

## Supplementary figures

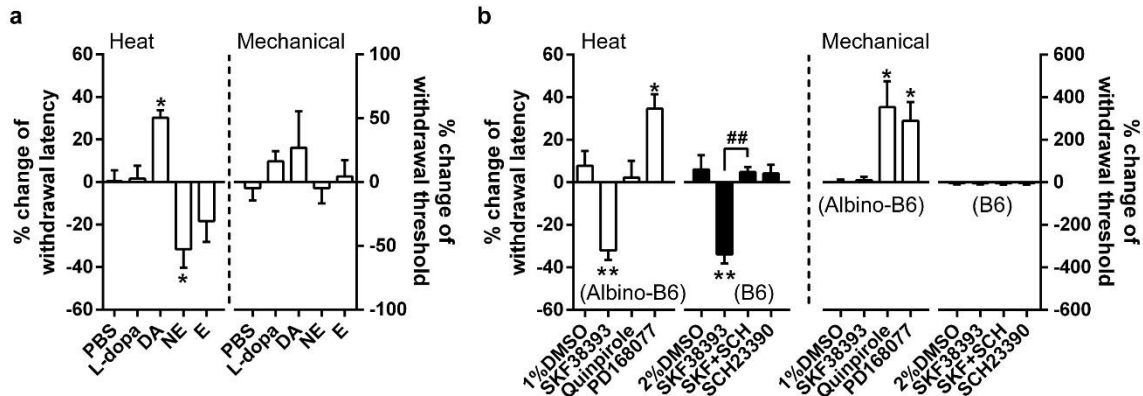
### Cutaneous pigmentation modulates skin sensitivity via tyrosinase-dependent dopaminergic signalling

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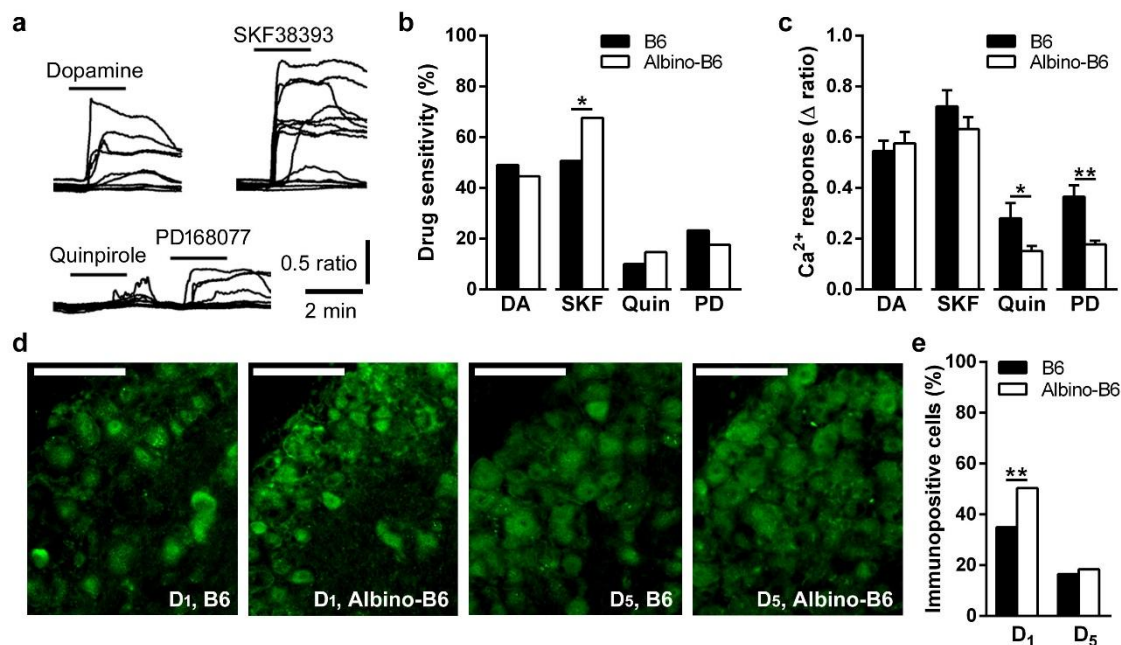
**Table S1 | Characteristics of the studies included in the meta-analysis**

