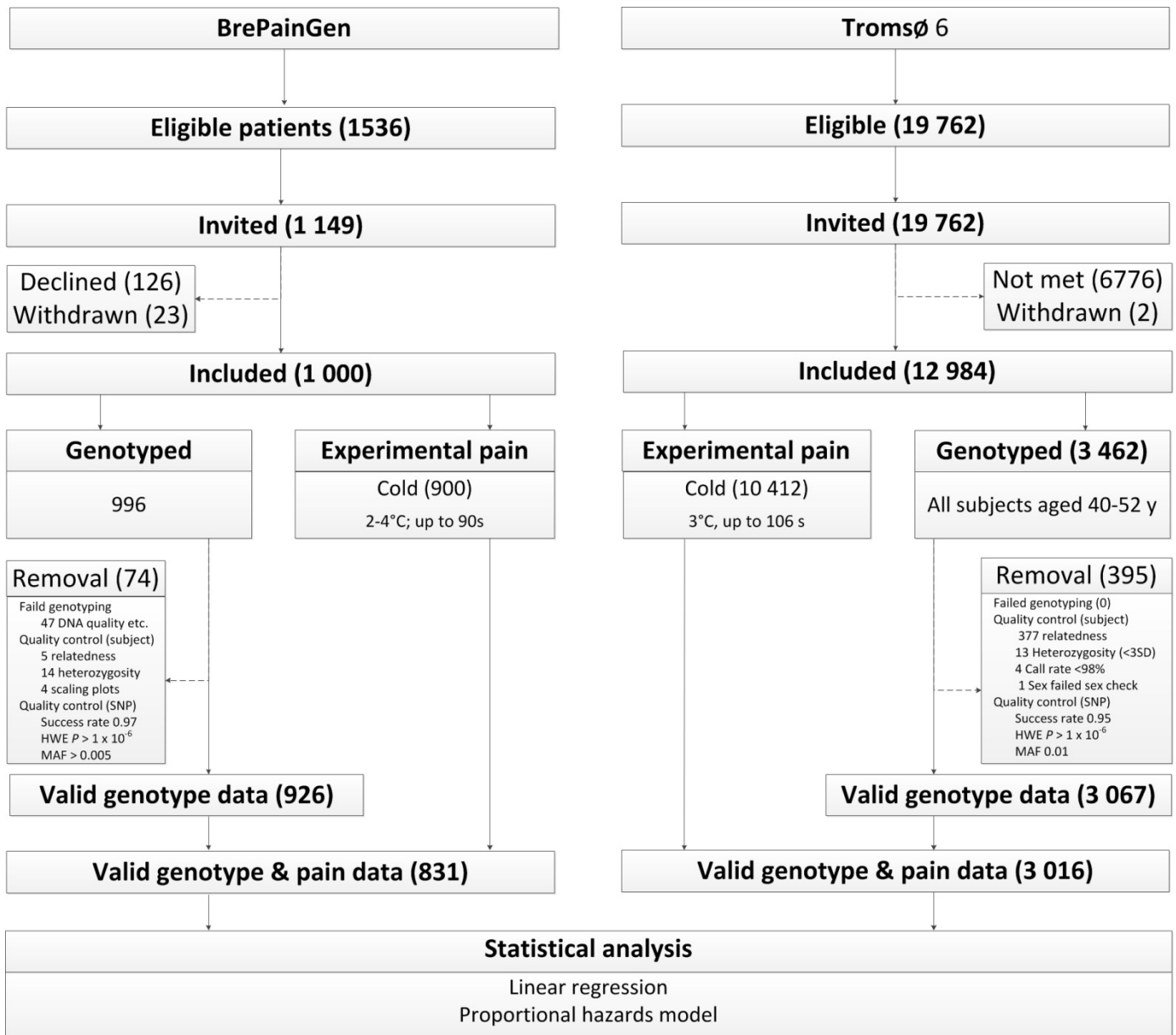


# Supplementary figures and tables



**Figure S1. Sample recruitment and selection.** Abbreviations: s – seconds, y – years, C - Celsius

**Table S1. Stratified demographics.**

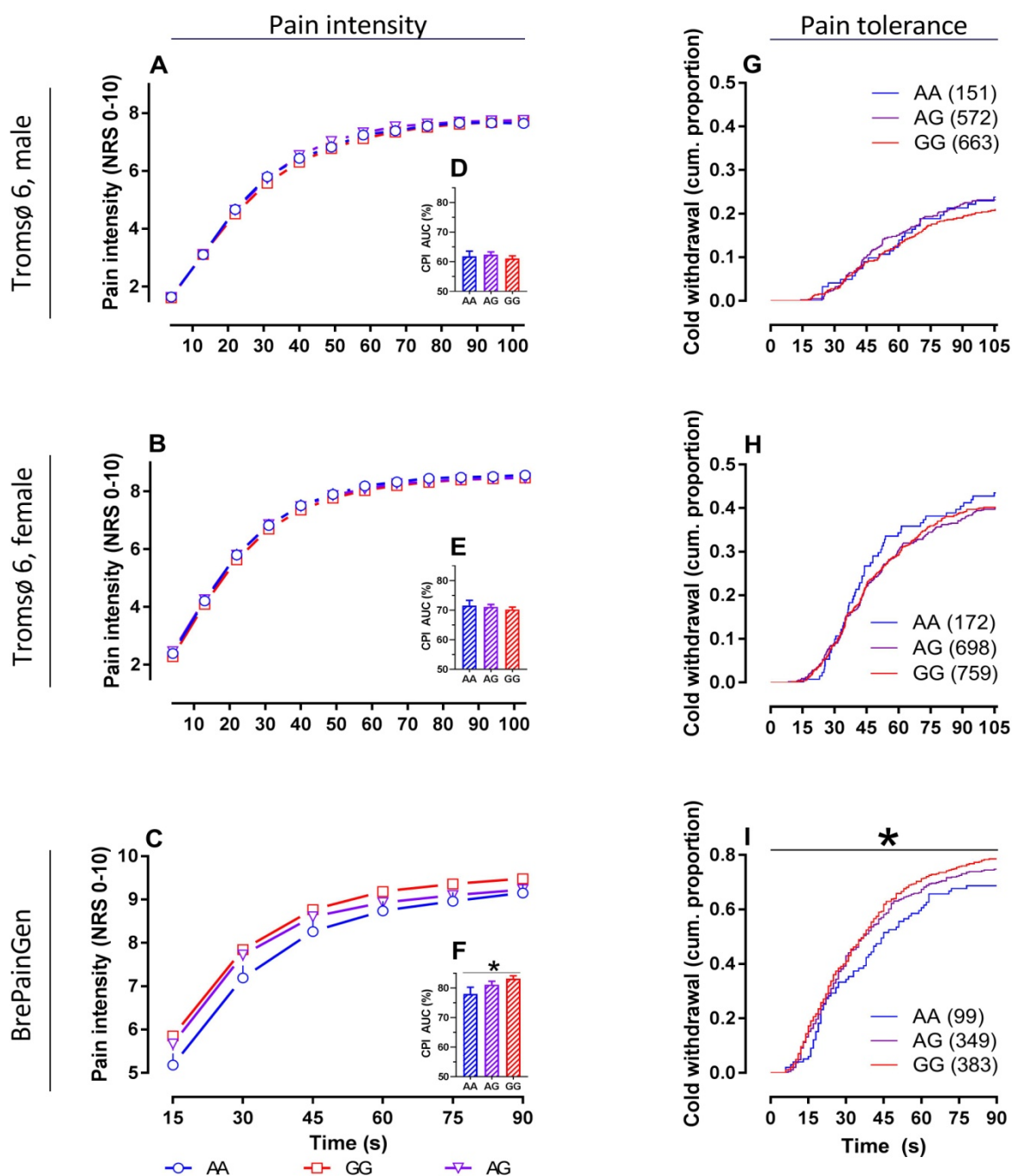
	SNP	Source	a	A	age (yr)			weight			BMI			CP		
					aa	aA	AA	aa	aA	AA	aa	aA	AA	aa	aA	AA
Tromsø (m, n=1,387)	rs7958311	<i>g</i>	A	G	44.5±3.9	44.7±3.8	44.5±4.1	85.3±12.0	87.3±13.5	88.0±13.9	26.6±3.9	27.2±3.8	27.3±3.9	30.5	27.7	28.8
	rs208296	<i>i</i>	A	G	44.7±3.9	44.6±3.9	44.5±3.8	88.2±14.6	87.2±13.4	87.7±13.4	27.4±3.8	27.2±3.8	27.3±3.9	23.0	30.3	28.3
	rs208294	<i>g</i>	A	G	44.3±3.7	44.8±3.9	44.4±3.9	86.8±11.8	87.7±13.7	87.8±14.2	27.1±3.5	27.4±3.8	27.2±3.9	26.3	29.3	28.5
