

High variability of expression profiles of homeologous genes for Wnt, Hh, Notch, and Hippo signaling pathways in Xenopus laevis

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#### 24 <Abstract>

Cell signaling pathways, such as Wnt, Hedgehog (Hh), Notch, and Hippo, are essential for 25 26 embryogenesis, organogenesis, and tissue homeostasis. In this study, we analyzed 415 genes 27 involved in these pathways in the allotetraploid frog, Xenopus laevis. Most genes are 28 retained in two subgenomes called L and S (193 homeologous gene pairs and 29 singletons). 29 This conservation rate of homeologs is much higher than that of all genes in the X. laevis 30 genome (86.9% vs 60.2%). Among singletons, 24 genes are retained in the L subgenome, a 31 rate similar to the average for all genes (82.8% vs 74.6%). In addition, as general 32 components of signal transduction, we also analyzed 32 heparan sulfate proteoglycan 33 (HSPG)-related genes and eight TLE/Groucho transcriptional corepressors-related genes. In 34 these gene sets, all homeologous pairs have been retained. Transcriptome analysis using 35 RNA-seq data from developmental stages and adult tissues demonstrated that most 36 homeologous pairs of signaling components have variable expression patterns, in contrast to 37 the conservative expression profiles of homeologs for transcription factors. Our results 38 indicate that homeologous gene pairs for cell signaling regulation have tended to become 39 subfunctionalized after allotetraploidization. Diversification of signaling pathways by 40 subfunctionalization of homeologs may enhance environmental adaptability. These results 41 provide insights into the evolution of signaling pathways after polyploidization.

42

43 <Keywords>

44 cellular communication, signaling pathway, development, organogenesis, allotetraploid,
45 subfunctionalization, *Xenopus*

46

47 Short running title: Signaling components in *Xenopus laevis* 

#### 48 <Introduction>

Whole genome duplication (WGD) caused by polyploidization is considered to have been a major driver of organismal evolution by providing new functions and networks of genes (Holland et al., 1994; Ohno, 1970; Van de Peer et al., 2009). WGD, however, could also cause gene-dosage defects. Furthermore, in the case of allopolyploidization, it could also lead to protein-protein incompatibilities. How gene expression levels and patterns are modulated since genome duplication remains to be elucidated.

The African clawed frog, Xenopus laevis, is widely used as a model organism for 55 56 embryology and cellular physiology. *Xenopus laevis* is an allotetraploid frog that arose from 57 interspecific hybridization of diploid progenitors only 17-18 million years ago (Session et al., 58 2016). By comparing its genome with that of a closely related diploid frog, X. tropicalis, X. 59 laevis can be a good model system for evolutionary studies regarding genome duplication. In 60 X. laevis, two subgenomes, L (long) and S (short), were identified as sets of homeologous 61 chromosomes with different lengths and distributions of inactivated transposon sequences 62 ("fossil" transposons) (Matsuda et al., 2015; Session et al., 2016). Orthologous genomic 63 positions between subgenomes are termed "homeologous" and homeologous genes are known 64 as "homeologs."

65 Previous whole genome analyses suggested that the L subgenome has higher gene 66 retention rates and gene expression levels (Session et al., 2016). In addition, it was shown that 67 genes involved in DNA repair, RNA polymerase pathways, and other metabolic pathways 68 have tended to lose the one homeolog, whereas homeolog pairs for DNA-binding proteins and 69 major developmental signaling pathways are retained at higher rates (Session et al., 2016). 70 Similarly, a large scale transcriptomic data analysis suggested that genes for DNA-binding 71 proteins manifest conservative expression profiles between homeologs, whereas some 72 metabolic pathway genes exhibit variable expression profiles (Session et al., 2016). However,

it was unclear whether some genes of developmental signaling pathways have specific expression profiles. Because automated annotation analyses are superficial, more detailed analyses need to be performed. Particularly, subcellular localization varies among components of cell signaling pathways and may influence expression profile variation.

77 In this study, we examined Wnt, Hedgehog (Hh), Notch, and Hippo signaling 78 components. These signaling pathways have essential roles in development and disease. 79 Although some components of Wnt, Hh, and Hippo signaling pathways in the X. laevis 80 genome have been analyzed (Session et al., 2016), we analyzed many additional gene pairs 81 involved in those pathways (Wnt, 108 vs 48; Hh, 18 vs 13 Hippo, 48 vs 15). In addition, we 82 also analyzed Notch signaling components and some factors involved in signal transduction 83 in general, heparan sulfate proteoglycans (HSPG), and TLE/Groucho transcriptional 84 corepressors. HSPG and TLE are also important for modulating cell signaling levels in the 85 extracellular space and in nuclei. Other major signaling pathways (TGF $\beta$  and FGF) have been 86 analyzed by other groups (Suzuki et al. in press-1; Suzuki et al., in press-2). Utilizing the 87 genomic sequences and transcriptomes of X. laevis, we examined retention rates and 88 expression profiles of genes involved in cell signaling pathways between homeologs. Our 89 results describe notable cases of subfunctionalization of genes related to cell signaling 90 pathways just after genome duplication.

91

#### 92 <Materials and Methods>

# 93 Gene identification and syntenic analysis

All analyzed genes were identified with *X. laevis* genome assembly v9.1 and gene models v1.8. For unannotated genes, we performed BLAST or BLAT searches, using sequences in the NCBI *X. laevis* cDNA/EST database and gene models from *X. tropicalis* genome assembly v9. We manually corrected gene models with gaps (Ns) and incorrect splicing, based on 98 RefSeq and sequence homology. The FASTA file of primary transcript sequences used in this 99 study is available in the Supplementary Data of Watanabe et al. (in press). Syntenic analysis 100 was also performed with genome assemblies of *X. laevis* (v9.1) and *X. tropicalis* (v9), 101 *Nanorana parkeri*, v2 (Tibetan frog), *Homo sapiens*, hg38 (human), *Gallus gallus*, Galgal4 102 (chicken), *Lepisosteus oculatus*, LepOcu1 (spotted gar), *Danio rerio*, GRCz10 (zebrafish), 103 and *Oryzias latipes*, HdrR (medaka). The *Xenopus* database, Xenbase (Karpinka et al., 2015), 104 was used for gene identification and expression analyses.

105

# 106 **RNA-seq data analysis**

107 RNA-seq data of oocyte stages, embryonic stages, and adult tissues of Xenopus laevis J-strain 108 (Session et al., 2016) were used for transcriptomic analyses (accession numbers in NCBI Gene 109 Expression Omnibus: GSE73430 for oocytes and embryos, GSE73419 for adult organs). 110 Expression levels were quantified as TPM (transcripts per million) as described in Session et 111 al. (2016). Briefly, RNA-seq reads were mapped to primary transcript sequences using bwa-112 mem, and transcripts per million (TPM) were calculated using RSEM. To reveal differences 113 in the expression of homeologous genes, before running RSEM we removed read hits with 114 either (1) additional targets, or (2) partial alignments to genome segments containing 115 insertions or deletions. RNA-seq data contained two biologically independent replicates (named "Taira201203" and "Ueno201210") for embryos and adult tissues, but only 116 117 "Ueno201210" for oocytes. For stage 35, we used "Ueno201302" because "Ueno201210" 118 has a much smaller number of reads (data of "Ueno201210" and "Ueno201302" are from 119 siblings). These clutches will be called Clutch T for Taira's data and Clutch U for Ueno's data, 120 respectively. To make comparisons with expression profiles in X. tropicalis, we used public 121 transcriptome data from embryonic stages (Tan et al., 2013). RNA-seq reads of X. tropicalis 122 embryonic samples were mapped to the v9 genome assembly and expression levels were

123 calculated as described above. TPM values of each gene in each clutch are presented in
124 Suppl.Data 1 for *X. laevis* and Suppl. Data 2 for *X. tropicalis*.