Study name	Published year	Age range (mean)	Sex	Race/ethnicity	Sample size (dark/light)	Pain measurements
Sheffield (22)	2000	20-73 (38.0)	F/M mixture	AA, W	51 (24/27)	HPI
Yosipovitch (23)	2004	19-59 (35.6)	F/M mixture	Chi, I, M	49 (29/20)	HPTh
Campbell (24)	2005	NR (21.1)	F/M mixture	AA, W	120 (62/58)	HPI, HPTh, HPTo
Watson (25)	2005	Adults (NR)	M only	SA, WB	40 (20/20)	HPI, HPTh
Mechlin (26)	2007	18-47 (NR)	F and M	AA, NHW	84 (45/39)	HPTh, HPTo
Rahim-Williams (27)	2007	18-53 (24.0)	F and M	AA, H, NHW	206 (124/82)	HPTh, HPTo, PPTH
Grewen (28)	2008	NR (27.4)	F only	AA, NHW	48 (25/23)	HPTh, HPTo
Wang (29)	2010	19-47 (NR)	F/M mixture	AA, H, C, EA	40 (20/20)	HPTh
Sibille (30)	2011	18-45 (23.1)	F/M mixture	AA, NHW	142 (23/119)	HPI, HPTh, HPTo, PPTH
Hastie (31)	2012	18-54 (23.7)	F/M mixture	AA, H, NHW	247 (160/87)	HPI, HPTo, HPTh, PPTH
Riley III (32)	2014	45-76 (57.6)	F/M mixture	NHW, NHB	191 (53/138)	HPI, HPTo, HPTh, PPTH

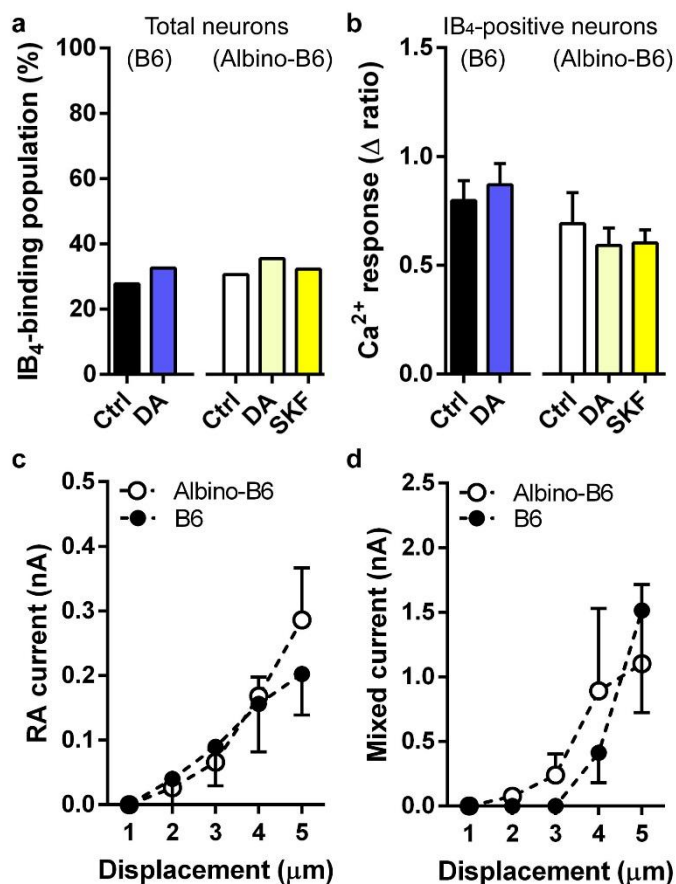
Mean age (in years): Age range: NR, not reported. Sex: F, females; M, males. Race/ethnicity: AA, African Americans; C, Caucasians; Chi, Chinese; EA, East Asians; H, Hispanics; I, Indians; M, Malays; NHW, non-Hispanic Whites; SA, South Asians; W, Whites; WB, White British. Sample size: Dark, dark skin group including AA, H, I, M and SA; Light, light skin group including C, Chi, EA, NHW, W and WB, based on native skin color distributions (21). Pain measurement: HPI, heat pain intensity at 48 or 49°C; HPTh, heat pain threshold; HPTo, heat pain tolerance; PPTH, pressure pain threshold in trapezius and/or masseter.



