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5	Molecular reconstruction of recurrent evolutionary switching
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45 Abstract

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47 Olfactory receptor repertoires exhibit remarkable functional diversity, but how 48 these proteins have evolved is poorly understood. Through analysis of extant and 49 ancestrally-reconstructed drosophilid olfactory receptors from the lonotropic 50 Receptor (IR) family, we investigated evolution of two organic acid-sensing 51 receptors, IR75a and IR75b. Despite their low amino acid identity, we identify a 52 common "hotspot" in their ligand-binding pocket that has a major effect on 53 changing the specificity of both IRs, as well as at least two distinct functional transitions in IR75a during evolution. Ligand-docking into IR models predicts that 54 55 the hotspot does not contact odor molecules, suggesting that this residue 56 indirectly influences ligand/receptor interactions. Moreover, we show that odor 57 specificity is refined by changes in additional, receptor-specific sites, including 58 those outside the ligand-binding pocket. Our work reveals how a core, common 59 determinant of ligand-tuning acts within epistatic and allosteric networks of 60 substitutions to lead to functional evolution of olfactory receptors. 61

62 Introduction

63 64 Amongst the senses, olfaction is particularly flexible over evolutionary time, 65 enabling animals to adapt their recognition of the vast, ever-changing universe of volatile chemicals in the environment (Bargmann, 2006; Ramdya and Benton, 66 67 2010). This flexibility is reflected in the evolution of large, divergent families of 68 olfactory receptors with different odor tuning properties. Several functional 69 surveys of receptor repertoires in vertebrates (e.g., humans and the house mouse 70 Mus musculus) and insects (e.g., the vinegar fly Drosophila melanogaster and the 71 malaria mosquito Anopheles gambiae) have identified ligands for many receptors 72 (Carey et al., 2010; Hallem and Carlson, 2006; Saito et al., 2009). Moreover, 73 comparative sequence and functional analyses of orthologous receptors across 74 species have started to identify amino acid differences that can explain species-75 specific receptor tuning properties (Adipietro et al., 2012; Auer et al., 2020; Butterwick et al., 2018; Del Mármol et al., 2021; Leary et al., 2012; Mainland et 76 al., 2013; Prieto-Godino et al., 2017; Yang et al., 2017). However, the molecular 77 78 basis of functional changes in receptors over evolutionary timescales - and 79 whether common principles in this process exist between different receptors -80 remains unclear.

81 A powerful model to study olfactory receptor evolution is the lonotropic 82 Receptor (IR) repertoire, a protostomian chemosensory subfamily of ionotropic 83 glutamate receptors (iGluRs) (Benton et al., 2009; Croset et al., 2010; Ni, 2021; 84 Rytz et al., 2013). Although IRs and iGluRs have limited amino acid sequence 85 identity, their overall conserved (predicted) secondary and tertiary structural 86 organization suggests that the chemosensory receptors share many mechanistic 87 similarities with their iGluR ancestors (Abuin et al., 2011). The best-characterized IRs are predicted to be hetero-tetramers formed of two subunits of a conserved 88 89 co-receptor and two subunits of a "tuning" receptor (Abuin et al., 2019, 2011). The 90 latter are more variable in sequence both within and between species, particularly 91 in the extracellular ligand-binding domain (LBD), consistent with their diverse 92 odor-recognition properties.

93 Functional characterization of IRs in different drosophilid species has 94 revealed orthologous receptors that have distinct odor recognition properties 95 (Prieto-Godino et al., 2017, 2016), notably IR75a, a receptor that likely originated in the Neodipteran ancestor (>200 million years ago) and its paralog IR75b, which 96 97 arose through duplication of Ir75a in the Drosophilidae ancestor (~60-70 million 98 vears ago) (Croset et al., 2010: Prieto-Godino et al., 2017). In D. melanogaster 99 and D. simulans, two cosmopolitan species that feed on a wide range of 100 fermented fruit, these receptors exhibit different sensitivity towards carboxylic 101 acids: IR75a is tuned predominantly to acetic acid, while IR75b responds maximally to butyric acid (Prieto-Godino et al., 2017, 2016; Silbering et al., 2011). 102 103 By contrast, in the closely-related island endemic D. sechellia, which feeds and 104 breeds exclusively on the ripe noni fruit of the *Morinda citrifolia* shrub (Figure 1A), 105 IR75a and IR75b preferentially respond to butyric acid and hexanoic acid, 106 respectively (Prieto-Godino et al., 2017, 2016). These differences are likely to be 107 ecologically significant: for example, acetic acid is a key product of microbial 108 fermentation of vegetal material and regulates numerous behaviors in D. 109 melanogaster including attraction (Becher et al., 2010) sexual receptivity (Gorter et al., 2016) and oviposition (Joseph et al., 2009; Kim et al., 2018). Hexanoic acid 110 is a dominant component of noni fruit and elicits attractive behaviors in D. 111 sechellia (Amlou et al., 1998; Dekker et al., 2006; Prieto-Godino et al., 2017). In 112 113 this work, we combine comparative in vivo functional analyses of these receptors 114 across the drosophilid phylogeny, with ancestral sequence reconstruction, site-115 directed mutagenesis and protein modelling to investigate their evolution.

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117 **Results**

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Evolution of olfactory responses of IR75a across the drosophilid phylogeny

121 The distinct responses of *D. sechellia* IR75a (*Dsec*IR75a) compared to orthologs 122 in its two generalist cousins (Prieto-Godino et al., 2016) suggested that acetic 123 acid-sensing was the ancestral function of IR75a. We tested this hypothesis by 124 measuring odor-evoked responses of IR75a-expressing olfactory sensory neurons (OSNs) across the drosophilid phylogeny, representing >40 million years 125 divergence time (Figure 1A-C, see Material and methods). As stimuli we used a 126 127 panel of linear carboxylic acids spanning from one- to six-carbon chains 128 (hereafter abbreviated to C1-C6, where acetic acid is C2 and butyric acid is C4). 129 All tested species within the *melanogaster/obscura* group (except for *D. sechellia*) 130 displayed strongest responses to C2, similar to D. melanogaster and D. simulans 131 (Figure 1B-C). Unexpectedly, the responses of more divergent species were 132 more similar to those of *D. sechellia*, exhibiting strongest responses to C4 (Figure 1B-C). 133

To simplify data visualization and discern in an unbiased way which odors contribute maximally to differential tuning of Ir75a neurons across species, we performed principal component analysis (PCA) on their response profiles. The first principal component (PC1) explains 67.5% of the variance in the data, mostly capturing the inverse variation between C2 and C4 (Figure 1D). When plotting the C2 and C4 responses against each other, Ir75a neurons of different species segregated into two clusters with either high responses to C2 and low to C4 or 141 vice versa (Figure 1E). The clustering matched well the phylogeny with the 142 exception of *D. sechellia*, which grouped together with *D. willistoni*, *D. mojavensis* 143 and *D. virilis* (Figure 1A and 1E). These observations suggested a new model in 144 which the ancestral drosophilid IR75a was predominantly a C4 sensor that 145 evolved to become a C2 sensor in the last common ancestor of the melanogaster 146 and obscura groups, before reverting to an ancestral-like state in *D. sechellia* 147 (Figure 2A).

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Functional analysis of ancestrally-reconstructed IR75a

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151 To test this hypothesis, we "resurrected" the ancestral IR75a receptors at the 152 ancestral drosophilid and *melanogaster/obscura* group phylogenetic nodes by 153 inferring their sequence via maximum likelihood (Randall et al., 2016) from the 154 sequence of orthologs from sixteen extant species (Figure 2A and Figure 2 figure supplement 1 and Materials and methods). We synthesized genes 155 encoding the inferred ancestral proteins – termed here IR75a^{Dros} and IR75a^{mel-obs}, 156 157 respectively - and integrated these into a common genomic location to avoid differential positional influence on their expression. These transgenes were 158 159 expressed individually in the D. melanogaster "IR decoder neuron", an OSN that 160 lack the endogenous tuning receptor subunit but expresses the IR8a co-receptor 161 (Abuin et al., 2011; Grosjean et al., 2011; Prieto-Godino et al., 2016). When expressed in this system, the tuning curves of D. melanogaster IR75a 162 163 (DmellR75a) and D. sechellia IR75a (DsecIR75a) recapitulate the response 164 profile of these receptors expressed in their endogenous neurons, with strongest 165 responses to C2 and C4, respectively (Figure 2B-C), consistent with previous observations (Prieto-Godino et al., 2016). As predicted, IR75a^{mel-obs} responded 166 similarly to DmellR75a (Figure 2B-C). Importantly, the more ancient, resurrected 167 receptor, IR75a^{Dros}, had a tuning profile that was almost identical to DsecIR75a, 168 with maximal responses to C4 (Figure 2B-C). These results indicate that IR75a 169 170 has switched tuning profile at least twice during its evolutionary history, from C4-171 to C2-sensing and, in *D. sechellia*, back again.

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173 Identifying the molecular basis of the functional evolution of IR75a

174 175 To determine the molecular basis of the functional evolution of IR75a, we aligned the sequences of IR75a^{mel-obs} and IR75a^{Dros}. 114 positions in these proteins 176 exhibit different amino acids (82% identity), of which 45 are located within the 177 LBD (Figure 2 – figure supplement 1). As this level of divergence precluded 178 179 straightforward experimental determination of the relevant sites, we first 180 approached the problem by focusing on the more recent "reverse" transition of C2-sensing to C4-sensing that occurred on the branch leading to DsecIR75a. We 181 182 had previously narrowed down this tuning switch to three amino acid positions within the internal pocket of the bilobed (S1-S2) LBD (Prieto-Godino et al., 2016) 183 (Figure 3A). Simultaneous substitution of these sites in DmellR75a with the 184 residues found in DsecIR75a (i.e., T289S, Q536K and F538L) produced a 185 receptor that faithfully recapitulated the response properties of *Dsec*IR75a when 186 assessed in the IR decoder neuron (Figure 3B), as previously described (Prieto-187 188 Godino et al., 2016). Furthermore, reverse amino acid substitutions in DsecIR75a

189 (S289T, K536Q and L538F) conferred response properties characteristic of 190 *Dmel*IR75a (Figure 3B). These results indicate that the change in tuning is 191 encoded entirely within these three sites. Thus, there are only $2^3 = 8$ variants to 192 transit between *Dmel*IR75a and *Dsec*IR75a (including the wild-type sequences) – 193 compared to $2^{114} = 2 \times 10^{34}$ possible variants between IR75a^{Dros} and IR75a^{mel-obs} – 194 offering an excellent opportunity to study the functional evolution of an olfactory 195 receptor.