125

#### 126 Transcriptome correlation analysis

127 The work flow of transcriptome correlation analysis is shown in Figure 1A. Prior to analysis, 128 all TPM values  $\leq 0.5$  were reduced to 0 because they are supposed to be irreproducible (Session 129 et al., 2016). For correlation analysis of homeologous genes, transcriptomic datasets from 11 developmental stages (egg to st40) and from 14 adult tissues were analyzed separately to 130 131 examine reproducibility. Correlations between homeologs were examined using Pearson's 132 correlation coefficient and Student's paired t-test on log2-transformed data [log2(TPM+1)] as described in the rainbow trout paper (Berthelot et al., 2014) with a python package. Homeolog 133 134 pairs were categorized into four groups based on (1) correlation (HC: high correlation,  $P \le 0.05$ ; 135 NC: no-significant correlation, P>0.05, Pearson's correlation test) and (2) expression levels 136 (SE: similar/slightly different expression levels, P>0.05; DE: different expression levels, 137  $P \le 0.05$ , Student's paired t-test). Finally, we collected homeolog pairs that were categorized 138 into the same group in both Clutches T and U. If the category was inconsistent between 139 clutches (a typical case is in Fig. 1F), those genes were categorized as "inconsistent (inc. in 140 Suppl. Data 3)" and were excluded from subsequent comparative analyses (see Results).

141

# 142 Epigenetic analysis and comparative genomics

143 Chromatin-immunoprecipitation sequencing (ChIP-seq) data of trimethylated histone H3 144 lysine 4 (H3K4me3) and p300 and methylated DNA sequencing (Methyl-seq) data at st10.5 145 of X. laevis embryos (Session et al., 2016, and G. J. C. Veenstra, personal communication) 146 were visualized using track hub of the UCSC а genome browser 147 (http://veenstra.ncmls.nl/trackhub.htm). A Vista plot was generated with Vista tool

148 (http://genome.lbl.gov/vista/index.shtml) to show the sequence conservation between *X*.
149 *tropicalis* genome and *X. laevis* subgenomes.

150

#### 151 <**Results and Discussions**>

# 152 **Overview of gene annotation and transcriptome correlation analysis**

153 Here we identified 204 Wnt signaling pathway genes, 33 Hh signaling pathway genes, 88 154 Notch signaling pathway genes, 91 Hippo pathway genes, 32 HSPG related genes, and 8 155 TLE/Groucho corepressors in X. laevis genome (Suppl. Data 3). They include 213 homeolog 156 pairs and 29 singletons. Among them, all orthologs of X. tropicalis genes were found, and no 157 *Xenopus* lineage-specific gene expansions were found, except for two *wnt11b* genes in X. 158 tropicalis (see below). This contrasts with *Xenopus* lineage-specific tandem duplications of 159 some TGFβ signaling ligands (vg1, nodal3, and nodal5; Session et al., 2016, Suzuki et al., in 160 press-1) and some transcription factors (bix1, sox17b, and ventx; Session et al., 2016, 161 Watanabe et al., in press). 24 singleton genes (82.8%) originated from the L subgenome. 162 This tendency is consistent with the whole genome analysis of X. laevis (Session et al., 2016). 163 In addition to genes identified by automated annotation in v1.8 gene models, we identified 31 164 genes (see Suppl. Data 3 for details). Consequently, two singletons (ppp2ca.S and neurl4.S) 165 was newly identified and a misidentified singleton (dll4.L) was found (see below for details).

For all genes analyzed in this study, expression data and results of transcriptome correlation analysis at developmental stages and in adult tissues are provided in Suppl. Data 1 and Suppl. Data 3. Unfortunately, we could not analyze transcriptome correlation of homeolog pairs for *dvl2* and *dll4* due to the loss of gene models (see below). On the basis of transcriptome correlation analysis (see Materials and Methods and Fig. 1A), we divided homeolog pairs into four groups: HCSE (high correlation with similar/slightly different expression levels, a typical case is in Fig. 1B), HCDE (high correlation with different

173 expression levels, a typical case is in Fig. 1C), NCSE (no-significant correlation with 174 similar/slightly different expression levels, a typical case is in Fig. 1D), and NCDE (no-175 significant correlation with different expression levels, a typical case is in Fig. 1E). HCSE 176 indicates conservative expression profiles. The NC groups potentially include 177 subfunctionalized or neofunctionalized genes, and DE groups potentially include 178 nonfunctionalized genes. 119 homeologs (56%) exhibited consistent results between clutches 179 during developmental stages and 140 in adult tissues (66%) also did (see Suppl. Data 3 for details). These levels are comparable to those of all 8,789 homeolog pairs identified in Session 180 et al. (2016) (48% and 64%, respectively). 181

182 During developmental stages, signaling pathway components are categorized into the four groups at similar rates for all homeologous gene pairs in v1.8 gene models ( $p = 0.18, 4x^2$ 183 184 Fisher's exact test, two-sided). On the other hand, in adult tissues, significant differences in 185 distributions of genes in 4 groups were observed between signaling genes and all genes (p= 186 0.0098, 4x2 Fisher's exact test, two-sided), in which signaling genes showed a higher rate in 187 HCDE (Table 1). These results indicate that homeologous pairs of cell signaling components 188 exhibit more variable expression profiles in adult tissues than in embryos, suggesting that 189 genes involved in signaling pathways are prone to become subfunctionalized spatially, rather 190 than temporally. In addition, signaling components include far fewer "HCSE" genes than 191 transcription factors (thoroughly analyzed in Watanabe et al., in press) in both developmental 192 stages and adult tissues (Table 1; P=0.00024 and 2.8e-11 for developmental stages and adult 193 tissues, respectively, 2x2 Fisher's exact test, two-sided). These data suggest that expression 194 profiles of cell signaling components are much more variable than transcription factors, 195 although both play important roles in embryogenesis and organogenesis. Detailed analyses of 196 singletons and variable expression profiles are described below.

#### 198 Wnt signaling

199 The Wnt signaling pathway is widely conserved in metazoans and participates in embryonic 200 patterning (Adamska et al., 2010; Niehrs, 2010). Wnt signaling also serves various functions 201 in tissue differentiation and cellular morphogenesis in development and disease (Clevers, 202 2006; Clevers and Nusse, 2012; Hoppler and Kavanagh, 2007; MacDonald et al., 2009). Many 203 studies have shown that numerous factors participate in the Wnt pathway (Fig. 2A). In this 204 study, we analyzed 108 gene pairs (listed on Suppl. Table 1) that were chosen from the Wnt 205 homepage (http://web.stanford.edu/group/nusselab/cgi-bin/wnt/) and recent reports (Cruciat 206 and Niehrs, 2013; Kakugawa et al., 2015; Zhang et al., 2015).

207

208 (I) Syntenic analysis

At first, we performed syntenic analysis to examine whether each gene possesses a homeologous pair in *X. laevis* (Fig. 2B-E and 3A-B; Suppl. Fig. 1; Session et al., 2016). Among Wnt signaling-related genes, 13 genes (*wnt2b*, *wnt11b*, *lrp5*, *porcn*, *rspo3*, *dkkx*, *sfrp4*, *shisa4*, *tiki1*, *notum2*, *csnk1g2*, *ppp2ca*, and *tcf7*) lost a homeolog in *X. laevis*; *wnt2b*, *wnt11b*, *lrp5*, and *tcf7* were described in Session et al. (2016). All of these except *shisa4* and *tcf7* retained their homeologs on the L chromosomes.