**Figure S1 | Acute effects of L-dopa, catecholamines, dopamine receptor agonists and antagonists on cutaneous sensitivities in mice.** (a) Percent changes of withdrawal latency to heat stimulation (heat sensitivity) 1 hour following injections of PBS, L-dopa, DA, NE and E and threshold to von Frey stimulation (mechanical sensitivity) in 2-3 hours after injections of the same agents in albino-B6. \* $P < 0.05$ , vs PBS, in Dunnett's multiple *post hoc* test, following one-way ANOVA test. (b) Percent changes of withdrawal latency to heat stimulation and mechanical withdrawal threshold from 30-40 min after injections of dopamine receptor agonists and antagonists in B6 and albino-B6. \*  $P < 0.05$ , \*\* $P < 0.01$ , vs controls (1% or 2% DMSO in PBS), in Dunnett's multiple *post hoc* test, following one-way ANOVA test. ## $P < 0.01$ , vs a SKF38393-injected group, in *t*-test. Each experimental group,  $n = 5$ . All bars show mean  $\pm$  s.e.m.. The analyses present % change against pre-values (before drug injections), which are presented in Fig. 3.



**Figure S2 | Dopamine receptor expression in cultured TG neurons of B6 and albino-B6.** (a) Ca<sup>2+</sup> responses by dopamine and receptor-specific agonists; DA concentration was 10  $\mu$ M. The D<sub>1/5</sub> agonist SKF38393 (SKF), the D<sub>2/3</sub> agonist quinpirole (Quin) and the D<sub>4</sub> agonist PD168077 (PD) at 30  $\mu$ M. Quin and PD were applied to the same neurons. (b) Sensitivities to dopaminergic agents. DA, SKF, Quin and PD in B6: total n=75/153, 45/89, 9/90 and 21/90, respectively. DA, SKF, Quin and PD in albino-B6: total n=70/157, 69/102, 15/102 and 18/102, respectively. \**P*<0.05, in Fisher's test. (c) Peak of dopaminergic agent-induced Ca<sup>2+</sup> responses. \**P*<0.05, \*\**P*<0.01, in *t*-test. All bars show mean  $\pm$  s.e.m.. (d) Immunoreactivities to D<sub>1</sub> and D<sub>5</sub> dopamine receptor in the mouse TG neurons. Scale bar, 100  $\mu$ m. (e) Cell populations showing D<sub>1</sub> and D<sub>5</sub> immunoreactivities in total neurons of B6 (n=86/246 and 55/171, respectively) and albino-B6 (n=148/294 and 73/233, respectively). \*\**P*<0.01, in Fisher's test.



**Figure S3 | Effects of dopaminergic stimulations on capsaicin-induced Ca<sup>2+</sup> responses and mechanically-activated currents in cultured TG neurons.** (a) IB<sub>4</sub> binding cell populations. Ctrl and DA in B6: total n=35/126 and 45/138, respectively. Ctrl, DA and SKF in albino-B6: total n=30/98, 55/155 and 40/124, respectively. (b) Peak of capsaicin-induced Ca<sup>2+</sup> responses in IB<sub>4</sub>-positive neurons. Ctrl and DA in B6: n=27 and 29, respectively. Ctrl, DA and SKF in albino-B6: total n=12, 37 and 23, respectively. (c) Displacement-dependency of rapidly-adapted (RA) currents. (d) Displacement-dependency of mixed currents with RA and slowly-adapted currents. All bars and plots show mean ± s.e.m..