196 We generated versions of *Dmel*/R75a in which each of these three sites 197 were substituted individually as well the three possible double substitutions. All 198 single amino acid changes had an impact on receptor responses, shifting tuning 199 towards C4 (and C3) to different extents, while still retaining some sensitivity to 200 C2 (Figure 3C). Double substitutions showed further shifts towards the DsecIR75a tuning profiles but to varying degrees: DmelIR75a^{T289S,Q536K} is a 201 broadly-tuned receptor that responds maximally (albeit weakly) to C2, C3 and C4, 202 DmellR75a^{Q536K,F538L} displays maximum responses to both C3 and C4, and 203 DmelIR75a^{T289S,F538L} responds maximally to C4 alone (Figure 3C). To move 204 205 beyond simple descriptions of the effects of these mutations, we used 206 visualizations and analyses that give insights into the evolutionary landscape of 207 this receptor, as described below.

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209 Mapping the evolutionary landscape of IR75a

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Evolutionary landscapes map genotypes onto a quantitative phenotype to 211 212 illustrate evolutionary change as a "navigation" process. The roughness of the 213 landscape determines how accessible each of all possible paths are, and 214 therefore the likelihood that evolution proceeds through each path (Aguilar-215 Rodríguez et al., 2017; Wright, 1932). We reasoned this approach was useful to 216 understand the evolution of IR75a as the lack of informative intraspecific genetic 217 diversity within these receptor genes in drosophilid species (data not shown) 218 precluded the direct identification of evolutionary intermediates.

219 Responses properties of a receptor are multidimensional, where each odor 220 defines a dimension. However, PCA of the responses of all DmellR75a receptor mutants to all odors revealed that PC1 explains most of the variance (54.5%) and 221 222 captures the inverse variation between C2 and C4 – similar to the IR75a neuron 223 response PCA across the drosophilid phylogeny (Figure 1D) – and, to a lesser 224 extent, the co-variation of C5 with C4 (Figure 3D). We therefore plotted the phenotypic data for each single, double and triple DmelIR75a mutant in the C2 225 226 versus C4 space alone (Figure 3E) and in the PC1 space (Figure 3F), 227 acknowledging these simplifications represents only part of the functional 228 changes (albeit potentially the most important).

The C2 vs C4 plot enables visualization of all possible evolutionary paths 229 by joining the stepwise mutations from *Dmel*IR75a to *Dmel*IR75a^{T289S,Q536K,F538L}. 230 Most receptor variants are plotted close to the straight line (i.e., the shortest path) 231 that joins the initial and final state, with the *Dmel*IR75a^{F538L} single mutant showing 232 233 the largest individual "step" along this line (Figure 3E). If we assume that all steps along this line would be favoured by selection, this observation suggests the 234 hypothesis that the F538L change might have been the first one of the three 235 236 substitutions to occur, as *de novo* mutations with larger effect are typically

237 substituted first followed by those with smaller effect (Holder and Bull, 2001; Orr, 2005). An alternative hypothesis is that T289S variant already existed, perhaps 238 239 as standing variation in the population: T289S has little phenotypic consequence 240 by itself (Figure 3C,E), but it greatly augments the effect of the F538L substitution (Figure 3C,E). In this case, T289S and F538L would have reached fixation 241 together in the same genetic background because their combined effect allows 242 243 for a large adaptive leap from one peak (C2) to the other (C4). The Q536K change 244 alone has an intermediate phenotype, but we suspect is unlikely to have been the 245 first to occur, as combination with either other amino acid change leads to a less specific receptor (*Dmel*IR75a^{Q536K,F538L}, lying to the top-right of the line), or a 246 receptor with overall weak sensitivity (*Dmel*IR75a^{T289S,Q536K}, lying to the bottom-247 248 left of the line) (Figure 3C,E).

To formalize this analysis, we calculated epistasis (*i.e.*, non-additive effects 249 250 of different mutations), which can constrain the available evolutionary paths 251 (Aguilar-Rodríguez et al., 2017; Phillips, 2008). Using the projection of our 252 physiological responses onto PC1 as our phenotypic readout, we calculated for 253 each of the combinations of mutants (*i.e.*, single with single, or single with double) 254 whether the sum of the effects of each of the starting substitutions on the wild-255 type background was significantly different from the effect of introducing both 256 mutations simultaneously (see Materials and methods). Notably, negative 257 magnitude epistasis was observed in all combinations of Q536K and F538L 258 (whether T289S was also present the background or not) (Figure 3F, red lines). 259 This observation supports our previous hypothesis that whether F538L or T289S 260 was the first mutation to occur, the second one would be the other of these two, 261 because Q536K incurs in negative epistasis when combined with F538L and it 262 does not lead to a monotonic increase in responses when combined with T289S 263 (Figure 3F). Furthermore, this visualization highlights the significant effect on 264 tuning of the F538L substitution, as well as the minimal (statistically non-265 significant) effect of the T289S substitution, supporting its possible segregation in the population without deleterious effects. It remains unclear what, if any, is the 266 function of Q536K; it is possible it was fixed by drift or affects some other aspect 267 of receptor activity not analyzed here. 268

269

270 A hotspot for evolution of IR odor tuning

271 272 We next asked whether the knowledge of the molecular basis of the C2 \rightarrow C4 273 tuning change on the *D. sechellia* branch offers insight into the ancestral switch 274 from C4 to C2 in the last common ancestor of the *melanogaster/obscura* group. 275 Strikingly, examination of the identity of residues aligned with DmellR75a F538 in 276 orthologs across the drosophilid phylogeny revealed a perfect correspondence 277 between the identity of this position and the best agonist for the receptor: all 278 IR75a orthologues of species responding most strongly to C2 have an F, while 279 those that respond to C4, have an L (Figure 4A and Figure 2 – figure supplement 280 1). Such correspondence was not seen for amino acid identities at position 289 and 536: for example, DwillR75a has a Q at the position equivalent to Q536 of 281 282 DmellR75a (Figure 2 - figure supplement 1), but this species' Ir75a neurons respond to C4, like *D. sechellia* (Figure 1C). 283

284 These observations suggest that position 538 (or equivalent in orthologous sequences of slightly different lengths) has been a "hotspot" for odor response 285 286 evolution, changing from L to F in the *melanogaster/obscura* ancestor and then 287 changing back on the *D. sechellia* branch. The reversion of amino acid identity in 288 DsecIR75a is not due to an inverse mutation in the corresponding DNA 289 sequence: a $C \rightarrow T$ mutation in codon position one led to the L to F substitution in 290 the melanogaster/obscura ancestor, while in D. sechellia a C \rightarrow A mutation in 291 codon position three led, convergently, to restoration of the L-encoding codon 292 (Figure 4A).

293 The important contribution of a single amino acid in IR75a in determining 294 the specificity for shorter- or longer-chain acids was reminiscent of our 295 observation of the evolution of the paralogous receptor IR75b: the difference in 296 tuning of *Dmel*/R75b and *Dsec*/R75b to C4 and C6, respectively, is determined in 297 large part by a T523S substitution in the LBD (Prieto-Godino et al., 2017). IR75b 298 and IR75a exhibit only 38% amino acid identity. However, alignment of these 299 receptors revealed that position 523 in DmellR75b corresponds precisely to the 300 538 hotspot in IR75a (Figure 4B). Thus, evolution of novel specificities in two 301 different receptors – which diverged from a common ancestor >60 million years 302 ago (Prieto-Godino et al., 2017) – is specified by changes in the same site within 303 their LBDs.

304 To gain insights into the molecular mechanisms underlying the role of the hotspot in determining the functional properties of IR75a, we performed docking 305 306 analysis of ligands in a protein homology model of the DmelIR75a LBD (Prieto-307 Godino et al., 2016). The top-ranked pose of C2 (or C4) in this model predicts an ionic bond of the carboxyl group of this acid with R297 (Figure 4C and Figure 4 -308 309 figure supplement 1). This arginine residue is conserved in all acid-sensing IRs (Benton et al., 2009), and is essential for odor-evoked activity of IR84a (Abuin et 310 311 al., 2011); consistently, a similar interaction was predicted in a model of the IR84a 312 LBD with its ligand phenylacetic acid (Figure 4 – figure supplement 1). Moreover, this interaction is equivalent to that of the α -carboxyl group of the glutamate 313 ligand with a conserved arginine in iGluRs (Figure 4C and figure 4 – figure 314 315 supplement 1), suggesting a conserved mode of ligand-recognition in IRs and iGluRs. By contrast, the DmelIR75a hotspot residue F538 is not predicted to 316 interact with ligand molecules, as it is >4 Å away from any of the top-ranked 317 318 ligand poses (Figure 4C and figure 4 – figure supplement 1). These observations 319 suggest that the hotspot is not directly involved ligand binding; how changes in 320 the hotspot might alter odor response properties of IRs is considered in the 321 Discussion.

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Functional interactions between the IR75b hotspot and surface residues of the LBD

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Although mutation of the hotspot in *Dmel*IR75b is sufficient to confer novel responses to C5 and C6, this single change did not fully recapitulate the response profile of *Dsec*IR75b, as *Dmel*IR75b^{T523S} retained sensitivity to shorter chain acids (Figure 5A). Compared to *Dmel*IR75b and *D. simulans* IR75b (*Dsim*IR75b), *Dsec*IR75b contain three additional changes within the LBD pocket region (P473S, G492S and A520T; like the hotspot, all are within the S2 lobe), but in our previous work none of these appeared to contribute substantially – individually or
 together – to the refinement of specificity for C6 (Prieto-Godino et al., 2017). The
 *Dsec*IR75b LBD contains six additional derived residues located in S1 (Prieto Godino et al., 2017), leading us to test whether these sites contribute to the
 observed changes in odor responses.