215 In X. tropicalis, two wnt11b genes, which were annotated as wnt11b and wnt11-like.1, 216 are located adjacently, but in opposite directions. Now they were renamed as wnt11b.1 and 217 wnt11b.2 in Xenbase, respectively (Fig. 3A), although they had been named as wnt11b.e1 and wnt11b.e2 (Session et al., 2016). On the other hand, X. laevis has only one wnt11b gene. 218 219 wnt11b.L, due to the loss of wnt11b.S (Fig. 3A). A phylogenetic tree of wnt11 genes suggested 220 that two wnt11b genes in X. tropicalis emerged by gene duplication (Suppl. Fig. 2A). 221 Originally, the wnt11b gene was annotated as "wnt11" in Xenopus and zebrafish (Heisenberg 222 et al., 2000; Ku and Melton, 1993; Makita et al., 1998), whereas another wnt11 gene was

223 annotated as "wnt11r" in Xenopus and zebrafish (Garriock et al., 2005; Matsui et al., 2005) 224 (Fig. 3A). However, in mammals, the ortholog of "wnt11r" has been identified as wnt11 225 because wnt11b was lost in the lineage (Fig. 3A). After the discovery of wnt11b in chickens, 226 these two groups of *wnt11* genes were finally identified by a phylogenetic analysis (Hardy et 227 al., 2008), which was confirmed by our more comprehensive phylogenetic and syntenic 228 analyses (Fig. 3A and Suppl. Fig. 2A). To avoid confusion between old names and new ones, 229 here we renamed orthologs of "wntllr" as wntlla in Xenopus (Fig. 3B). Interestingly, wntllb 230 was also lost in a teleost lineage, including medaka (Fig. 3A). Frequent losses of wnt11b genes 231 in several vertebrate lineages may be related to the loss of wnt11b.S in X. laevis, implying that 232 wnt11b has dispensable roles which can be compensated by other wnt genes. Conversely, 233 orthologs of *wnt11a* are conserved in all vertebrates and in both subgenomes of X. laevis, 234 indicating that *wntlla* has indispensable roles in vertebrate systems. This difference between 235 *wnt11a* and *wnt11b* seems to be related to their expression profiles, as described below.

236

# 237 (II) Differences of expression profiles between homeologs

We next examined expression profiles of Wnt signaling factors obtained from comprehensive transcriptome data (Session et al., 2016), especially focusing on differences between homeologs. According to subcellular localization, we classified these genes into six groups (1) Wnt ligands, (2) Frizzled (Fzd) receptors, (3) other extracellular/membrane factors for positive regulation (EC/M-pos), (4) extracellular /membrane factors for negative regulation (EC/M-neg), (5) cytoplasmic factors (CP), and (6) nuclear factors (Nuc) (Fig. 2A).

Transcriptome correlation analysis showed that Wnt signaling components exhibit similar expression properties to those of all analyzed genes in Session et al. (2016) during developmental stages and in adult tissues (p=0.57 and 0.32, 4x2 Fisher's exact test, two-sided). However, when we carefully examined signaling components in different subcellular

248 locations, we found that Fzd receptors are prone to show higher correlation coefficient scores 249 of homeolog expression patterns during development in both clutches (Suppl. Fig. 3A,B). 250 Second, extracellular components (ligands, receptors and other extracellular/membrane 251 factors) and intracellular components (cytoplasmic and nuclear factors) are associated with 252 different transcriptome correlation groups in adult tissues (Table 1, p=0.026, 4x2 Fisher's 253 exact test, two-sided). Extracellular components include more NC genes and intracellular 254 genes include more HCDE genes (Table 1). Third, extracellular components showed lower 255 correlation coefficient scores of homeolog expression patterns than intracellular components 256 in adult tissues of both clutches (Suppl. Fig. 3C,D). From these results, it seems that 257 extracellular components of Wnt signaling are relatively more subfunctionalized than 258 intracellular components in X. laevis, particularly in adult tissues. Detailed features of 259 homeologous gene expression are described below.

260

#### 261 (1) Wnt ligands

262 In Xenopus, 21 Wnt paralogs have been identified. These paralogs, except for wnt2b and 263 wnt11b, retain their homeologous pairs in X. laevis (Figs. 2B and 3A). Among Wnt ligands, 264 only wnt5a.S and wnt11b.L are expressed at significant levels (TPM>1) in eggs (wnt5a.S, TPM=2.93~3.29; wnt11b.L, TPM=152.97~240.85; Suppl. Data 1, Figs. 3C and 4B), 265 266 consistent with their maternal expression; they function together for body axis formation in X. 267 laevis (Cha et al., 2008; Tao et al., 2005). In contrast to wnt5a.S, wnt5a.L is not expressed in 268 eggs (TPM=0~0.06) (Suppl. Data 1 and Figs. 3C and 4B). These facts suggest that wnt11b.L, 269 which is also highly expressed during oogenesis and in ovary (Fig. 3C), is enriched in eggs 270 for body axis determination via Wnt signaling and that only single copies of wnt11b and wnt5a 271 are used as maternal Wnt ligands in X. laevis, possibly due to dosage-sensitive regulation after 272 allotetraploidization.

273 In X. tropicalis, transcriptomic data from embryos (Tan et al., 2013) showed that 274 wnt11b.1 and wnt5a were maternally expressed at higher levels (TPM= 23.91 and 18.55 at the 275 two-cell stage). On the other hand, *wnt11b.2* and *wnt11a* are not so highly expressed during 276 cleavage stages (TPM=3.05 and 3.84 at the two-cell stage). It is likely that X. tropicalis also 277 uses wnt5a and wnt11b for axis determination, because other Wnt ligands, except for wnt1 278 (TPM=1.47 at the two-cell stage) are not significantly expressed during cleavage stages 279 (TPM<1). However, although we cannot compare TPM values for different conditions, organisms, and filtering methods, the comparison between X. laevis and X. tropicalis suggests 280 281 that the amount of *wnt11* mRNA stored in eggs changed dramatically after divergence of the 282 two species. Our transcriptomic analysis of X. laevis and X. tropicalis suggests that wnt11b 283 mainly functions for maternal axis determination and early development, but that wntlla 284 functions during later development and adulthood (Garriock et al., 2005; Garriock and Krieg, 285 2007; Glinka et al., 1996; Ku and Melton, 1993; Tao et al., 2005). In zebrafish and chicken, 286 wnt11b also functions as a maternal factor and its expression is restricted to early 287 embryogenesis (Hardy et al., 2008; Heisenberg et al., 2000; Makita et al., 1998). This limited 288 function of *wnt11b* may be related to loss of *wnt11b* genes in several vertebrate lineages (Fig. 289 3A).

Transcriptomic data also revealed embryo-specific and adult-specific Wnt ligands. For example, Wnt8a is an embryo-specific Wnt ligand, because *wnt8a.L* and *wnt8a.S* are abundantly expressed from st 9 to 25, but not in adult tissues (TPM<1) except *wnt8a.L* in testis of clutch T (TPM=1.24) (Suppl. Fig. 4F, Suppl. Data 1). This suggests that Wnt8a is a highly specific Wnt ligand for AP-patterning of the early embryo. On the other hand, Wnt2 and Wnt7c are adult-specific Wnt ligands, although their expression levels are not so high (Suppl. Fig. 4A,E, Suppl. Data 1).

297

With regard to differential expression of Wnt ligands, wnt11 homeologs showed

298 HCDE expression profiles with higher expression levels of the L gene in both developmental 299 stages and adult tissues (Fig. 3C). This result indicates that wnt11a.L dominates wnt11a.S. 300 Similarly, wnt4 and wnt8a exhibited HCDE expression profiles with stronger expression of 301 the L gene (Suppl. Fig. 4B, F). Conversely, wntl showed DE expression profiles in both 302 developmental stages and adult tissues with stronger expression of the S gene (Fig. 4A). In 303 cases of NCSE expression profiles such as wnt6 and wnt10a (Suppl. Fig. 4C, H), a homeolog 304 showed stronger expression in specific tissues. Together with other examples (Suppl. Fig. 4), variable expression profiles of Wnt ligand genes appear to reflect subfunctionalization of 305 306 homeologs in X. laevis.