Tromsø (f, n=1,629)	rs7958311	<i>g</i>	A	G	44.0±3.6	44.8±4.0	44.7±3.9	70.9±11.5	72.0±13.4	71.7±14.3	25.8±4.2	26.3±4.8	26.2±4.9	41.2	38.1	36.4
	rs208296	<i>i</i>	A	G	45.1±4.0	44.5±3.9	44.7±3.9	72.9±13.9	71.8±13.7	71.2±13.8	26.7±4.8	26.1±4.8	26.0±4.8	34.4	37.7	37.3
	rs208294	<i>g</i>	A	G	44.3±3.9	44.6±3.9	44.8±4	71.47±13.4	72.4±14.1	71.5±13.7	26.0±4.8	26.2±4.9	26.1±4.7	37.4	38.1	36.4
BrePainGen (f, n=831)	rs7958311	<i>g</i>	A	G	56.5±8.5	57.1±9.4	57.0±9.3	70.0±12.6	69.13±11.9	69.1±12.3	25.6±4.3	25.5±4.3	25.4±4.3	15.6	23	25.3
	rs208296	<i>g</i>	A	G	57.4±8.4	57.0±9.2	56.9±9.7	69.5±12.1	69.51±12.4	68.8±12.0	25.5±4.3	25.6±4.4	25.3±4.1	26.1	20.9	26.4
	rs208294	<i>g</i>	A	G	57.2±9.9	56.6±9.4	57.4±9.1	69.6±12.3	69.0±12.2	69.3±12.1	25.5±4.4	25.3±4.2	25.6±4.3	31.5	22.7	23.3