Replacement of the entire S1 lobe in DmellR75b with that of DseclR75b 337 generated a receptor, *Dmel*IR75b^{DsecS1}, with significantly increased responses to 338 339 C6 and lower (albeit not statistically significant; Figure 5 source data 1) sensitivity to C3, when compared to DmellR75b (Figure 5A). Addition of the hotspot 340 substitution (T523S) produced a receptor (*Dmel*IR75b^{DsecS1,T523S}) that is more 341 similar in response profile to DsecIR75b than either DmelIR75b^{DsecS1} 342 or DmelIR75b^{T523S} (Figure 5A). However, this receptor still has robust sensitivity to 343 C4, like DmellR75b but unlike DseclR75b (Figure 5A). Further incorporation of 344 the three additional substitutions of residues in the S2 domain (Prieto-Godino et 345 al., 2017), generated a receptor (DmellR75b^{DsecS1,4mutS2} that, in terms of 346 specificity, is indistinguishable from DsecIR75b (Figure 5A). However, this 347 348 receptor has overall reduced sensitivity for all acids when compared with DsecIR75b, and its response to C6 is significantly smaller than that of DsecIR75b 349 (Figure 5A). Despite this overall reduced sensitivity, *Dmel*IR75b^{DsecS1,4mutS2} still 350 351 has a significantly increased sensitivity to C6 when compared with DmellR75b 352 (Figure 5A).

To visualize how the S1 residues might impact receptor function, we 353 354 mapped the position of the six derived changes within this lobe onto a protein 355 homology model of DmelIR75b (Figure 5B). All of these are located on the 356 surface of the LBD and therefore unlikely to contact ligands directly. IRs and 357 iGluRs are thought to exhibit the same global structure and stoichiometry (Abuin 358 et al., 2019, 2011), prompting us to align the modelled DsecIR75b LBD onto a 359 homotetrameric iGluR structure (PDB 3KG2) (Figure 5C). This analysis did not 360 suggest particularly close proximity of most of these residues to the interaction interface between subunits (Figure 5C). 361

362

363 **Discussion**

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As species adapt to new ecological niches, olfactory receptors evolve to define 365 new relationships between external signals and internal neural representations. 366 367 Population genetic analyses of *D. melanogaster* strains isolated from diverse 368 global habitats reveal that olfactory receptors (and other chemosensory protein families) display some of the strongest genomic signatures of recent selection 369 370 (Arguello et al., 2016), suggesting these proteins act as "first responders" in local 371 adaptation to new environments. In this work we have used comparative sequence and functional analyses across the well-defined phylogeny of the 372 373 Drosophila genus to study how members of the organic-acid sensing clade of IRs 374 have changed over evolutionary timescales.

Our most important finding is the discovery of a "hotspot" residue in these IRs, whose mutation had a major effect on the odor specificity of one receptor (IR75a) at two different timepoints during species diversification, as well as on the tuning change of a distinct receptor (IR75b). For IR75a, our data support a model in which the ancestral drosophilid IR75a was – contrary to previous assumptions 380 - a C4 sensor that switched, through mutation at the hotspot (and other sites), to C2 sensing in the melanogaster/obscura ancestor before "reverting" to C4-381 sensing in *D. sechellia*. The ancestral function of IR75b is still unclear: we have 382 383 not been able to unambiguously identify Ir75b neurons across the drosophilid 384 phylogeny, as they are not easily distinguishable from those expressing a related 385 receptor, IR75c (Prieto-Godino et al., 2017). However, like IR75a, IR75b has 386 adapted through hotspot substitution along the lineage leading to D. sechellia. 387 Neither the identity nor even the chemical class of amino acids occupying the 388 hotspot are conserved in these receptors (phenylalanine (F, aromatic) or leucine 389 (L, hydrophobic) in IR75a; threonine (T) or serine (S) (both polar) in IR75b). 390 These observations indicate that the position of the hotspot in these IRs' LBDs, 391 and not its identity per se, must explain its central role in defining odor-response 392 properties in different receptors. Studies of other families of olfactory receptors in 393 invertebrates and vertebrates have revealed enormous inter- and intra-specific 394 sequence variation, some of which have been linked to differences in odor tuning 395 (Adipietro et al., 2012; Auer et al., 2020; Block, 2018; Butterwick et al., 2018; Del 396 Mármol et al., 2021; Leary et al., 2012; Mainland et al., 2013; Prieto-Godino et al., 397 2017: Yang et al., 2017). Within this molecular and function diversity, it will be of 398 interest to examine whether analogous hotspots exist, revealing favored (or 399 constrained) mechanisms through which evolution selects for new odor-detection 400 properties.

401 The mechanistic role of the hotspot remains unknown. Our ligand docking 402 into an IR75a LBD model suggest this residue does not contact ligands directly, 403 located at a distance of >4 Å away. While we acknowledge the caveats of 404 interpreting ligand-docking into protein models, our predictions are consistent with 405 experimentally-determined glutamate/iGluRs interactions, as well as our previous 406 structure-function analysis of IR84a (Abuin et al., 2011). IR75a orthologs across the drosophilid phylogeny conserve all three main agonist-binding residues 407 characteristic of iGluRs (R297, T456, E507 in DmellR75a) (Benton et al., 2009; 408 409 Mayer, 2006), suggesting that the core contacts between odors and this receptor 410 are unchanged, and that their mutation might be more likely to lead to a non-411 functional protein. By contrast, mutation of more distant residues that could, for 412 example. (de)stabilize ligand-induced LBD conformational changes to alter the 413 coupling between ligand binding and channel gating, may be a more subtle way 414 of modifying the tuning profile of these receptors, without the risk of drastic loss of 415 function. Future determination of the mechanistic impact of hotspot mutations will 416 be an important priority, which will likely require experimentally-determined structures of odor-free and odor-bound IR LBDs. Such knowledge may also 417 418 inform our understanding of the mechanism of ligand-induced gating in iGluRs, 419 where the equivalent position (Y732 (Figure 5C)) is thought to have a function in 420 ligand-gating although its precise role is unclear (Armstrong and Gouaux, 2000; 421 Mamonova et al., 2008).

While the hotspot is clearly important, its contribution to modification of tuning properties is shaped by additional changes in these receptors. For IR75a, there are two additional substitutions within the ligand-binding pocket, while for IR75b, one or more residues located on the external surface of the LBD are relevant. In both cases, the functional consequences of combining these substitutions with that of the hotspot are not easily predicted from their individual 428 impact, revealing complex epistatic interactions. Moreover, the distance of these 429 additional sites from the predicted odor-binding site, suggest the existence of 430 allosteric effects of certain sites on odor/receptor interactions. These results are 431 of interest in light of molecular evolutionary analyses of olfactory receptor 432 repertoires, which have identified numerous residues under positive selection (or 433 relaxed purifying selection) in different receptors - implying a contribution to 434 functional divergence – in regions far from the predicted ligand-binding pocket 435 (Arguello et al., 2016; Chen et al., 2010; Gardiner et al., 2009; Smadja et al., 436 2009; Steiger et al., 2010). Together such observations argue that the evolution 437 of olfactory receptor specificity does not simply arise by alterations in direct 438 interactions of receptors with odor ligands, but rather can emerge from a complex 439 network of interactions of amino acid substitutions - with major or minor effects -440 both near and far from the ligand-binding pocket.

441 One clear limitation of our study is the restriction of our profiling to a set of 442 linear carboxylic acids at a single concentration. While these ligands are found in 443 nature and are the best agonists for these receptors among many screened odors 444 (Silbering et al., 2011), they necessarily only give a partial insight into the functional changes of individual receptors. The C4 to C6 switch of IR75b in D. 445 sechellia is likely related to high abundance of C6 in its sole host fruit (noni). For 446 447 IR75a the ecological framework is less clear: we speculate that the C4 to C2 448 switch in the *melanogaster/obscura* ancestor may be related to the use of host 449 fruits with acetic-acid producing bacteria, which may then have been no longer 450 relevant for *D. sechellia* which preferentially feeds upon ripe (non-fermenting) 451 noni fruit (which contains much more C4 than C2 (Auer et al., 2020; Farine et al., 452 1996)). Future expansion of the odor profiling of these species' receptors will be 453 essential to understand the pressures in the natural world that have selected for 454 olfactory receptor proteins with new chemical recognition properties. Such 455 knowledge, together with mechanistic insight into ligand/receptor interactions, 456 may be useful to re-engineer the ligand-binding specificities of receptors (for or desian 457 chemogenetic tools (Fukabori et al., 2020)) example. as 458 pharmacological manipulators to control the olfactory-guided behaviors of pest 459 insects.

460

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479 Author contributions

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L.L.P.-G. and R.B. conceived the project. L.L.P.-G. designed and performed all experiments and analyses, except for the ligand docking studies, which were performed by H.R.S. All authors contributed to interpretation of results. L.L.P.-G.

484 and R.B. wrote the paper, with contributions from H.R.S.

485 Materials and methods

486487 *Drosophila* strains and culture

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Flies were maintained at 25°C in 12 h light:12 h dark conditions. We used the 489 following published *D. melanogaster* strains: Ir84a^{Gal4} (Grosjean et al., 2011), 490 UAS-Dmellr75a, UAS-Dseclr75a, UAS-Dmellr75a^{T289S,Q536K,F538L} (Prieto-Godino 491 et al., 2016). Other drosophilid species were obtained from the Drosophila 492 493 Species Stock Center: D. sechellia (14021-0248.25), D. simulans (14021-494 0251.195), D. vakuba (14021-0261.01), D. erecta (14021-0224.01), D. 495 ananassae (14024-0371.13), D. pseudoobscura (14011-0121.94), D. willistoni 496 (14030-0811.24), D. mojavensis (15081-1352.22), D. virilis (15010-1051.87).

497

498 Molecular biology

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500 cDNAs of *D. melanogaster* and *D. sechellia Ir75a* and *Ir75b* were previously 501 described (Prieto-Godino et al., 2017, 2016). Site-directed mutagenesis was 502 performed using standard procedures, and mutant cDNAs were subcloned into 503 *pUAST attB* for transgenesis of *D. melanogaster* using the phiC31 site-specific 504 integration system (landing site attP40) by BestGene Inc. and Genetic Services 505 Inc. All transgenes were sequence-verified both before and after transformation.