307

### 308 (2) Fzd receptors

309 Frizzled (Fzd) is a receptor that interacts with Wnt ligands in the extracellular space. In 310 *Xenopus*, ten paralogs have been identified. Unlike Wnt ligands, no singletons were found. 311 Transcriptome correlation analysis revealed seven genes during embryogenesis and four genes 312 in adult tissues that showed variable expression profiles between the L and S subgenomes 313 (Table 1). As mentioned above, Fzd genes showed higher correlation coefficient scores during 314 developmental stages (Suppl. Fig. 3A, B). However, no genes were consistently categorized 315 as HCSE between the two clutches and five genes were categorized as HCDE (Table 1), 316 suggesting that expression levels of Fzd homeologs were highly variable even though their 317 temporal expression patterns are highly correlated.

Among Fzd genes, the expression level of fzd7 is highest during embryonic stages, while fzd7.L is dominant to fzd7.S during embryogenesis (NCDE) and in some adult tissues (kidney, ovary, and spleen; HCDE) (Fig. 4D). Similar to fzd7, fzd5 homeologs also showed NC expression profiles during development (NCSE, Fig. 4C). In adult tissues, fzd9 showed NCSE patterns, although fzd9 homeologs are similarly expressed during development (Suppl.

Fig. 5D). On the other hand, *fzd2*, *fzd4*, and *fzd8* homeologs showed DE expression profiles in which S genes are more highly expressed than L genes (Suppl. Fig. 5A-C). These data indicate that homeologs of Fzd receptors are also highly subfunctionalized in *X. laevis*, possibly due to dosage-sensitive regulation of membrane factors in the limited space of the plasma membrane.

328

# 329 (3) Extracellular/membrane factors for positive regulation (EC/M-pos)

330 Together with Wnt ligands and Fzd receptors, other extracellular/membrane factors activate 331 What signaling as agonists (*rspondin* (*rspo*), *norrin* (*ndp*)), (co)receptors (*lrp*, *lgr*, *ror*, and *rvk*), 332 or secretion promoters (porcupine (porcn), wntless (wls)) of Wnt ligands. In the EC/M-pos 333 group, *lrp5*, *porcn*, and *rspo3* were singletons on L chromosomes (Fig. 2C, Suppl. Fig. 1A; 334 Session et al., 2016). Transcriptomic data showed that ror1.L was primarily expressed in 335 embryos (st12-25) and also in adult tissues such as heart, kidney, and testis, expression profiles 336 of which were categorized as DE (Fig. 4E). On the other hand, in cases of *lgr4* and *rvk*, the S 337 gene is more strongly expressed in some embryonic stages and adult tissues, categorized as 338 HCDE, except lgr4 in adult tissues of clutch T (Suppl. Fig. 6A, F). Interestingly, rspo2 339 homeologs showed an NCSE expression profile at developmental stages with an expression 340 shift from S to L at embryonic st10-12, possibly corresponding to higher expression of *rspo2.L* 341 in brain, eye, and lung, and of *rspo2.S* in ovary, although it was categorized as HCSE in adult 342 tissues (Fig. 4F). *lrp6* also showed an NCSE pattern with a shift of expression dominance 343 from L to S at st10-12 during developmental stages, and an HCDE pattern in adult tissues with 344 higher expression levels of the S gene (Suppl. Fig. 6C). Together with other examples of 345 variable expression patterns (Suppl. Fig. 6B, D, E), homeologous genes in the EC/M-pos 346 group are suggested to be also well subfunctionalized in X. laevis.

347

348 (4) Extracellular/membrane factors for negative regulation (EC/M- neg)

EC/M-neg factors have crucial roles in modulation of Wnt signaling levels by inhibiting Wnt/receptor interactions (such as *cerberus*, *dkk*, and *sfrp*), processing Wnt proteins (*notum* and *tiki*), ubiquitinating Fzd receptors (*rnf43* and *znrf3*), and inhibiting receptor maturation (*shisa*) (Cruciat and Niehrs, 2013; Kakugawa et al., 2015; Zhang et al., 2015).

353 In the EC/M-neg group, dkkx.L, notum2.L, sfrp4.L, shisa4.S, and trabd2a.L (tiki1.L) 354 are singletons. As for other components, transcriptomic data indicated that many homeologous 355 gene pairs are differentially expressed during embryogenesis or in adult tissues (Table 1). For 356 example, in *sfrp1*, the L gene predominates during embryogenesis and in some adult tissues, 357 categorized as DE (Fig. 4G), whereas, in cerl, the S gene is dominant, although it was 358 categorized as HCSE in clutch U, possibly due to few stages expressing *cerl* genes (Fig. 4H). 359 In other cases, apcdd1, dkk3, frzb2, kremem1, shisa1, shisa2, and znrf3 show L-dominant DE 360 profiles, whereas notum1, rnf43, sfrpx, and tpbg show S-dominant DE profiles, in 361 developmental stages, adult tissues, or both (Fig. 4I, Suppl. Fig. 7A, B, D-F, H-J, M, O). Notably, 362 *sfrp5* and *sostdc1* exhibit NCSE profiles during developmental stages with changing dominant 363 homeologs (Suppl. Fig. 7G, K). These results suggest that many homeologous genes in the 364 EC/M-neg category have been highly subfunctionalized in X. laevis.

365 To examine how these variable expression patterns of homeologs are regulated, we 366 also investigated epigenetic states on genomic loci around those homeologs (Fig. 5). At stage 367 10.5 (early gastrula), ChIP-seq data of H3K4me3 and p300 demonstrated that homeologs with 368 stronger expression (cer1.S and sfrp1.L) exhibit stronger enrichment of H3K4me3 around 369 promoters and of p300 at enhancers (Fig. 5B, C). It has been shown that an enhancer of cer1 370 (named U1 enhancer) activates *cer1* in dorsal endomesoderm (Sudou et al., 2012; Yamamoto 371 et al., 2003). A comparison of core sequences of the U1 enhancer in Xenopus showed that the 372 enhancer sequence of *cer1.S* is the most derived among *Xenopus* genes and it exhibits stronger

373 enhancer activity in the dorsal region of the embryo than an ancestral sequence (Sudou et al., 374 2012). In the case of *sfrp1*, a binding peak of p300 in the first intron disappears in the locus 375 of sfrp1.S (Fig. 5C). A comparison of genomic sequences of sfrp1 loci between the X. laevis 376 L subgenome, S subgenome, and the X. tropicalis genome demonstrated that the sequence 377 corresponding to the *sfrp1.L*-specific p300 peak is conserved in *X. tropicalis*, but deleted from 378 the X. laevis S subgenome. These observations indicate that enhancer sequence alterations 379 lead to preferential enrichment of enhancer/promoter epigenetic markers of a homeolog, 380 resulting in biased expression levels between homeologs.

381

#### 382 (5) Cytoplasmic factors (CP)

383 CP factors transduce Wnt signaling to modulate gene expression and cellular morphology. 384 Among them, Dishevelled (Dvl) is a key factor to transduce Wnt signaling pathways from Fzd 385 receptors. As mentioned above, two singleton genes were identified, casein kinasely2 386 (csnk1g2) and protein phosphatase 2 catalytic subunit alpha (ppp2ca) in CP genes (Fig. 2E 387 and Suppl. Fig. 1B). Although *dvl2.S* was not identified in gene models v1.8, it was previously 388 identified in gene models v1.6 of genome assembly v7.1. dvl2.S sequences also exist in the 389 corresponding region of scaffold 20 of genome assembly v9.1. RNA-seq analysis using 390 v1.6 gene models demonstrated that dvl2.S had similar expression levels to dvl2.L in embryos 391 and adult tissues (data not shown). Therefore, we concluded that dvl2 homeologs are 392 conserved in X. laevis.

