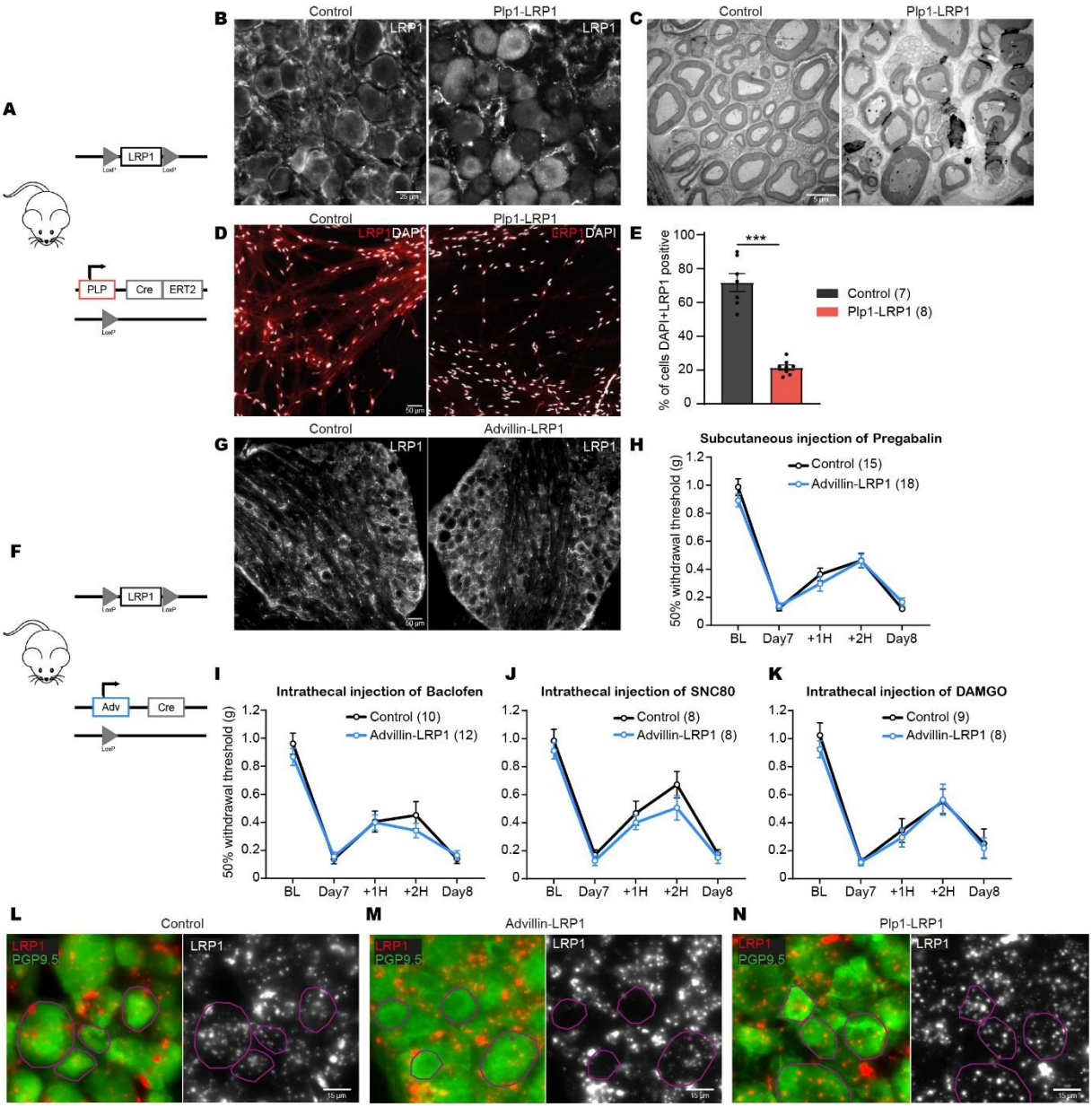
Supporting Information for:

LRP1/AMPK/mTORC1 signaling in Large-Diameter Sensory Neurons Is Essential for TAFA4 Analgesia

Aude Charron[1], Catarina Santos[2], Luc Camoin[3], Stéphane Audebert[3], Stéphane Gaillard[2], Francis Castets[1,*] and Aziz Moqrich[1,2,4,*]