506 507

Ancestral protein reconstruction

508 The 16 "modern" sequences of IR75a shown in Figure 2 – figure supplement 1 509 510 were used to computationally infer the ancestral sequences at all of the nodes of 511 the tree using the known phylogeny. Ancestral sequences were calculated using the bio-informatic tool FastML (Ashkenazy et al., 2012) with rate variation 512 modelled as a gamma distribution. The marginal posterior probability for most of 513 514 the amino acids of all of the reconstructed nodes was above 0.8. For the hot-spot 515 mutation the marginal posterior probability was 1. To ascertain the robustness of the inferences made by FastML, we also inferred ancestral sequences of the 516 nodes using a different bioinformatic tool, codeml within the PAML package. The 517 inferred sequences had a global identity of 96.5% and were fully identical at the 518 519 three amino acid substitutions under study. DNA sequences encoding the IR75a^{Dros} and the IR75a^{obs-mel} sequences predicted by FastML were synthesized 520 by Eurofins-Genomics, subcloned into pUAST attB and transformed into flies as 521 described above. 522

523

524 *In vivo* electrophysiology

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Single sensillum extracellular recordings were performed essentially as described in (Benton and Dahanukar, 2011; Prieto-Godino et al., 2017). For all stimuli, 10 μ l odor (10% v/v in water) were use, and presented to the animal in a 1 s pulse. ac2 sensilla were identified in different species by targeting sensilla at antennal locations where ac2 are found in *D. melanogaster*, and using pyridine as a diagnostic odor, which activates the ac2 neuron expressing IR41a and appears to be conserved across species (Figure 1B). CAS numbers and sources of odors 533 are as follows: formic acid (64-18-6), acetic acid (64-19-7), propionic acid (79-09-534 4), butyric acid (107-92-6), pentanoic acid (109-52-4), hexanoic acid (142-62-1), 535 pyridine (110-86-1) (diagnostic for ac2), octanol (111-87-5) (diagnostic for ac3). 536 Odor-evoked responses were calculated by summing the activity of all OSNs in a 537 sensillum to a given stimulus, as reliable spike-sorting is not possible and other neurons housed in the ac2 or ac4 sensilla do not respond to acidic odors 538 539 (Silbering et al., 2011). We counted the number of spikes in a 500 ms window at 540 stimulus delivery (200 ms after stimulus onset due to a delay introduced by the air 541 path), subtracted the number of spikes in a 500 ms window 2 s before stimulus 542 delivery, and doubled the result to obtain spikes/s. To calculate solvent-corrected 543 responses (as shown in the figures), we subtracted from the response to each 544 diluted odor, the response obtained when stimulating with the corresponding 545 solvent (water for all odors except for pyridine and octanol, which were dissolved 546 in paraffin oil (8012-95-1). A maximum of three sensilla were tested per animal, 547 and individual genotypes were measured, in an interleaved fashion, on multiple 548 independent days. Normalized responses were calculated by dividing solvent-549 corrected responses of a given sensillum to each odor by the maximal response 550 of that sensillum, such that each sensillum always had one odor whose normalized response was 1. A pre-requisite for PCA analysis is to input z-scored 551 552 responses; these were calculated with the in-built function of MATLAB, which 553 works according to the definition of z-scoring, i.e., across each sensillum 554 recording, each response was subtracted from the mean response of all sensillar 555 responses and divided by the standard deviation.

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557 Statistical analysis

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559 Principal component analysis was carried with in-built MATLAB functions. Statistical analyses were carried out with in-built functions in R Studio or Igor. For 560 561 all statistical tests, a Shapiro test for normally was first performed. If both samples 562 being compared were normally distributed, a t-test was performed; if one of the samples was not normally distributed, a Wilcoxon test was run. When performing 563 multiple comparisons, p-values were corrected using the Bonferroni method. 564 565 Epistasis was calculated by determining whether the effects of each individual mutation were added linearly by comparing the observed responses of the 566 567 combination of two genetic manipulations with the expected distribution of 568 individual mutations were added linearly. Briefly, to generate expected 569 distributions for the linear combination of two mutations, we subtracted the mean responses of the initial receptor from the two "intermediate" receptors, this 570 571 provides the "effect" of each mutation(s) individually, we then we took 1000 572 random samples from the "effects" of each of the two mutations and summed 573 them to generate a distribution of the expected responses if the two effects of each mutation added linearly. To determine whether two mutations interacted 574 epistatically, we statistically compared the expected distribution with the actual 575 576 distribution (the double manipulation combination) using a Wilcoxon test. If the 577 result of this test was p < 0.05 after correction for multiple comparisons using 578 Bonferroni method, the two mutations were considered to interact epistatically. 579

580

581 Ligand docking

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AutoDock Vina version 1.1.2 (Trott and Olson, 2009) was used to dock ligands 583 584 into homology models of the LBDs of DmellR75a and DmellR84a (K205-N354-L451-W583) (Prieto-Godino et al., 2016) . The crystal structure of RnorGluA2 585 bound to glutamate (PDB accession 1FTJ) was used to optimize the grid 586 conditions and docking procedure for IRs. A12×12×12 Å grid was placed along 587 588 the axis between the CZ atom in a conserved arginine residue (R96 in 589 RnorGluA2, R100 in DmellR75a) and the CD atom in a conserved glutamate residue (E193 in *Rnor*GluA2, E197 in the IR75a, this glutamate is not conserved 590 591 in *Dmel*[R84a). The center of the grid was placed closer to the arginine than to 592 the glutamate, such that if a straight line was drawn from the arginine to the 593 glutamate, the grid center was one-third of the way along this line. For 594 DmellR84a, the conserved glutamate is not present, and the position of the grid 595 was manually determined using the conserved arginine (R317) as a guide and 596 the grids for RnGluA2 and IR75a as reference. Docking was performed using an 597 exhaustiveness of 8, with the default settings for AutoDock Vina; these were sufficient to accurately predict the position of the co-crystallized glutamate in 598 599 RnGluA2 (Figure 4 – figure supplement 1). Ligand poses were inspected manually, but in all cases the top-ranked pose was judged to be the most 600 plausible. Structure visualization was performed using PyMol version 2.3.3. The 601 DsecIR75b LBD model (Prieto-Godino et al., 2017) was aligned to the GluA2 602 homotetramer using the "align" command in PyMol. 603

604 605

606 Figure Legends

607 Figure 1. Evolution of olfactory responses of Ir75a neurons across the 608 drosophilid phylogeny.

609 (A) Phylogeny of analyzed drosophilid species and their known ecological niches610 (Markow, 2015).

611 (B) Representative traces of extracellular recordings of neuronal responses in 612 antennal coeloconic 2 (ac2) sensilla (schematized top left) to the indicated odors 613 in different drosophilid species. ac2 sensilla were identified based on their morphology, their location on the antennal surface - either near the entry to the 614 sacculus or in the distal posterior part intermingled with ac3 sensilla (Silbering et 615 616 al., 2011) – their pattern of basal firing, and the conserved responses of the Ir41a 617 neuron towards pyridine and the lack of response to octanol (which is detected by 618 the Or35a neuron in ac3 sensilla (Yao et al., 2005)).

(C) Heatmap of electrophysiological solvent-corrected responses (see Materials
 and methods) of ac2 sensilla of all species in (A) to a series of linear carboxylic
 acids; the color-scale is on the right. Each rectangle represents the responses
 measured in a single sensillum.

623 (**D**) Loadings of the first principal component of all responses shown in (**C**).

(E) Responses of ac2 sensilla for all species plotted as z-scored responses (see
 Material and methods) of C2 against z-scored responses to C4. This plotting
 reveals two clear clusters with species responding maximally to C2 (orange) or
 C4 (blue).

628

Figure 1 Source data 1. Data for Figure 1 showing the solvent-corrected spikes/second responses of ac2 sensilla for each of the species (Figure 1C). The same responses z-scored (Figure 1E) and the results of the PCA analysis, showing loadings and variance explained by each PC (Figure 1D). Here and in subsequent source data files "NaN" ("not a number") indicates cases where data was not available, usually due to the electrode coming out of the sensillum before the end of the series of stimulations.

636

637 Figure 2. Ancestral sequence reconstruction of IR75a.

(A) Phylogeny of the protein sequences of drosophilid IR75a orthologs used for
the reconstruction of ancestral nodes (IR75a^{Dros} and IR75a^{mel-obs}) (see Figure 2 –
figure supplement 1). The orange and blue dots indicate maximal responses of
the corresponding neurons to C2 and C4, respectively (Figure 1C). The branches
of the tree have been similarly color-coded according to predicted receptor
responses based on parsimony.

(B) Representative traces of extracellular recordings of neuronal responses to the
indicated odors of receptors expressed in the IR decoder neuron (see text).
Genotypes are of the form: UAS-xxx/UAS-xxx;Ir84a^{Gal4}/Ir84a^{Gal4}, here and in all
subsequent figures.

648 (**C**) Quantification of responses of the indicated receptors expressed in the IR 649 decoder neuron. In this and subsequent similar figure panels, the top row shows 650 barplots of responses normalized by maximal response, and the bottom row 651 shows individual datapoints, mean and SEM of raw solvent-corrected responses 652 to odor stimuli. 653

Figure 2 – figure supplement 1. Alignment of IR75a orthologs.

Multiple sequence alignment of IR75a orthologs used for the ancestral protein reconstruction. The ancestral versions that were functionally tested, IR75a^{Dros} and IR75a^{obs-mel}, are also shown. Dark blue indicates identical residues, light blue indicates similar residues, grey indicates dissimilar residues. The red lines indicate the spans of S1 and S2 lobes of the LBD. The amino acids colored in red are those positions that were estimated by FASTML (see Materials and methods) to have a marginal posterior probability < 0.7.

662

Figure 2 Source data 1. Data for Figure 1C, responses in spikes/s of ac2 sensilla from each of the genotypes, and normalized with respect the maximal response of each sensilla.

666

Figure 3. Mapping the evolutionary landscape of IR75a.

(A) Top: cartoon of the domain organization of IR75a; bottom: protein homology
 model of the *Dmel*/R75a LBD (adapted from (Prieto-Godino et al., 2016)). The
 three functionally-important amino acid positions that differ between *Dmel*/R75a
 and *Dsec*/R75a are highlighted in red.