It should be noted that expression levels of dvl2 and  $\beta$ -catenin (ctnnb1) are very high in eggs (dvl2.L, TPM=191.87~700.12; ctnnb1.L, TPM=268.1~492.53; ctnnb1.S, TPM=459.02~502.81). This result is consistent with the fact that for induction of a secondary axis by microinjection, higher doses of cytoplasmic factor mRNA, such as *disheveled* (dvl) or  $\beta$ -catenin, are necessary than for extracellular factors such as xWnt8 (Sokol et al., 1992; Smith

398 and Harland 1991; Sokol et al., 1995; Funayama et al., 1995).

Expression profiles of CP genes exhibited a greater tendency to DE categories in 399 400 adult tissues than all other Wnt signaling components (Table 1; P=0.0096, Fisher's exact test, 401 two-sided). For example,  $\beta$ -catenin homeologs are similarly expressed in embryos (HCSE), 402 but their expression levels are variable in adult tissues (HCDE) (Fig. 1B, Suppl. Fig. 8G). 403 Moreover, *axin2* showed HCDE expression profiles in both embryos and adult tissues with 404 stronger expression of the L gene, whereas the S gene is dominantly expressed in gsk3b (Fig. 4J,K). ChIP-seq data around axin2 homeologs suggested that H3K4me3 enrichment on the 405 406 promoter and p300 enrichment on an enhancer are correlated with their biased expression 407 levels (Fig. 5A). Other examples also indicate variable expression levels of CP genes; axin1, 408 ccdc88c, csnk1a1, csnk1d, cxxc4, dvl1, dvl3, and gsk3a are L gene dominant, csnk2a1, csnk2b 409 and ctnnb11 are S-dominant (Suppl. Fig. 7). Because many CP genes are involved in 410 destabilization of  $\beta$ -catenin, our results imply that single copies of genes related to enzymatic 411 processing of  $\beta$ -catenin are sufficient, allowing homeologs to diversify expression levels.

412

413 (6) Nuclear factors (Nuc)

414 The HMG box transcription factor, Tcf/Lef, is one of the important transcription factors for 415 canonical Wnt signaling transduction (Clevers and Nusse, 2012; MacDonald et al., 2009) (see 416 Fig. 6A). Tcf genes are highly conserved among metazoans (Adamska et al., 2010) and there 417 are four subfamilies in vertebrates, Tcf7 (Tcf1), Tcf7l1 (Tcf3), Tcf7l2 (Tcf4), and Lef1 (Arce 418 et al., 2006; Hoppler and Kavanagh, 2007). Each subfamily has various splicing isoforms and 419 molecular functions of these subfamilies are diversified in development and disease (Arce et 420 al., 2006; Hoppler and Kavanagh, 2007). In Xenopus, it has been shown that Tcf7 and Lef1 421 mainly activate Wnt target genes, whereas Tcf7l1 and Tcf7l2 function as both activators and 422 repressors for Wnt target genes.

423 According to transcriptomic data, Tcf/Lef genes, tcf7.S, tcf7ll.L, and tcf7ll.S are maternally expressed, and *tcf7ll.S* expression is especially persistent during embryogenesis 424 425 (Fig. 6B,C). During later developmental stages and in adult tissues, there are slight differences 426 with stronger expression of *tcf7l1.S* (HCDE categories) (Fig. 6C). Expression levels of both 427 tcf7l2.L and tcf7l2.S are low (less than 5 tpm) during embryogenesis, but they showed NCSE 428 profiles in both clutches, suggesting temporal subfunctionalization. In adult tissues, tcf7l2 429 homeologs showed HCSE expression profiles with strong expression (more than 5 tpm) in 430 brain, intestine, and spleen (Fig. 6D). *lef1.L* starts to be expressed at an early gastrula stage 431 (st10), earlier than *lef1.S* (late gastrula stage, st12), and expression levels of *lef1.L* are higher 432 than those of *lef1.S* during development (HCDE) (Fig. 6E). However, there are no strong 433 differences between *lef1.L* and *lef1.S* in adult tissues, categorized as HCSE (Fig. 6E). These 434 data suggest that Tcf/Lef homeologous pairs in X. laevis are subfunctionalized to some extent, 435 but not so dramatically as other Wnt signaling components.

436

## 437 Hedgehog signaling

438 Hedgehog (Hh) is an important morphogen that is evolutionarily conserved from Drosophila 439 to humans (McMahon et al., 2003). The Hh ligand binds to its receptor Patched, which results 440 in de-inhibition of Smoothened (Smo, a downstream membrane-bound signaling mediator), 441 and activation of signal transduction (Fig. 7A). In Xenopus, however, the Hh signaling 442 pathway has not been studied in sufficient detail to understand the diversity of pathway 443 components. In this study, we analyzed 18 gene pairs in the Hh pathway (including genes 444 analyzed in Session et al., 2016). A whole gene list examined here and in Session et al. 445 (2016) is summarized in Suppl. Table 2.

446 (I) Syntenic analysis

447 Syntenic analyses revealed that, in addition to *hhat* (Session et al., 2016), two more genes lost

their homeologs on S chromosomes (*stk36* [a homolog of *Drosophila fused* (*fu*)], *kif7* [a homolog of *Drosophila costal2* (*cos2*)]). In genomic regions corresponding to *stk36.S* and *kif7.S*, neighboring genes are also missing (Fig. 7B,C), while loss of *hhat.S* appears to be a single gene deletion (Session et al., 2016).

452

453 (II) Expression profiles

We also examined expression profiles of Hh signaling components using RNA-seq data (Session et al., 2016) during development and in adult tissues, focusing on differences in their homeologs. We classified these genes into three groups: (1) ligands and extracellular factors, (2) receptor and membrane-bound factors, and (3) cytoplasmic, ciliary, and nuclear factors, according to their subcellular localizations (Fig. 7A). Most L genes are expressed at higher levels during developmental stages and in adult tissues than S genes, consistent with overall gene expression profiles (Session et al., 2016). Expression patterns are detailed below.

461

## 462 (1) Hh ligands

463 In mammals, three ligands, i.e., Sonic Hedgehog (Shh), Indian Hedgehog (Ihh), and Desert 464 Hedgehog (Dhh) have been identified (Ingham and Placzek, 2006). Similarly, X. laevis has 465 three ligands (Ekker et al., 1995; Takabatake et al., 1997). According to RNA-seq results, *shh* 466 and *dhh* are highly expressed during embryogenesis (Fig. 8A). Expression profiles of *shh* 467 homeologs were highly correlated, but the expression level of *shh*.*L* is higher than that of *shh*.*S* 468 (HCDE in clutch T, but HCSE in clutch U), while *dhh* homeologs were categorized as HCSE 469 during embryogenesis. *ihh* homeologs were also categorized as HCSE, but homeologs showed 470 lower expression during early embryogenesis (although they are expressed at certain levels 471 from the tailbud stage). In adult tissues, all pairs of ligands are categorized as HCDE and L 472 genes of all ligands are dominant (Fig.8A).

473

# 474 (2) *Hh receptor/membrane factors*

475 L genes of *ptch1* and *ptch2* were predominantly expressed during embryogenesis (both 476 HCDE). However, in adult tissues, homeologous pairs of *ptch1* and *ptch2* showed similar 477 expression levels, except for *ptch2* in spleen (Fig. 8B). *smo* homeologs showed HCDE profiles 478 in both embryos and adult tissues, in which *smo.L* was more heavily expressed (Suppl. Fig. 479 9A). ptch1, ptch2, and smo show higher expression around the neurulation stage, possibly 480 reflecting the importance of Hh signaling in neural tube patterning. A hedgehog-binding 481 inhibitor gene, *hhip*, showed dominant expression in the L gene during embryogenesis and in 482 adult tissues, particularly in lung (Suppl. Fig. 9B).