Data are summarized as mean ± SD. a=minor allele, A=main allele, BMI=body mass index, CP= chronic pain, f=female, g=genotyped, i=imputed, m=male, SNP= single nucleotide polymorphism, yr=years.

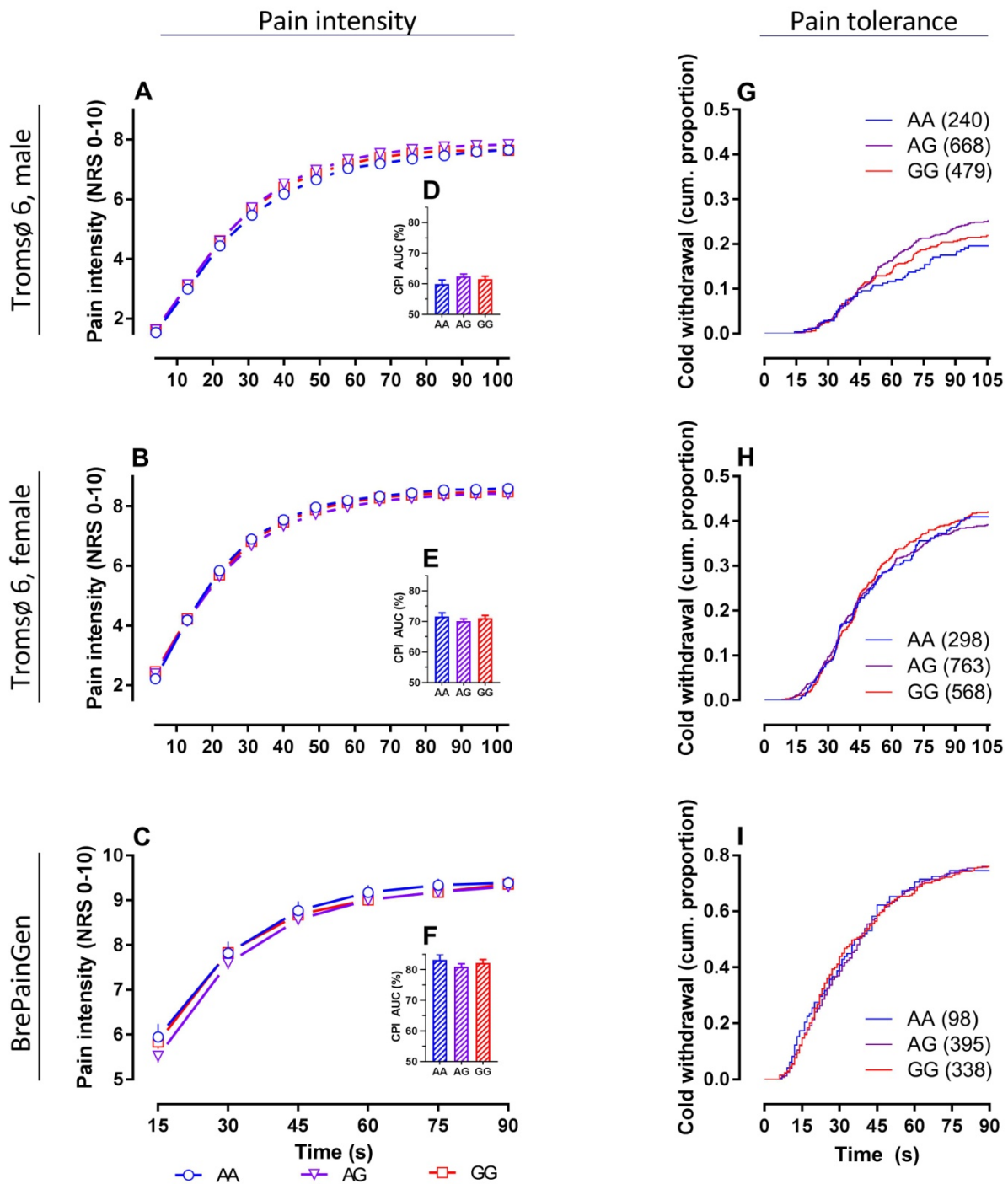
**Table S2. Human *P2RX7* variants and pain in cold pressor task in BrePainGen and Tromsø datasets: secondary SNPs rs208296 and rs208294.**