- 672 (B-C) Quantification of responses of the indicated receptor versions expressed in673 the IR decoder neuron.
- 674 (**D**) Loadings of the first principal component of all responses shown in (**C**).
- 675 (E) Responses of each of the indicated receptor versions plotted in the C2 vs C4 676 space.
- (F) Visualization of epistasis and accessible mutational pathways. Each of the 677 678 individual, double and triple mutations are plotted in the PC1 axis (error bars are 679 standard error of the mean). Possible evolutionary paths join these with lines. 680 Solid lines indicate when the path joins two points that significantly increase PC1 value (i.e. increased responses to C4 and C5 and decreased responses to C2); 681 682 dashed lines denote paths that, while accessible, do not lead to significantly increased PC1 values (see Source Data, for statistical values). Red lines indicate 683 the cases where two mutations interact epistatically when combined, *i.e.*, the 684 685 combination of the two mutations is not equal to the expected response if their 686 effects added linearly (see Materials and methods for details and Source Data for 687 statistical values).
- 688

Figure 3 Source data 1. First tab: Data for Figure 3B and 3C, responses in spikes/second of ac2 sensilla from each of the genotypes indicated, and normalized with respect the maximal response of each sensilla. Second tab: Results from the PCA analysis. Third tab: P-values resulting from the statistical analysis in Figure 3F.

694

695 **Figure 4. A hotspot for tuning IR sensitivity.**

(A) Phylogeny of species' IR75a receptors used for the reconstruction of
 ancestral nodes. The inferred identity of hotspot mutation for key nodes is shown
 as well as for each of the extant receptors at the end of each leaf, together with
 the measured (solid circle) or predicted (empty circle) sensitivity. On the right, the
 nucleotides encoding the hotspot amino acid position in IR75a across species.

Drosophila species abbreviations (where not presented in Figure 1): Dmir
(miranda), Dper (persimilis), Dame (americana), Dbuz (buzzatii), Dgri
(grimshawi), Dalb (albomicans).

(B) Top: Protein sequence alignment of *Dmel*IR75a and *Dmel*IR75b. Dark blue
indicates identical residues, light blue indicates similar residues, grey indicates
dissimilar residues. The red lines indicate the spans of S1 and S2 lobes of the
LBD. The red box indicates the common amino acid position ("hotspot"). Bottom:
separate alignments of the hotspot region in IR75a and IR75b for *D. melanogaster* and *D. sechellia* proteins showing that while the residue position is
conserved, the identity of the amino acids is different for these two receptors.

(C) Left: homology model of *Dmel*IR75a LBD (blue) with docked ligands; the insets show the top-ranked poses for C2 (cyan) and C4 (purple) in the LBD pocket. Right: crystal structure of the *Rattus norvegicus* (*Rnor*) iGluR GluA2 LBD (gray) in complex with glutamate (yellow) (PDB accession 1FTJ). The hotspot residue is shown in orange in *Dmel*IR75a, and the equivalent residue in *Rnor*GluA2 in magenta. Amino acid numbering corresponds to that of the full-length sequence.

719 Figure 4 – figure supplement 1. Ligand docking in IRs and iGluRs.

720 Top-three docked poses for the indicated ligands in the DmellR75a and 721 DmellR84a LBD homology models, and the RnorGluA2/glutamate crystal 722 structure (PDB 1FTJ), ranked by AutoDock Vina docking score. In DmelIR75a, all 723 three poses of C2 occupy a similar space in the binding pocket, contacting the 724 conserved arginine R297 and >4 Å from the hotspot residue 538 (orange). 725 Similarly, in DmellR84a, all three poses of phenylacetic acid occupy a similar 726 position in the binding pocket and make contact with the conserved arginine 727 R317, which is essential for ligand-evoked currents from IR84a in vivo (Abuin et al., 2011). In RnorGluA2, the docked poses of docked glutamate (green), 728 729 particularly the top-ranked pose, are similar to the positioning of co-crystallized 730 glutamate (yellow). Amino acid numbering corresponds to that of the full-length 731 sequences.

732

733 Figure 5. Epistasis in the ligand binding domain of IR75b.

(A) Quantification of responses of the indicated wildtype and mutated IR75b
 variants expressed in the IR decoder neuron. Note that the *Dmel*IR75b^{DsecS1}
 variant includes the six derived changes between *D. sechellia* and *D. simulans/D. melanogaster* as well as a seventh amino acid substitution common to *D. sechellia* and *D. simulans* receptors.

(B) Protein homology model of the *Dsec*IR75b LBD (adapted from (Prieto-Godino et al., 2017)). The S1 and S2 lobes are colored pale and dark green, respectively.
Surface-located amino acids that differ between *Dmel*IR75b and *Dsec*IR75b in the S1 domain are depicted in magenta; the hotspot (position 523) and other residues in the ligand-binding pocket in the S2 domain are depicted in red.

(C) Homology model of the *Dmel*IR75b LBD (colored as in (B)) aligned to the fulllength homotetrameric crystal structure of *Rnor*GluA2 (PDB accession 3KG2),
which is colored by chain in faded gray, red, blue, and yellow. The *Rnor*GluA2
amino-terminal domain (which is not present in most IRs (Rytz et al., 2013)) has
been removed for clarity.

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Figure 5 Source data 1. First tab: Data for Figure 5A, responses in spikes/second of ac2 sensilla from each of the genotypes indicated, and normalized with respect to the maximal response of each sensilla. Second tab: P-values resulting from the statistical analysis, as discussed in the text.

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Supplementary file 1. Nucleotide sequences encoding the reconstructed ancestral IR75a orthologs.