We also examined epigenetic states of *smo* homeologs in embryos (Suppl. Fig. 10A). ChIP-seq data at st10.5 showed stronger enrichment of H3K4me3 and p300 at the promoter and enhancer of *smo.L* than of *smo.S*. Interestingly, enhancer sequences showing biased enrichment of p300 at st10.5 are globally conserved between *smo.L*, *smo.S*, and *X. tropicalis smo* (Suppl. Fig. 10B), suggesting that either very slight modifications of transcription factor binding sequences in enhancers caused the difference, or that other controlling regions far away from genes contribute to them.

490

# 491 (3) Cytoplasmic, ciliary and nuclear factors

One of the striking features of Hh signaling is that the primary cilium is essential in vertebrates (Wilson and Chuang, 2010). Several key components of the Hh pathway, including Ptch1, Smo, and Gli transcription factors, are known to be enriched in cilia (Goetz and Anderson, 2010). Here, we analyzed transcriptional data of a transducer of Hh signaling located in cytoplasm and nucleus and in cilium length mediators.

497

Three Gli transcription factors are identified in X. laevis, as in mammals. All gli genes

498 are expressed from late gastrula stage, and almost all of their homeologs showed correlated 499 expression at developmental stages and in adult tissues (Suppl. Fig. 9C-E). gli1.S was more 500 heavily expressed especially in Clutch T (Suppl. Fig. 9C). gli2.L was dominant during 501 embryogenesis and in adult tissues, resulting in HCDE (Suppl. Fig. 9D). Except for Clutch T 502 at developmental stages, the homeologous pair of gli3 showed similar expression levels in 503 embryos and adults (Suppl. Fig. 9E). Other transducers of Hh signaling (sufu and prkaca) 504 showed correlated expression between homeologs, except for singleton genes (*stk36* and *kif7*) 505 during embryogenesis and in adult tissues (Suppl. Fig. 9F-I). It should be noted that the 506 requirement of stk36 for Hh signaling in Xenopus remains to be tested, because the 507 requirement diverged in vertebrates (Chen et al., 2005; Murone et al., 2000; Wilson et al., 508 2009; Yamamoto et al., 2015), in contrast to the critical role of *fu* in *Drosophila* Hh signaling.

509 Arl13b and Foxj1 are known to regulate Hh signaling so as to positively control 510 ciliary length (Caspary et al., 2007; Cruz et al., 2010; Lu et al., 2015). The expression level of 511 arl13b was significantly different between homeologs (Suppl. Fig. 9J). Although foxil was 512 categorized as HCSE, somewhat different expression was observed just around neurulation 513 (st12-15) (Suppl. Fig. 9K). These results imply that ciliary length became regulated by 514 subfunctionalization of ciliary genes just after genome duplication in X. laevis, due to the 515 importance of ciliary length for Hh ligand gradient formation or reception during neural 516 patterning.

517

### 518 Proteoglycans

Heparan sulfate (HS) proteoglycans (HSPGs) are cell surface molecules that are important for morphogen gradient formation and reception of signaling factors including Wnt, Hh, FGF, and BMP signaling pathways (Sarrazin et al., 2011; Yan and Lin, 2009). HSPGs consist of a core protein and covalently attached HS chains (Fig. 9A). They can serve as co-receptors, and

523 also facilitate ligand-receptor interactions.

524 (I) core proteins

HSPG core proteins are conserved through the animal kingdom and are expressed in a stage- and tissue-specific manner. They are divided into three groups according to their localization: transmembrane HSPGs including *syndecans*, glycosylphosphatidylinositolanchored HSPGs (*glypicans*), and secreted HSPGs. Here, we focus on the two membranebound types of HSPGs.

530 In vertebrates, six glypicans are identified and divided into two groups orthologous 531 to Drosophila dally and dally-like protein (dlp). gpc3/5 is the dally family and the others 532 belong to the *dlp* family. The transmembrane protein Syndecan has four genes in vertebrates, 533 but only one in *Drosophila*. The amount of HSPG protein on the cell surface is critical for 534 growth factor distribution or signaling activity, but it remains an open question whether 535 expression changes after genome duplication. Therefore, we analyzed HSPG expression 536 profiles (all genes analyzed are listed in Suppl. Table 3) during embryogenesis and in adult 537 tissues in *X. laevis*.

538 There are no singletons among syndecans or glypicans. During embryogenesis, 539 almost all homeologous pairs of each proteoglycan showed correlated expression patterns 540 through developmental stages. For instance, expression levels of *sdc2* homeologs are lower in 541 oocytes, but higher during developmental stages (Fig. 9C). However, sdc4 homeologs were 542 categorized as NCSE (Fig. 1D). sdc4.S is higher, especially during egg and blastula stages (st8 543 and 9), whereas sdc4.L is higher from gastrula to early neurula stages (st12 and 15). High 544 expression of *sdc4* in gastrula stages is consistent with the function of Syndecan in planar cell 545 polarity (Escobedo et al., 2013); however, roles of maternal Syndecans are still unknown. On 546 the other hand, in X. tropicalis, sdc4 is not highly expressed during cleavage stages (Tan et al., 547 2013, Suppl. Data2). Taken together, these results suggest that *sdc4.S* acquired a new function

548 at about the egg stage in *X. laevis*.

Expression levels of *glypican* genes during embryogenesis are similar between homeologs (Fig. 9B; Suppl. Fig. 11A-D), except for *gpc4* during neurulation stages, at which the L gene predominated (Suppl. Fig. 11C). In adult tissues, *glypicans* are highly expressed in brain, including *gpc3* and *gpc6*, which are not highly expressed during embryogenesis (Fig. 9B, Suppl. Fig. 11A-E). Comparing each homeologous gene pair, L gene expression levels of *gpc1*, *gpc2*, and *gpc4* are higher in many tissues, categorized as HCDE, except *gpc4* in clutch U.

556

557 (II) Modification enzymes

558 Sugar chains are attached to their core proteins and processed by a series of modifications. 559 Sugar chain modifications are initiated by N-deacetylase/N-sulfotransferase (NDST), which 560 removes an N-acetyl group from GlcNAc of a nascent sugar chain (N-acetyl heparosan) and 561 substitutes the free amino group with sulfate, forming N-sulfo HS (Fig. 9A). This process is 562 essential for generation of sulfated, ligand binding sites in HS (Lindahl et al., 1998) and both 563 Syndecans and Glypicans could be substrates of Ndst. Subsequently HS is modulated by O-564 sulfotransferases (Sulf). Recently, it was shown that 6-O-sulfatation by sulf1 influences the 565 Shh gradient in the neural tube in X. tropicalis (Ramsbottom et al., 2014). Here we analyzed 566 *ndst* and *sulf* genes.

Homeologs of *ndst1* showed NC expression patterns during development. *ndst1.L* expression increased from the egg stage to st12 and decreased from st25~30 to st40, whereas *ndst1.S* expression decreased from st8 to st12 and increased from st15 to st25~30. Although it was categorized as NCSE in clutch U, expression levels of the L gene are stronger than those of the S genes in many stages. *ndst1.L* is also more strongly expressed in oocytes and adult ovary (Fig. 9D). In addition, the L gene of *ndst2* is dominant during embryonic stages and

adult tissues (Suppl. Fig. 11G). In embryos, *ndst3 and ndst4* homeologs show only faint expression (TPM <1; see Suppl. Data 1). Therefore, S genes of *ndst* are not highly expressed in eggs, where *sdc4.S* is highly expressed (Fig. 1D), suggesting no substrate specificity in Ndst with regard to subgenome. In adult tissues, all *ndst* genes are highly expressed in brain, similar to the expression of *glypicans*, and homeologs other than *ndst2* showed conservative expression profiles (HCSE).