	snp	CWT		CPI, AUC%	
		HR (95%CI)	<i>p</i>	$\beta$ ( $\beta$ se)	<i>p</i>
Tromsø (m, n=1387)	rs208296	1.09 (0.74-1.60)	0.22	0.84 (0.85)	0.33
	rs208294	0.98 (0.84-1.14)	0.79	0.48 (0.78)	0.54
Tromsø (f, n=1629)	rs208296	1.12 (0.85-1.47)	0.96	0.61 (0.8)	0.45
	rs208294	0.97 (0.87-1.08)	0.62	0.11 (0.71)	0.88
BrePainGen (f, n=831)	rs208296	0.82 (0.68-0.99)	0.04	-2.4 (1.01)	0.02
	rs208294	1.01 (0.88-1.16)	0.88	-0.08 (1.04)	0.94
Meta-analysis (ff)	rs208296	0.906 (0.77-1.05)	0.30	-0.56 (2.00)	0.38
	rs208294	0.985 (0.90-1.07)	0.57	0.05 (0.40)	0.93

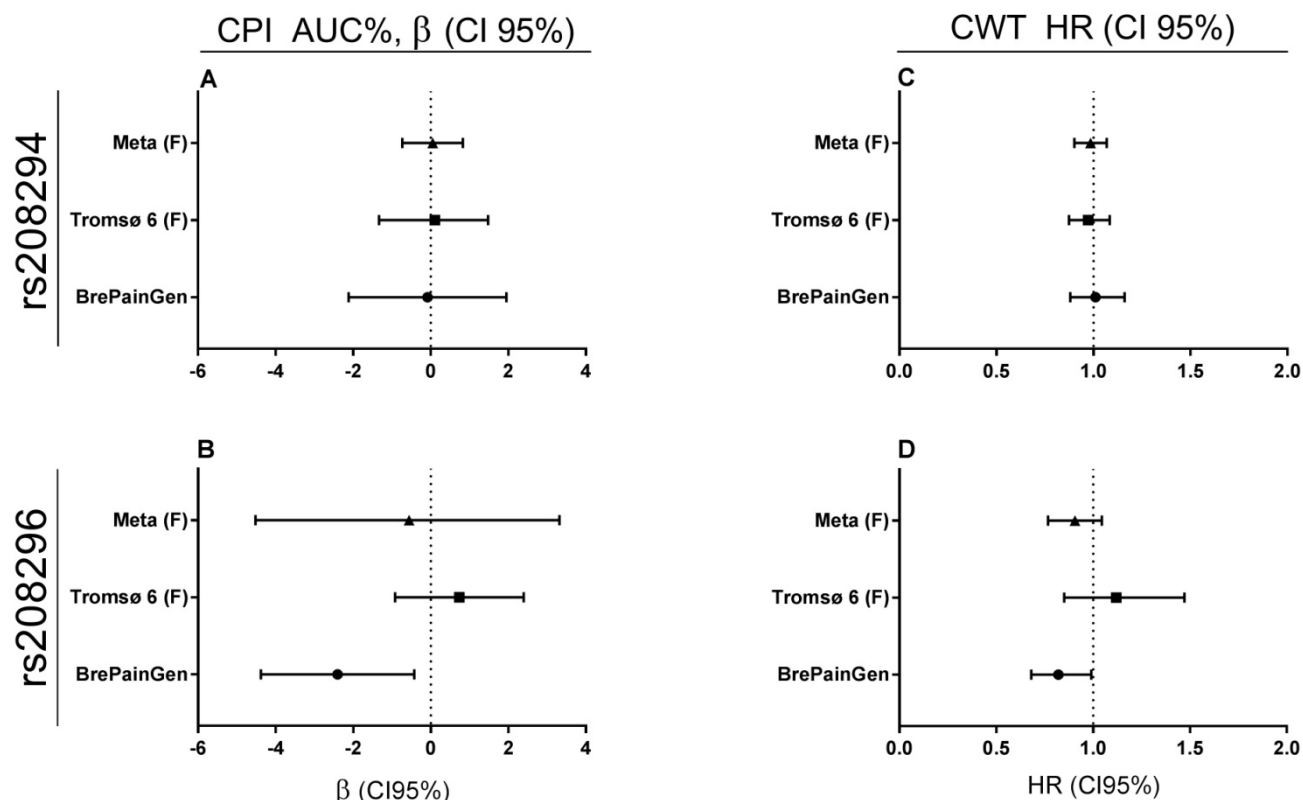
Cold pain was assessed using cold pressor task. Cold withdrawal time (CWT) has been used as an indicator of pain tolerance and pain intensity has been assessed using CPI area under the time-effect curve (AUC%). CWT was analyzed using additive model of Cox proportional hazards model/Cox regression and CPI AUC with linear regression. A meta-analysis of females from both cohorts has been performed using fixed effect model.