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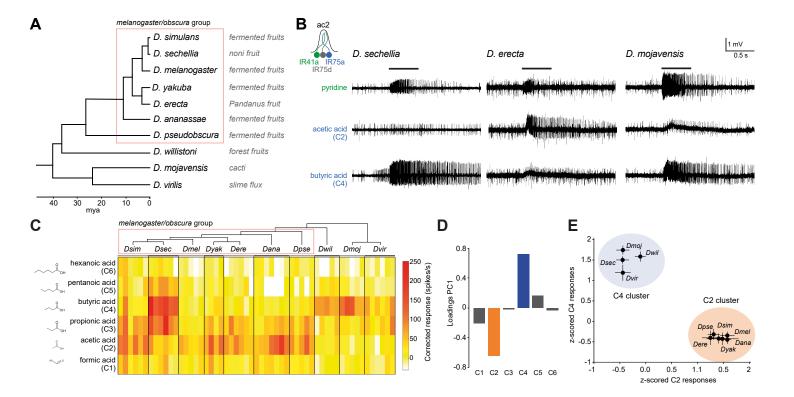
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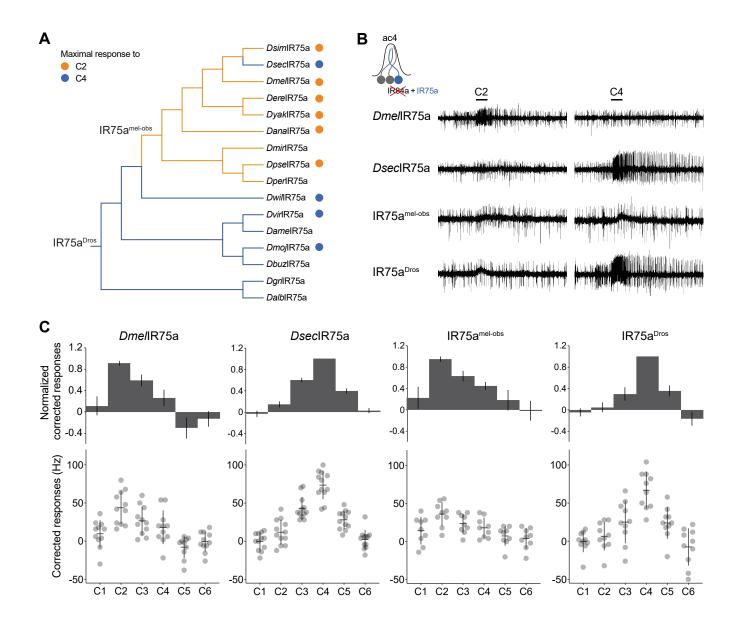
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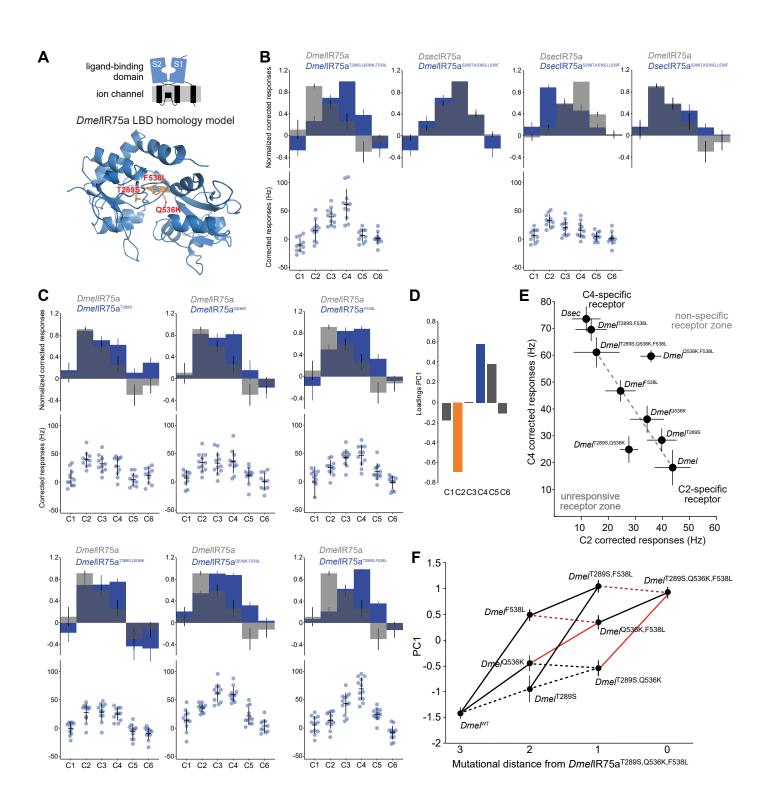
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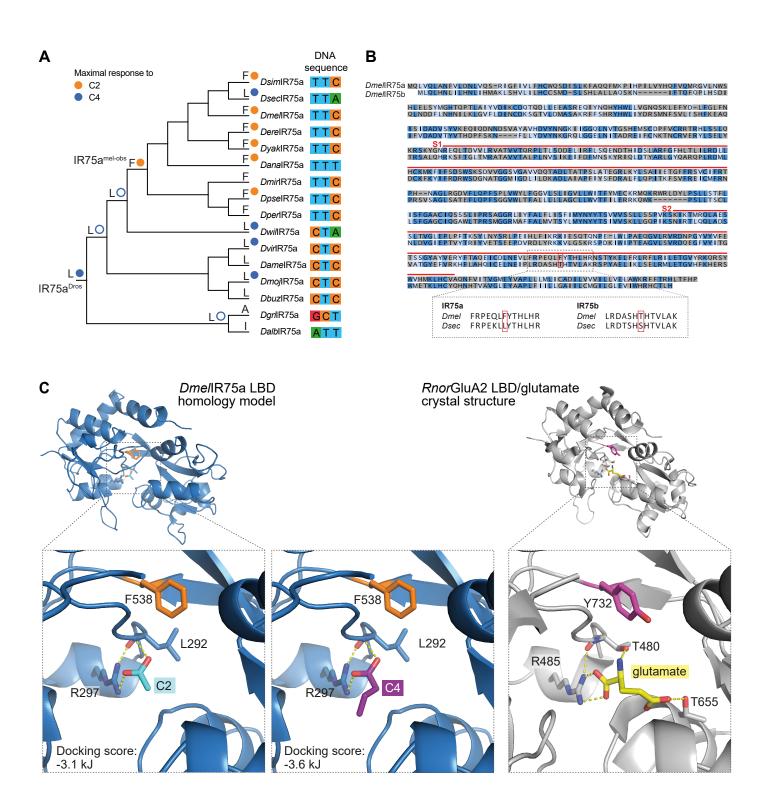
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1 10 20	30 40	50 60	70	80 90 100
DmellR75a MQL - VQLANF VLDNL VQSR I GF DseclR75a MQL - VQLANF VLDNL VQSR I GF				
DsimIR75a MQL – VQLANEVL DNLVQSR I GE DereIR75a MQL – VQLANEVL DNLVQSR I GE	VLFHCWQSDES-LKFAQC	FIKPMHPIL <mark>VYHQF</mark> VQLRG	VLDWSHELNYMGHTQPT	LAVYVDIKCQEAQDLLEEASREQIYNQH
DyaklR75a MQL - VQLANF VLDNLVQSR I GF DanalR75a MQL - LQLANF VLDNLLQSR I GF	VFFHCWQRDES-LKFYQC	FVNPIERHEVYNQFVQMKG	IQNWTDLELKYLDHSQPT	LAIYVDFQCQQAKDLLKEASLEKLYNQH
DmirlR75a MQLQVQLANFLLDNLVQSRIGEV DpselR75a MQLQVQLANFLLDNLVQSRIGEV DpsedR75a MQLQVQLANFLLDNLVQSRIGEV	VLFFHCWQQHEI-RDFAQC	FMKPLEQHEIYEQFLQMHA	VRDWEDLELRFLDHLQPT	LAIYVDMKCHKAAGLLEEASREQLYNQH
DperlR75a MQLQVQLANFLLDNLVQSR GEN DwillR75a MQLVNFLLNNLLDVH ASI DvirlR75a MQL-LHLANFVLHNLLQSR SF		IF HNSYEKQE <mark>IYEQF</mark> VHFKS	VENFENLEERFLEHLQPT	LAIYVDMKCEKSKILLTMANENQLYNQH
DamelR75a MQL - L HLANF VL QNL LQSR I SF DmojlR75a MQL - LQLANF VL QNL LQSR I SF	FFHCWAGNES-FQFAQC	INKP-EHQPIYEQFAHEND	-WNWDHLEQRYLDHLQPT	LA I YVDLNCLRSRSLLVEASRSKLYNQH
DbuziR75a MQL-LQLANFVLQNLLHSRISF DgriR75a NALIQLANFVLHNLLQSRISF	F FHCWANNESGLHEVKA	KVKI-QHQLIYHQFAHLND	-WNWEHLEQRYLDHAQPT	LAVYVDLSCMRSRSLLAEASRSRLYNQH
DalbIR75a YNLLQSRITE	VIFHCWORNES-LOFAOC	YNSPQL <mark>YHQF</mark> VHLDD	-WNWEHLEQRYLDHQQPT	'LA I YVDLQCKRSEAL LKEASHSQLYNQH 'LA I YVDLKCMRSRSLLAEASRSQLYNQH
IR75a ^{mel-obs} MQLQVQLANFVLDNLVQSRTGF	IVFFHCWQRDESGLKFAQC	FMKPLEQHLIYHQFVQMKG		LATY VDENCWKSKSELAEASKSRETNON
DmellR75a HWLLVGNQSKLEFYDLFGLFNIS				
DsecIR75a HWLLVGNQSELEFNDLFALFN DsimIR75a HWLLVGNQSELEFNDLFALFN	SIDADVSYVKEQIQDN	IND SVAYAVYDVYNNGK I G	GQLNVTGSHEMSCDPFEC	RRTRYLSSLQKRSKYGNREQLTDVVLRV
DereIR75a HWLLVGNQSELKFYDCFALFNLS DyakIR75a HWLLVGNQSELEFYDLFALFNLS	S DADVSYVKEEYRNN	IND S VYAVYDVYNNGKM G	GQLNVTASHEMS CDPFEC	RRTRYLSSLLKRSKYGNREQLTDVVLRV
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DereIR75a TVVTQR SLTL SDDEL IR FLSQEN	NDTHIDSLARFGFHLTLIL	RDLLHCKMKFIFSDSWSKS RDLLHCKMKFIFSDSWSKS	DVVGGSVGAV <mark>V</mark> D <mark>Q</mark> SADLT	ATPSLATECRLK-YLSAIIETGFFRSVC
DyakiR75a TVVTQR SLTL SDNEL I RFL SQE DanaiR75a TVVTQRPLTWSDDML I QFL SQE DmirlR75a TVVTQRPLYWSEDQLVLFL SQE	NDTHIDSLAREGENLTLIL	RDLLHCKMKFIFSDSWSKS RDLLHCKMKFIFSDSWSKS	DVVGGSVGAV <mark>V</mark> D <mark>Q</mark> SADLT	ATPSLATECRLK-YLSAIIETGFFRSVC
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330 340 DmeilR75a FRTPLNAGLRCDVFLQPFSPLVV DsecR75a FRTPLNAGLRCDVFLQPFSPLVV DerelR75a FRTPLNAGLRCDVFLQPFSPLVV DyaklR75a FRTPLNAGLRCDVFLQPFSPLVV DmirlR75a FRTPLNAGLRCDVFLQPFSPLVV DmirlR75a FRTPLNAGLRCDVFLQPFSPLVV DperlR75a FRTPLNAGLRCDVFLQPFSPLVV DyerlR75a FRTPLNAGLRCDVFLQPFSPLVV DyrlR75a FRTPLNAGLRCDVFLQPFSPLVV DyrlR75a FRTPLNAGLRCDVFLQPFSPLVV DyrlR75a FRTPLNAGLRCDVFLQPFSPLVV DyrlR75a FRTPLNAGLRCDVFLQPFSALVV DyrlR75a FRTPLNAGLRCDVFLQPFSALVV DyrlR75a FRTPLNAGLRCDVFLQPFSALVV DyrlR75a FRTPLNAGLRCDVFLQPFSALVV DyrlR75a FRTPLNAGLRCDVFLQPFSALVV DyrlR75a FRTPLNAGLRCDVFLQPFSALVV DyrlR75a FRTPLNAGLRCDVFLQPFSALVV	350 360 WYLEGGYL SU GVL WITT WYLEGGYL SU GVL WITT WYLEGGYL SU GVL WITT WYLEGGYL SU GVL WITT WYLEGGYL SU GUL WITT WYLEGGYL SU GUL WITT WYLEGGYL SU GLL WITT WYLEGGL SU GLL WITT WYLEGGL SU GLL WITT WYLEGGL SU GLL WITT WYLEGGL LU ALL WLAF WYLEGGL LU ALL WLAF WYLEGGL LU ALL WLAF WYLEGGIL LU ALL WLAF	370 380 I'ME CIKRMQIKRWR L DYLP S L I'ME CKRMQIKRWR L DYLP S L I'ME CKRMQIKRWR L DYLP S L I'ME CKRMQIKRWR L DYLP S L I'ME CKRMRIRWR L DYLP S L I'ME SKRMH SIZWR L Q FVP S L I'ME SKRMRIRWR L EFVP S L I'ME CKRMRIRWR L EFVP S L I'ME CKRMRIRWR L EFVP S L	390 LIST F LIISEGAACIQS SSL LIST F LIISEGAACIQS SSL LIT F LIISEGAACIQS SSL LIT F LIISEGAACIQS SSL LIT F LIISEGAACIQS SSL LIT CLIISEGAACIQS SSL LIT LIISEGAACIQS SSL LIT LIISEGAACIQS SSL LIT LIISEGAACIQS SSL LIT LIISEGAACIQS SSL LIT LIISEGAACIQS SSL	410 420 IPRSAGGRLIYEALELISE IMYNYYTSV IPRSAGGRLIYEALELISE IMYNYYTSV IPRSAGGRLIYEALELISE IMYNYYTSV IPRSAGGRLIYEALELISE IMYNYYTSV IPRSAGGRLIYEALELISE IMYNYYTSV IPRSAGGRLIYEALELISE IMYNYTSV IPRSNGRLIYEALELISE IMYNYTSV IPRSTGRLAVEALELISE IMYNYTSV IPRSNGRLAVEALELISE IMYNYTSV IPRSNGRLAVEALELISE IMYNYTSV IPRSTGRLAVEALELISE IMYNYTSV
330 340 DmellR75a FRT PLNAGLRCDVFLQPFSPLVV DsecR75a FRT PLNAGLRCDVFLQPFSPLVV DsimR75a FRTPLNAGLRCDVFLQPFSPLVV DyakR75a FRTPLNAGLRCDVFLQPFSPLVV DanalR75a FRTPLNAGLRCDVFLQPFSPLVV DyakR75a FRTPLNAGLRCDVFLQPFSALVV DyakR75a FRTPLNAGLRCDVFLQPFSALVV DyakR75a FRTPLNAGLRCDVFLQPFSALVV DyakR75a FRTPLNAGLRCDVFLQPFSALVV DyakR75a FRTPLNAGLRCDVFLQPFSALVV DyakR75a FRTPLNAGLRCDVFLQPFSALVV DatalR75a FRTPLNAGLRCDVFLQPFSALVV	350 360 WY FIGGVL SL GVL WITT WY FIGGVL SL GL WY TI WY FIGGVL SL GVL WY TI WY FIGGVL SL GVL WY TI WY FIGGVL SL GUL WY TI WY	370 380 YME CIKRMQIKRWR L DYLP S L YME CIKRMRIKRWR L DYLP S L YME CIKRMRIRWR L DYLP S L YME SIKRMRISWR L G FVP S L YME SIKRMRISWR L G FVP S L YME SIKRMRISWR L G FVP S L YME CIKRMRIRWR L DYLP S L	390 LIST F LITSEGAACIOS SSL LIST F LITSEGAACIOS SSL LIST F LITSEGAACIOS SSL LIST F LITSEGAACIOS SSL LIST F LITSEGAACIOS SSL LITF F LITSEGAACIOS SSL LITF F LITSEGAACIOS SSL LITF F LITSEGAACIOS SSL LITT F LITSEGAACIOS SSL LITT F LITSEGAACIOS SSL LITT LITSEGAACIOS SSL	410 420 IPRSAGGRLIYFALELISFIMYNYYTSV IPRSAGGRLIYFALELISFIMYNYYTSV IPRSAGGRLIYFALELISFIMYNYYTSV IPRSAGGRLIYFALELISFIMYNYYTSV IPRSAGGRLIYFALELISFIMYNYYTSV IPRSNGRLIYFALELISFIMYNYYTSV IPRSNGRLIYFALELISFIMYNYYTSV IPRSNGRLIYFALELISFIMYNYYTSV IPRSNGRLIYFALELISFIMYNYTSV IPRSNGRLIYFALELISFIMYNYTSV IPRSNGRLIYFALELISFIMYNYTSV IPRSNGRLIYFALELISFIMYNYTSV IPRSNGRLIYFALELISFIMYNYTSV IPRSTGRLAYFALELISFIMYNYTSV
