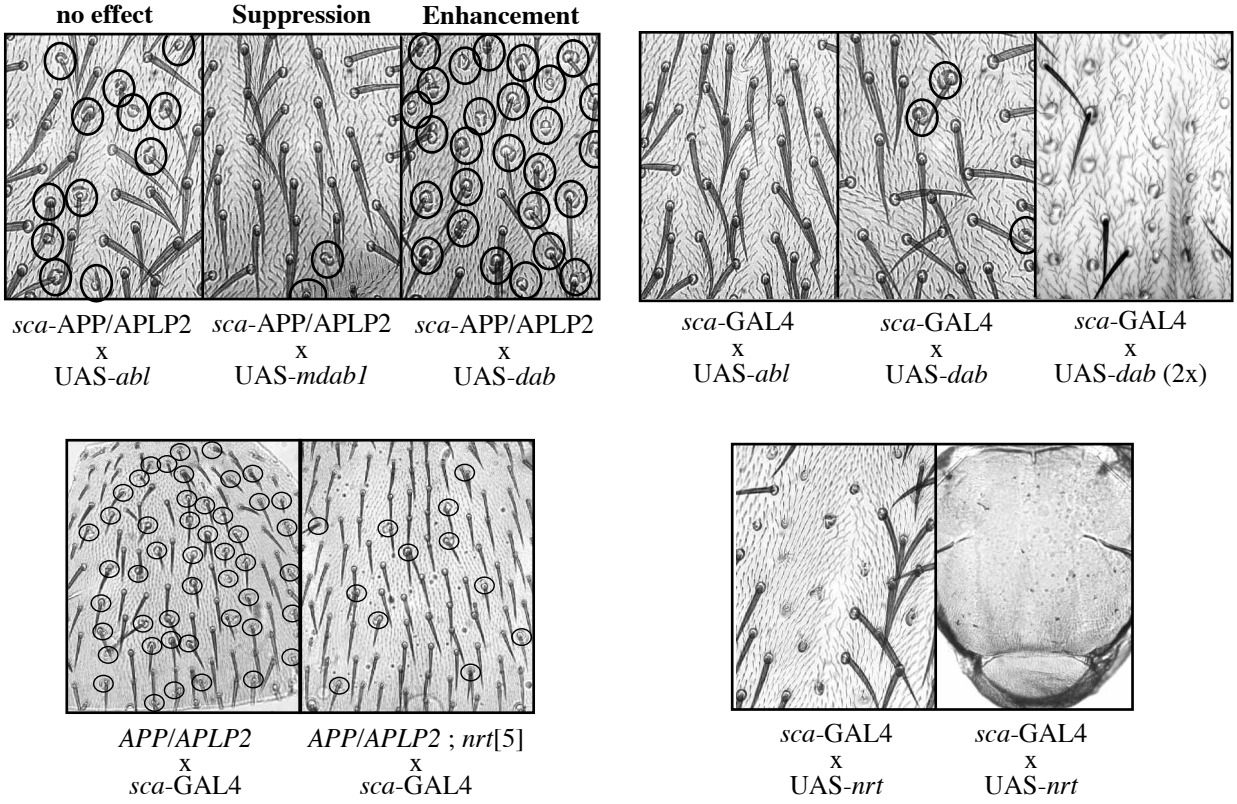

Gene	Enhancement	Suppression	no effect
abl			lof [1, 2, 3, DN], gof
dab	gof [UAS]	lof [RNAi]	
mdab-1		gof [UAS]	
hdab-2	gof [UAS]		
ena			lof [GC5, GC8], gof [UAS]
nrt	gof [UAS]	lof [1f, 2, 5, m54]	

Supplementary Figure 4 Disabled and Neurotactin but not Abelson are required for APP/APLP2-induced phenotypes.

We have shown that the NPTY-motif is the only essential motif within the ICD of the APP-family members required for their interference with Notch signaling. This motif is highly conserved in all identified APP homologs and it is also known to be required for the interaction of APP with the PTB-domain containing proteins of the Dab-family. Therefore, we analysed the APP-Dab interaction in more detail. In *Drosophila*, Dab and Enabled (Ena) have been identified through genetic interaction with the Abelson (Abl) tyrosine kinase. In mice and in humans two homologs of Dab have been isolated. Both proteins are highly conserved, but Dab-2 shows an higher homology to *Drosophila* Dab. There is also a significant difference in size between *Drosophila* Dab (2411 aa), Dab-1 (588 aa) and Dab-2 (770 aa). To test Dab functions in *Drosophila*, transgenic lines were generated or obtained carrying constructs for cDNAs of mouse *dab-1*, human *dab-2*, *Drosophila abl, dab* and *ena*. These lines were then crossed with *sca*-GAL4 or *sca-APP/APLP2*. Whereas the expression of Ena and Abl had no effect, hDab-2 enhanced the *sca-APP/APLP2* phenotype, and the phenotype was suppressed by mDab-1. The suppression suggests that mDab-1 is not able to participate in the APP/APLP2 triggered event, even though it can probably still bind with its N-terminal PTB-domain to the target (APP/APLP2) and act in a dominant-negative fashion. Furthermore, in a wildtype context overexpression of *Drosophila* Dab and hDab-2 induced Notch gain-of-function phenotypes in contrast to mDab-1.

To confirm the overexpression result, flies mutated for *dab*, *abl* and *ena* were crossed to *sca-APP/APLP2* flies in a genetic interaction assay. However, it has recently been reported that the previously isolated mutations were erroneously attributed to *dab*, and in fact affect the *neurotactin* (*nrt*) locus. Our own results support this conclusion, thus we repeated our genetic interaction assays including classic *nrt* alleles and UAS-*nrt* transgenes. Flies carrying a mutation for *abl* or *ena* did not show any influence on the bristle phenotype, but the phenotype was suppressed as soon as mutations for *nrt* were present. In contrast, overexpression of Nrt enhanced the *sca-APP/APLP2* phenotype and induced very strong Notch gain-of-function phenotypes itself if overexpressed in the SOP of *wt* flies. These phenotypes were dosage sensitive and in most cases resulted in flies where all the cells of the proneuronal clusters had been transformed into epidermal fate. lof, loss-of-function; gof, gain-of-function;[ ], alleles used; UAS, overexpression of cDNA under the control of GAL4.