**Figure S2. Human *P2RX7* variant SNP rs208296 and cold pressor pain in the Tromsø and BrePainGen datasets.** Experimental pain was assessed using cold pressor task. Cold pain intensity (CPI) was assessed using numeric rating scale (NRS0-10). CPI values missing after CWT were recoded to 10 (maximum). Time-CPI curves of different genotypes are shown (A-C) and CPI ( $\pm$ SEM) is plotted on y axis and time on x axis. Areas under the time-CPI curves (AUC%) were calculated by trapezoidal rule and are shown as genotype means  $\pm$ SEM (D-F). Withdrawal time (CWT; G-I) was used as an indicator of pain tolerance. CWT was analyzed using additive model of Cox proportional hazards model/Cox regression. The duration of cold pressor task is plotted on x axis, and y axis shows the cumulative proportion of cold withdrawal. Numbers in parentheses indicate *n* for each genotype group. Asterisks indicate the effect of genotypes (\*,  $p < 0.05$ , linear & Cox regression, additive model).



**Figure S3. Human *P2RX7* variant SNP rs208294 and cold pressor pain in the Tromsø and BrePainGen datasets.** Experimental pain was assessed using cold pressor task. Cold pain intensity (CPI) was assessed using numeric rating scale (NRS0-10). CPI values missing after CWT were recoded to 10 (maximum). Time-CPI curves of different genotypes are shown (A-C) and CPI ( $\pm$ SEM) is plotted on y axis and time on x axis. Areas under the time-CPI curves (AUC%) were calculated by trapezoidal rule and are shown as genotype means  $\pm$ SEM (D-F). Withdrawal time (CWT; G-I) was used as an indicator of pain tolerance. The duration of cold pressor task is plotted on x axis, and y axis shows the cumulative proportion of cold withdrawal. Numbers in parentheses indicate *n* for each genotype group.



**Figure S4. *P2RX7* variants rs208296 & rs208294 and pain in cold pressor task in BrePainGen and Tromsø datasets: meta-analysis.** Experimental cold pain was assessed using cold pressor task and withdrawal time (CWT) has been used as an indicator of pain tolerance. CWT was analyzed using additive model of Cox proportional hazards model (Cox regression). Pain intensity (CPI) was assessed using numeric rating scale (NRS0-10). Area under the time-CPI curve (CPI AUC%) was used as indicator of pain intensity and analyzed using additive model of linear regression. Figure shows associations of CPI AUC% (A,B) and CWT (C,D) with *P2RX7* variants rs208294 and rs208296 in BrePainGen and Tromsø 6 cohorts and meta-analysis (fixed effect model, F).