330 340 DmellR75a FRT PLNAGLRCDVFLQPFSPLVV DseclR75a FRT PLNAGLRCDVFLQPFSPLVV DerelR75a FRT PLNAGLRCDVFLQPFSPLVV DerelR75a FRT PLNAGLRCDVFLQPFSPLVV DyaklR75a FRT PLNAGLRCDVFLQPFSPLVV DyaklR75a FRT PLNAGLRCDVFLQPFSPLVV DpelR75a FRT PLNAGLRCDVFLQPFSPLVV DpelR75a FRT PLNAGLRCDVFLQPFSPLVV DpriR75a FRT PLNAGLRCDVFLQPFSPLVV DyirlR75a FRT PLNAGLRCDVFLQPFSPLVV DyirlR75a FRT PLNAGLRCDVFLQPFSPLVV DyirlR75a FRT PLNAGLRCDVFLQPFSPLVV DyirlR75a FRT PLNAGLRCDVFLQPFSALVV DyirlR75a FRT PLNAGLRCDVFLQPFSALVV DalbR75a FRT PLNAGLRCDVFLQPFSALVV A30 S2 440 450 DmeilR75a VSSLLSSPVKSKI KTMCQLAFS	350 360 WYLEGGYL SLI GVLWITE WYLEGGYL SLI GVLWITE WYLEGGYL SLI GVLWITE WYLEGGYL SLI GVLWITE WYLEGGYL SLI GULWITE WYLEGGYL SLI GLLWITE WYLEGGYL SLI GLLWITE WYLEGGYL SLI GLLWITE WYLEGGYL SLI GLLWITE WYLEGGYL SLI GLLWITE WYLEGGYL SLI GLLWITE WYLEGGLL SLI GLLWITE WYLEGGLL SLI GLLWITE WYLEGGLL SLI GLLWITE WYLEGGLL SLI GLLWITE WYLEGGIL LUI ALLWLAE WYLEGGIL LUI ALLWLAE WYLEGGIL LUI ALLWLAE WYLEGGIL LUI ALLWLAE WYLEGGIL LUI ALLWLAE WYLEGGIL LUI ALLWLTE WYLEGGIL LUI ALLWITE WYLEGGIL SLI GLLWITE WYLEGGIL SLI GYLWITE WYLEGGIL SLI GYLWITE WYLGYNE SLI GYLWITE WYLWITE	370 380 I'ME CIKRMQ KRWR L DYLP S L YME CKRMQ KRWR L DYLP S L YME CKRMQ KRWR L DYLP S L YME CKRMQ KRWR L DYLP S L YME CKRMR RRWR L GYLP S L YME CKRMR RRWR L GYLP S L YME SKRMR RSWR L GFVP S L YME SKRMR RRWR L GFVP S L YME SKRMR RRWR L GFVP S L YME CKRMR RRWR L GFVP S L YME CKRMR RRWR L GYLP S L YME CKRM RRWR L GYLP S L	390 LIST F LIISEGAACIQS SSL LIST F LIISEGAACIQS SSL LIT F LIISEGAACIQS SSL LIT F LIISEGAACIQS SSL LIT F LIISEGAACIQS SSL LIT F LIISEGAACIQS SSL	410 420 IPRSAGGRLIVEALELISE IMYNYTSV IPRSNGRLIVEALELISE IMYNYTSV IPRSNGRLIVEALELISE IMYNYTSV IPRSNGRLIVEALELISE IMYNYTSV IPRSNGRLIVEALELISE IMYNYTSV IPRSNGRLIVEALELISE IMYNYTSV IPRSNGRLIVEALELISE IMYNYTSV IPRSNGRLAVEALELISE IMYNYTSV IPRSTGRLAVEALELISE IMYNYTSV
330 340 DmelR75a FRT PLNAGLRCDVFLQPFSPLVV DsimR75a FRT PLNAGLRCDVFLQPFSPLVV DrerR75a FRT PLNAGLRCDVFLQPFSPLVV DrerR75a FRT PLNAGLRCDVFLQPFSPLVV DrerR75a FRT PLNAGLRCDVFLQPFSPLVV DmelR75a FRT PLNAGLRCDVFLQPFSPLVV DpseR75a FRT PLNAGLRCDVFLQPFSPLVV DwiRR75a FRT PLNAGLRCDVFLQPFSPLVV DwiRR75a FRT PLNAGLRCDVFLQPFSPLVV DwiRR75a FRT PLNAGLRCDVFLQPFSPLVV DwiRR75a FRT PLNAGLRCDVFLQPFSPLVV DwiRR75a FRT PLNAGLRCDVFLQPFSPLVV DmojR75a FRT PLNAGLRCDVFLQPFSPLVV DmojR75a FRT PLNAGLRCDVFLQPFSALVV DmojR75a FRT PLNAG RCDVFLQPFSALVV DirtR75a FRT PLNAG RCDVFLQPFSALVV DwiRR75a FRT PLNAG RCDVFLQPFSALVV DablR75a FRT PLNAG RCDVFLQPFSALVV DABLVCT PLNAG RCDVFLQPFSALVV DablR75a FRT PLNAG RCDVFLQPFSALVV DABLVCT PLNAG RCDVFLQPFSALVV DABLVCT PLSALVV DABLVCT PLNAG RCDVFLQPFSALVV	350 360 WYLEGGYL SU GVLWITE WYLEGGYL SU GVLWITE WYLEGGYL SU GVLWITE WYLEGGYL SU GVLWITE WYLEGGYL SU GVLWITE WYLEGGYL SU GULWITE WYLEGGYL SU GLUWTE WYLEGGYL SU GLUWTE SU SU GULWYTE SU SU GULWTE WYLEGGYL SU GLUWTE WYLEGGYL SU GLUWTE SU SU GULWTE SU SU S	370 380 IME CKRMQKRWR L DYLPS L IME CKRMQKRWR L DYLPS L IME CKRMQKRWR L DYLPS L IME CKRMQKRWR L DYLPS L IME CKRMRRWR L DYLPS L IME CKRMRRWR L DYLPS L IME CKRMRRWR L DYLPS L IME CKRMRRWR L DYLPS L IME SKRMHSRWR L QFVPS L IME SKRMHSRWR L QFVPS L IME SKRMRRWR L SFVPS L IME SKRMRRWR L SFVPS L IME SKRMRRWR L SFVPS L IME CKRMRRWR L SFVPS L IME CKRMR L SFVPS L IME CKRMRRWR L SFVPS L IME CKRMRRWR L SFVPS L IME CKRMR L SFVPS L IME CKRMRRWR L SFVPS L IME CKRMR L SFVPS	390 LIST F LIISEGAACIQS SSIL LIST F LIISEGAACIQS SSIL LIT F LIISEGAACIQS SSIL LIT F LIISEGAACIQS SSIL LIT F LIISEGAACIQS SSIL LIT CLIISEGAACIQS SSIL LIT CLIISEGAACIQS SSIL LIT LIISEGAACIQS SSIL	410 420 IPRSAGGRLIYEALELISE IMYNYYTSV IPRSAGGRLIYEALELISE IMYNYYTSV IPRSAGGRLIYEALELISE IMYNYYTSV IPRSAGGRLIYEALELISE IMYNYYTSV IPRSAGGRLIYEALELISE IMYNYYTSV IPRSAGGRLIYEALELISE IMYNYTSV IPRSAGGRLIYEALELISE IMYNYTSV IPRSAGGRLIYEALELISE IMYNYTSV IPRSNGRLIYEALELISE IMYNYTSV IPRSNGRLIYEALELISE IMYNYTSV IPRSNGRLIYEALELISE IMYNYTSV IPRSNGRLIYEALELISE IMYNYTSV IPRSNGRLIYEALELISE IMYNYTSV IPRSNGRLIYEALELISE IMYNYTSV IPRSTGGRLAYEALELISE IMYNYTSV IPRSTGGRLAYEA
