

Table S2. Genetic Conservation of GPS: Comparison of Ka/Ks ratios, Related to Figure S4

| Receptor | with HX(S/T) | without HX(S/T) |
|-----------------|---------------------|------------------------|
| <i>Celsr1</i> | 0.1399 | 0.12274 [#] |
| <i>Celsr2</i> | 0.0337 [*] | 0.03635 [#] |
| <i>Lphn2</i> | 0.0163 [§] | 0.01641 |

The evolutionary conservation of the GPS with and without the potential cleavage sequence (HX(S/T)) was compared between orthologs of *Celsr1*, *Celsr2*, and *Lphn2*. The analysis included the coding region of the GPS of *Celsr1*, *Celsr2* and *Lphn2* from 17 vertebrate orthologs (sequences are provided on request). Low Ka/Ks values of the GPS-coding sequences indicate strong purifying (negative or sequence-keeping) selection in all aGPCR investigated. Although there are significant differences of conservation between cleavable (*Celsr2*, *Lphn2*) and non-cleavable (*Celsr1*) GPS (**Celsr2* versus *Celsr1*: $p < 10^{-17}$; §*Lphn2* versus *Celsr1*: $p < 10^{-26}$), the cleavage sites ([#]with HX(S/T) versus without HX(S/T): $p < 10^{-6}$) do not contribute to the overall differences in GPS conservations between the aGPCR investigated. Note: no (*Lphn2*) or opposite directions of differences in HXS/T versus without HX(S/T) (*Celsr1*, *Celsr2*) were found.