Two sulfatases were identified in *Xenopus*, *sulf1* and *sulf2*. During embryonic stages, the L gene of *sulf1* was more highly expressed (Suppl. Fig. 11H, I), while homeologous genes of *sulf2* showed NC expression patterns with different temporal expression changes. Consistent with the *sulf1* requirement in neural tube patterning, *sulf1* was highly expressed during the early neurula stage. In adult tissues, *sulf1.S* is strongly expressed in lung, in contrast to its very low expression in embryos. Over all, homeologous genes of *sulf1* and *sulf2* are similarly expressed in adult tissues.

586

## 587 Notch signaling

Notch signaling is evolutionarily conserved in metazoans (Gazave et al., 2009), and controls differentiation, proliferation, and apoptosis during development and in multiple tissues (Guruharsha et al., 2012). Notch signaling is activated by the ligand (Delta/Jagged), and the receptor, Notch, is processed by series of proteolyses. After the receptor release from its transmembrane tether by proteolysis, the Notch intracellular domain (NICD) is transferred to the nucleus and activates target genes (Kopan and Ilagan, 2009) (Fig. 10A).

Here we analyzed 48 gene pairs that were chosen from the map of the Notch pathway on the KEGG website (Kyoto Encyclopedia of Genes and Genomes) (<u>http://www.genome.jp/kegg/</u>) and some reviews (Gazave et al., 2009; Guruharsha et al., 2012; Kopan and Ilagan, 2009) (listed on Suppl. Table 4).

598

# 599 (1) Syntenic analysis

Syntenic analysis revealed that seven genes lost their S homeologs (*dtx3-like1*, *dtx3l- like*, *dtx4*, *hey2*, *neurl2*, *pofut1*, and *rfng*), while *neurl4* lost the L homeolog (Figs. 2C and
10B-H, Suppl. Table 4). Among eight singleton genes, *pofut1.S* and *rfng.S* are pseudogenes
(Fig. 10B,C). Seven of eight Notch signaling-related singletons were caused by gene losses
on S chromosomes, similar to all analyzed genes (Session et al., 2016).

We found that dll4.L was misidentified as a singleton by genomic analysis (Session et al., 2016). Although the full sequence of the dll4 gene was only found on the L chromosome, partial sequences of putative S genes were found on some scaffolds. In particular, some putative dll4.S sequences are located on the edge of scaffold\_34, in which synteny of surrounding genes is conserved in the L subgenome and the *X. tropicalis* genome. Because we could not find any pseudogene-like sequences, such as frameshift mutations or stop codon insertions in putative dll4.S sequences, we concluded that dll4 retains the homeolog pair.

612

613 (2) Expression profiles

According to their subcellular localization, we classified genes into four groups (1) ligands/receptors, (2) other extracellular/membrane factors, (3) cytoplasmic factors, and (4) nuclear factors (Fig. 10A). Hes transcription factors are also involved in Notch signaling, but were analyzed separately in another paper in this special issue (Watanabe et al., in press).

We examined expression profiles of Notch signaling genes and compared expression levels between L and S genes. Transcriptome correlation analysis showed that extracellular components of Notch signaling exhibited more HCDE profiles than intracellular components in adult tissues (Table 1; P=0.030, 2x2 Fisher's exact test, two-sided). This result suggests that expression levels of extracellular components are more variable for the Notch signaling

623 pathway in adult tissues.

624 Expression patterns of *dlc* (one of the Delta ligands, also called *dll2*) homeologs are 625 categorized as HCDE, and expression of *dlc.L* is clearly dominant around gastrula stages (Fig. 626 11C). Epigenetic data showed that H3K4me3 and p300 on the promoter and enhancers at 627 gastrula stage are strongly enriched on *dlc.L*, but less so on *dlc.S* (Fig. 11A) However, 628 sequence comparisons of p300 binding regions between L and S subgenomes showed that all 629 enhancer sequences are conserved between *dlc.L* and *dlc.S* (Fig. 11B). Interestingly, levels of 630 DNA methylation of the *dlc.L* promoter are very low, but those of the *dlc.S* promoter are high 631 (Fig. 11A). These data suggest that differential expression of *dlc* homeologs is controlled by 632 DNA demethylation of their promoter regions.

633 A homeologous pair of *jag1* showed interesting temporal expression patterns, 634 categorized as NCSE. jag1.S is highly expressed during early developmental stages, while 635 *jag1.L* is high during late developmental stages (Fig. 11D), suggesting subfunctionalization 636 after allotetraploidization. In other factors in the extracellular/membrane category, the 637 metalloprotease gene, *adam17.L*, is more strongly expressed throughout embryogenesis and 638 in many adult tissues, being categorized as NCDE and HCDE (Fig. 11E). Among  $\gamma$ -secretase 639 subunits, aph1a.S showed stronger expression in embryos and adult tissues (Fig. 11F). In the 640 cytoplasmic factor category, dtx2.L and nedd4l.S, both of which encode the E3 ubiquitin ligase 641 for Notch receptor endocytosis, are more strongly expressed in embryos (Fig. 11G,H). Among 642 nuclear factors, the NICD interacting transcriptional activator, maml1, showed HCDE profiles 643 with stronger expression of the S gene in embryos (Fig. 1C). Together with other examples of 644 variable expression profiles (Suppl. Fig. 12), homeologous genes encoding Notch signaling 645 components are also well subfunctionalized in X. laevis.

646

### 647 Hippo signaling

648 The Hippo signaling pathway is evolutionarily conserved and controls organ size by 649 regulating cell proliferation, apoptosis, movement, and fate (Varelas, 2014; Yu et al., 2015). 650 Unlike other signaling pathways, the Hippo pathway does not have a simple ligand/receptor 651 mechanism for signaling input. To recognize cell density, activity of the Hippo pathway is 652 regulated by cell-cell contact, planar cell polarity, mechanical cues, and also by intracellular 653 stresses (Varelas, 2014; Yu et al., 2015). Such stimuli are finally transduced to inactivate 654 YAP/TAZ protein, which activates cell proliferation together with the TEAD transcription 655 factor (Fig. 12A).

656

657 (1) Syntenic analysis

658 Here we analyzed 48 gene pairs chosen from the Hippo pathway map on the KEGG 659 website (Kyoto Encyclopedia of Genes and Genomes) (<u>http://www.genome.jp/kegg/</u>) and 660 some reviews (Varelas, 2014; Yu et al., 2015) (listed on Suppl. Table 5).

661 Syntenic analysis revealed that four homeolog pairs lost the S gene (*crb1*, *limd1*, 662 *rassf4*, and *taz*) and *lats1* lost the L gene (Session et al., 2016) (Fig. 12B-E, Suppl. Table 5). 663 Interestingly, gene loss in *X. laevis* genome was also observed in one of the homeologous 664 genes of *cyclin H* and its partner gene *cdk7*, which are target genes of Hippo pathway (Session 665 et al., 2016). Simultaneous gene loss of *taz* and *cyclin H/cdk7* may imply that dosage-sensitive 666 regulation occurs in cell cycle regulation after allotetraploidization.

667

668 (2) Expression profiles

We examined expression profiles of genes in Hippo signaling and compared expression levels between homeologous gene pairs (Table 5). The ratio of the number of genes categorized into 4 groups are similar to that in all analyzed genes (Session et al., 2016), but slightly different in the adult, especially high rate in HCDE (p = 0.12, 4x2 Fisher's exact test,

two-sided; p=0.02, 2x2 (HCDE and others) Fisher's exact test, two-sided). Details of
individual gene expression patterns are described below.