330 340 DmellR75a FRT PLNAGL RCDVF LOP F SPLW DsecIR75a FRT PLNAGL RCDVF LOP F SPLW DerelR75a FRT PLNAGL RCDVF LOP F SPLW DerelR75a FRT PLNAGL RCDVF LOP F SPLW DyskIR75a FRT PLNAGL RCDVF LOP F SPLW DyskIR75a FRT PLNAGL RCDVF LOP F SPLW DprelR75a FRT PLNAGL RCDVF LOP F SPLW DprelR75a FRT PLNAGL RCDVF LOP F SPLW DyskIR75a FRT PLNAGL RCDVF LOP F SPLW DyriR75a FRT PLNAGL RCDVF LOP F SALW DyriR75a FRT PLNAGL RCDVF LOP F SALW DyriR75a FRT PLNAGL RCDVF LOP F SALW DmolR75a FRT PLNAGL RCDVF LOP F SALW DmolR75a FRT PLNAGL RCDVF LOP F SALW DmolR75a FRT PLNAGL RCDVF LOP F SALW DabIR75a FRT PLNAGL RCDVF LOP F SALW A30 S2 440 450 DmelIR75a VSSLL SS PVK SKIKT MOQLAE S3 DsecIR75a VSSLL SS PVK SKIKT MOQLAE S3 DyskIR75a VSSL SS PVK SKIKT MOQLAE S3 DyskIR75a VSSL SS PVK SKIKT MOQLAE S3 DyskIR75A	350 360 WYLFIGGYL SLI GVL WI TH WYLFIGGYL LII ALL WL AF WYLFIGGYL SLI GWL WI TH WYLFIGGYL SLI GWL WI TH WYLFIGGYL SLI GVL WI TH WYLFIGYL SLI GYL WI TH WYLFIGYL SLI YN TH WYLFIGYL YN TH WYLFIGYL SLI YN TH WYLFIGYL SLI YN TH WYLFIGYL SLU YN TH WYLFIGYL YN TH WYLFIGYL YN TH WYLFIGYL SLU YN TH WYLFIGYL SLU YN TH WYLFIGYL YN TH WYLFIGYL YN TH WYLFIGYL SLU YN TH WYLFIGYL YN TH WYLFI	370 380 I'ME CICRMO, KIWR L DYLP S L I'ME CICRMO, KIWR L DYLP S L I'ME CICRMO, KIWR L DYLP S L I'ME CICRMORE WILD DYLP S L I'ME CICRMORE VILL DYLP S L I'ME CICRMORE VILL DYLP S L I'ME SIGNER SIGNEL OF VP S L I'ME SIGNER S	390 LIST F LIISEGAACIQS SSL LIST F LIISEGAACIQS SSL LITT F LIISEGAACIQS SSL LITT F LIISEGAACIQS SSL LITT F LIISEGAACIQS SSL LITT LIISEGAACIQS SSL DITT LIISEGAACIQS SSL LITT LIISEGAACIQS SSL DITT LIISEGAACIQS SSL	410 420 IPRSAGGRLIVEALELISE IMYNYTSV IPRSNGRLIVEALELISE IMYNYTSV IPRSNGRLIVEALELISE IMYNYTSV IPRSNGRLIVEALELISE IMYNYTSV IPRSNGRLIVEALELISE IMYNYTSV IPRSNGRLIVEALELISE IMYNYTSV IPRSNGRLIVEALELISE IMYNYTSV IPRSTGRLAVEALELISE IMYNYTSV
330 340 Dmel/R75a FRT PLNAGL RCDVF L QP F SPLVV DsciR/75a FRT PLNAGL RCDVF L QP F SPLVV Derel/R75a FRT PLNAGL RCDVF L QP F SPLVV Derel/R75a FRT PLNAGL RCDVF L QP F SPLVV DanalR75a FRT PLNAGL RCDVF L QP F SPLVV DanalR75a FRT PLNAGL RCDVF L QP F SPLVV DysklR75a FRT PLNAGL RCDVF L QP F SALVV DysklR75a FRT PLNAGL RCDVF L QP F SALVV DyriR75a SV SSLL SS PVK SKI KT MCQL AE SS Dser R75a V SSLL SS PVK SKI KT MCQL AE SS DyaklR75a V SSLL SS PVK SKI KT MCQL AE SS DyaklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS DysklR75a V SSLL SS PVK SKI KT MCQL AE SS	350 360 WY FGGYL SU GVLWITE WY FGGYL SU GULWY F WY FGGYL SU GLUWTE WY FGGYL SU GULWYTE SU SU GYLWITE WY FGGYL SU GULWYTE WY FGGYL SU GULWYTE WY FGGYL SU GULWYTE SU SU GULWYTE SU SU GULWYTE WY FGGYL SU GULWYTE SU SU S	370 380 IME CIK RMQ KRWR L DYLP S L YME CIK RMQ KRWR L DYLP S L YME CIK RMQ KRWR L DYLP S L YME CIK RMQ RRWR L DYLP S L YME CIK RMR RRWR L DYLP S L YME SIK RMR RRWR L DYLP S L YME CIK RH RRWR L DYLP S L Y	390 LIST F LIISEGAACIQS SSIL LIST F LIISEGAACIQS SSIL LIT LIISEGAACIQS SSIL LIT L LIISEGAACIQS SSIL LIT L LIISEGAACIQS SSIL LIST CLIISEGAACIQS SSIL LIST F LIISEGAACIQS SSIL DI LIISEGAACIQS SSIL LIST F LIISEGAACIQS SSIL LIST F LIISEGAACIQS SSIL LIST F LIISEGAACIQS SSIL DI LIISEGAACIQS SSIL LIST F LIISEGAACIQS SSIL DI LIISE SSIL DI LIISEGAACIQS SSIL DI LIISEGAACIQS SSIL DI LIISEGAA	410 420 IPRSAGGRLIYEALELISE IMYNYYTSV IPRSAGGRLIYEALELISE IMYNYYTSV IPRSAGGRLIYEALELISE IMYNYYTSV IPRSAGGRLIYEALELISE IMYNYYTSV IPRSAGGRLIYEALELISE IMYNYYTSV IPRSAGGRLIYEALELISE IMYNYTSV IPRSAGGRLIYEALELISE IMYNYTSV IPRSNGRLIYEALELISE IMYNYTSV IPRSTGGRLAYEALELISE IMYNYTSV IPRSTGGRLAYEAL
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330 340 DmellR75a FRT PLNAGLRCDVFLOPFSPLVV DsecIR75a FRTPLNAGLRCDVFLOPFSPLVV DyskiR75a FRTPLNAGLRCDVFLOPFSPLVV DyskiR75a FRTPLNAGLRCDVFLOPFSPLVV DmellR75a FRTPLNAGLRCDVFLOPFSPLVV DyskiR75a FRTPLNAGLRCDVFLOPFSALVV DiviR75a FRTPLNAGIRCDVFLOPFSALVV DiviR75a FRTPLNAGIRCDVFLOPFSALVV DiviR75a STSTRNAGIRCDVFLOPFSALVV DiviR75a SSSLSSPVKSKIKTMRCLAESS DiviR75a VSSLLSSPVKSKIKTMQLAESS DyskiR75a VSSLLSSPVKSKIKTMQLAESS	350 360 WYEFGGYLSEIGYLWITE WYEFGGYLSEIGYLWITE WYEFGGYLSEIGYLWITE WYEFGGYLSEIGYLWITE WYEFGGYLSEIGYLWITE WYEFGGYLSEIGYLWITE WYEFGGYLSEIGYLWITE WYEFGGYLSEIGYLWITE WYEFGGYLSEIGULWITE WYEFGGYLSEIGLUWTE WYEFGYLSEIGLUWTE WYEFGYLSEIGLUWTE WYEFGYLSEIGLUWTE WYEFGYLSEIGLUWTE WYEFGYLSEIGLUWTE WYEFGYLSEISIGLUWTE WYEFGYLSEISIGLUWTE WYEFGYLSEISIGLUWTE WYEFGYLSEISIGLUWTE WYEFGYLSEISIGUUWTE WYEFGYLSE	370 380 YME CKRMQKRWR L DYLP S L YME CKRMQKRWR L DYLP S L YME CKRMQKRWR L DYLP S L YME CKRMQERWR L DYLP S L YME CKRMRRWR L EFVP S L YME CKRMRRWR L S SOLONN R P E H L E I KRK I E SOLONN R P E H L E I KRK I E SOLONN R P E H L E I KRK I E SOLONN R P E H L E I KRK I E SOLONN R P E H L SKRK I E SOLONN R P E H L E I KRK I E SOLONN R P E H L E I KRK I E SOLONN R P E H L E I KRK I E SOLONN R P E H L E I KRK I E SOLONN R P E H L E I KRK I E SOLONN R P E H L E I KRK I E SOLONN R P E H L E I KRK I E SOLONN R P E H L E I KRK I E SOLONN R P E H L E KRK I E SOLONN R P E H L E KRK I E SOLONN R P E H L E KRK I E P SOLONN R P E H L	390 LIST F LIISEGAACIQS SSIL LIST F LIISEGAACIQS SSIL LIST F LIISEGAACIQS SSIL LIST F LIISEGAACIQS SSIL LIST F LIISEGAACIQS SSIL LIT L LY SEGAACIQS SSIL LIT L LY SE	410 420 IPRSAGGRLIYEALELISFIMYNYTSV IPRSAGGRLIYEALELISFIMYNYTSV IPRSAGGRLIYEALELISFIMYNYTSV IPRSAGGRLIYEALELISFIMYNYTSV IPRSAGGRLIYEALELISFIMYNYTSV IPRSAGGRLIYEALELISFIMYNYTSV IPRSAGGRLIYEALELISFIMYNYTSV IPRSAGGRLIYEALELISFIMYNYTSV IPRSNGRLIYEALELISFIMYNYTSV IPRSNGRLIYEALELISFIMYNYTSV IPRSNGRLIYEALELISFIMYNYTSV IPRSNGRLIYEALELISFIMYNYTSV IPRSNGRLIYEALELISFIMYNYTSV IPRSTGRLAVEALELISFIMYNYTSV
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Figure 4



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