This file includes figures S1 and S2

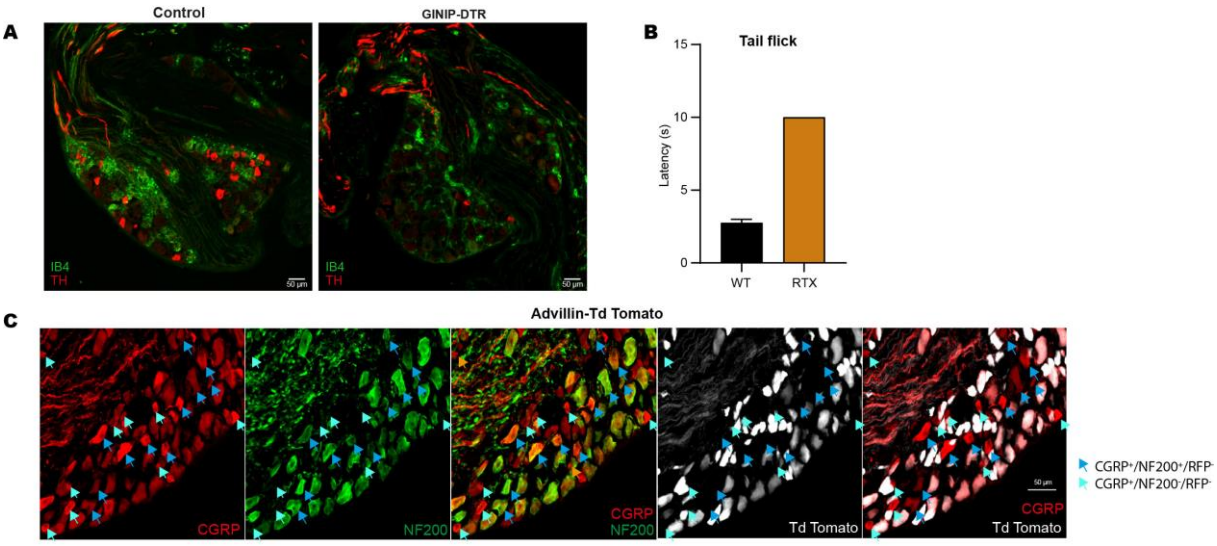
Supplemental Figure 1. Loss of LRP1 in PLP1-LRP1 and Advillin-LRP1 mice



(A) and **(F)** Schematic representation of control and cre mouse lines. **(B)** LRP1 immunostaining on DRG of control and Plp1-LRP1 mice. In Plp1-LRP1 mice, there is a loss of LRP1 immunostaining in satellite cells. **(C)** Electron microscopy on sciatic nerve of control and Plp1-LRP1 mice. In Plp1-LRP1 mice, axons in Remak bundles are abnormally shaped and unsheathed and myelin sheath is destroyed. **(D)** LRP1 immunostaining and DAPI labelling on teased nerve of control and Plp1-LRP1 mice. The percentage of double-positive cells has been quantified in **(E)**. Statistical tests were performed with Mann-Whitney test. **(G)** LRP1 immunostaining on DRG of control and Advillin-LRP1 mice. **(H to K)** The threshold of paw withdrawal in response to static mechanical stimulation (von Frey assay) on the ipsilateral paw of mice was assessed before (baseline) or 7 days post-SNI. **(H)** SC injection of Pregabalin (2 mM) or intrathecal injection of **(I)** Baclofen (0.47 nmol), **(J)** SNC80 (10 nmol) and **(K)** DAMGO (0.2 nmol) significantly increased the threshold 2h post-injection in both genotypes. Statistical tests were performed with two-way repeated measures ANOVA followed by

Bonferroni test. **(L)** RNAscope on *lrp1* transcript and PGP9.5 immunostaining on DRG slices of control mice, **(M)** Advillin-LRP1 mice and (N) Plp1-LRP1 mice. The contour of the neurons has been traced in purple. In Advillin-LRP1 mouse, the LRP1 labelling is loss except in the one with a star whereas in the Plp1-LRP1 mouse, it is the satellite cells that do not express LRP1. All results are expressed as mean ± SEM. The number in brackets represents the number of mice for each condition.

Supplemental Figure 2. Molecular and functional validation of the mouse lines used in this study



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	NF200					NP			PEP		TH
	NF1	NF2/3		NF4/5		NP1	NP2/3		PEP1	PEP2	
		NF2	NF3	NF4	NF5		NP2	NP3			
Lrp1	0	0,125	0	0,273	0,115	0,168	0,094	0	0,094	0,118	0,124
Parvalbumin	0	0,229	0	1,000	1,000	0,032	0,031	0	0,063	0	0,013
TrkC	0,161	0,271	1,000	0,545	0,731	0,104	0,063	0	0,031	0,176	0,309
P2rx3 (P2X3)	0,032	0	0,167	0	0	0,856	0,469	0,583	0,156	0,353	0,099
Nefh (NF200)	0,806	0,956	0,917	0,727	1,000	0,008	0	0	0,125	0,647	0,013
TH	0	0,021	0	0	0	0	0	0	0,016	0	0,670
Calca	0	0	0,083	0	0	0,200	0,875	0,083	0,781	1,000	0,009
Calcb	0,032	0,250	0,167	0	0	0,880	0,781	0	0,438	0,706	0,597

(A) TH and IB4 immunostaining on thoracic DRG on GINIP DTR and GINIP$^{fl/+}$ mice. **(B)** Effect of the loss of TRPV1 neurons in the tail flick test. RTX mice did not respond to 52°C water bath whereas control mice respond in less than 3 second (n=12 mice per condition). **(C)** Triple immunostaining with NF200, CGRP and RFP on L4 DRG of Advillin$^{-tdTomato}$ to highlight the lack of CRE recombination in a large number of small and medium diameter CGRP^{+} neurons. **(D)** Publicly available single-cell RNA sequencing data classify NF200^{+} neurons into five distinct subsets (NF1 to NF5). All results are expressed as mean ± SEM.