675 According to their subcellular localization, we classified genes into three groups, (1) 676 transmembrane factors, (2) cytoplasmic factors, and (3) nuclear factors (Fig. 12A). Expression 677 patterns of each homeologous pair of *stk3* and *stk4* (also called *mst2* and *mst1*, respectively) 678 and *Drosophila hippo* orthologs are highly correlated, but expression levels are significantly 679 different during embryogenesis and in adult tissues (except for *stk3* in adult tissues of Clutch 680 T) (Fig. 12F, G, Suppl. Fig. 13Q, R). *stk3.S* is more strongly expressed in oocytes and gastrula 681 stage embryos, whereas *stk4.L* is more strongly expressed in later stage embryos, and many 682 tissues.

683 The LATS/MOB complex causes cytoplasmic destruction or retention of YAP/TAZ 684 molecules, which results in inhibition of the nuclear localization of YAP/TAZ (Varelas, 2014; 685 Yu et al., 2015). Two orthologs of *lats* (homeologs of *lat1* and *lat2*) are identified in X. *laevis*. 686 *lats1.S* is a singleton, as described above. *lats2* homeologs are categorized as HCSE during 687 embryogenesis, but they show different expression levels in adult tissues (NCDE in Clutch T 688 and HCDE in Clutch U). *lats2.S* is more strongly expressed in almost all tissues (Fig. 12H). 689 On the other hand, *mob1a* homeologs show HCDE profiles with stronger expression of the L 690 gene in adult tissues (Fig. 12I).

Yorkie is a key factor for the *Drosophila* Hippo pathway, in which it regulates gene expression together with Scalloped. Two Yorkie paralogs, *yap1* and *taz*, are identified in vertebrates. The two paralogs are considered to have similar functions. However, it is known that *yap1* has essential roles in many tissues, but *taz* only functions in mesenchymal stem cell differentiation (Hong et al., 2005) and in Wnt signaling (Azzolin et al., 2012), according to assays in cell culture and zebrafish. As mentioned above, *taz.L* became a singleton, whereas homeologous genes of *yap1* are conserved, implying that *taz.S* was lost due to its limited utility.

698 However, expression profiles indicate that *taz.L* is strongly expressed throughout oogenesis 699 to early embryogenesis and in ovary (Suppl. Fig. 13X). In X. tropicalis, taz expression is 700 dramatically decreased after gastrulation (Suppl. Fig. 14). Thus, maternal expression of *taz* is 701 conserved in *Xenopus*, but strong expression of *taz* in later stage embryos is specific to X. 702 *laevis*. The expression pattern of *yap1* is categorized as HCDE in both embryos and adults. 703 *vap1.L* is more strongly expressed during embryonic stages and in many tissues such as eye, 704 lung, and skin (Fig. 12J). The relationship between the divergence of *yap1/taz* expression 705 patterns and allotetraploidization needs to be addressed in the future.

Together with other examples (Suppl. Fig. 13), many Hippo pathway genes possess
highly variable expression profiles between homeologs, especially in adult tissues. Because
the Hippo pathway controls organ sizes, our results may explain how *X. laevis* acquired its
larger body size after allotetraploidization.

710

# 711 TLE/Groucho transcriptional corepressors

712 TLE/Groucho family genes have crucial roles in gene repression, forming complexes 713 with various transcription factors and recruiting histone deacetylase (HDAC) (Buscarlet and 714 Stifani, 2007; Cinnamon and Paroush, 2008). By interacting with many kinds of transcription 715 factors, such as Fox, Nkx, Pax, Gsc, Hesx and Otx, TLE occupies cis-regulatory modules for 716 tissue-specific genes during development (Yasuoka et al., 2014). The Tcf/TLE complex 717 represses transcription of target genes of canonical Wnt signaling when signaling is off (Fig. 718 6A). Similarly, the Rbpj/TLE complex represses Notch signaling. Therefore, TLE has a 719 role to keep signaling turned off.

In vertebrates, there are four TLE paralogs, TLE1, TLE2, TLE3 and TLE4 and a truncated TLE paralog AES; however, TLE3 was lost in *Xenopus* (Roth et al., 2010). In *Xenopus*, all TLE related genes reside on XLA1, in which *tle2* and *aes* are tandemly located

in opposite directions and *tle1* and *tle4* are also (Fig. 13A). *X. laevis* retains all TLE-related gene homeologs, and interestingly, dominantly expressed homeologs are opposite between neighboring genes during development. That is, L genes are dominant in *tle1* and *tle2*, but S genes are dominant in *tle4* and *aes* (Fig. 13B-E). Except for *tle4* in clutch T, they showed HCDE expression profiles. In adult tissues, *tle1*, *tle2*, and *aes* showed HCDE profiles with the same tendencies of expression dominance as in embryos (Fig. 13B-C, E). But *tle4* showed stronger expression levels of the L gene in clutch T (Fig. 13D).

Notably, expression profiles of TLE-related genes in the L subgenome, but not those
in the S subgenome, resemble those in *X. tropicalis* during development (Suppl. Fig. 14).
These results suggest that the L subgenome retains an ancestral state conserved in *X. tropicalis*,
but that the S subgenome lost some evolutionary constraints and was more readily altered.

734

### 735 *Conclusion*

736 In this study, we analyzed 416 genes involved in Wnt, Hh, Notch, and Hippo pathways in X. 737 laevis. Also, 32 HSPG-related genes and 8 TLE/Groucho-related genes were analyzed. 738 Among them, we found 29 singletons, 24 of which are located on L chromosomes, a rate 739 similar to all analyzed genes (82.8% vs 74.6%). Through transcriptome correlation analysis, 740 signaling genes are often HCDE (highly correlated but different expression levels) in adult 741 tissues, compared with the genome average. This contrasts with genes encoding transcription 742 factors, which are more similarly expressed between homeologs (high rate of HCSE) 743 (Watanabe et al., in press). These results suggest that expression patterns and levels of 744 signaling factors are variable after genome duplication.

Considering the induction mechanism of differential expression, it is probably due to changes of transcriptional regulatory machineries, such as cis-regulatory sequences and epigenetic modifications. Indeed, preliminary epigenetic analysis showed that DNA

748 methylation levels and H3K4me3 enrichment on promoter regions, and p300 enrichment on 749 enhancer regions are associated with differential expression levels of homeologs (Session et 750 al., 2016). Our analyses illustrated three patterns of regulation and expression: 1. acquisition 751 of a cis-regulatory sequence leads to increased expression of a homeolog (cer1, Figs. 4H and 752 5B, see Sudou et al., 2012 for detail analysis on the sequence); 2. loss of a cis-regulatory 753 sequence leads to decreased expression of a homeolog (*sfrp1*, Figs. 4G and 5C); 3. DNA 754 methylation of the promoter leads to silencing of a homeolog (*dlc*, Figs 11A,C). Future 755 functional analyses of these cis-regulatory modules (e.g. transgenic reporter assays) should 756 reveal their roles in differential expression, leading to a better understanding of 757 subfunctionalization after genome duplication.

758 What biological meanings underlie the variable expression profiles of homeologs? 759 One may be protein-protein incompatibilities, meaning L gene to L gene or S gene to S gene-760 specific protein interactions. Actually, we observed more L gene-dominant expression profiles 761 among signaling genes than S gene-dominant, consistent with whole genome analysis 762 (Session et al., 2016). However, we did not find a strong tendency for genes from a given 763 subgenome to predominate throughout a protein complex, such as ligand/receptor, 764 enzyme/substrate, and transcription factor/cofactor complexes. Thus, there is no obvious 765 protein-protein incompatibility regarding the genes from different subgenomes. More simply, 766 it is likely that single copies of genes are sufficient for signal transduction, particularly 767 enzymatic reactions. For instance, cytoplasmic components of Wnt and Hippo pathways and 768 extracellular/membrane components of Notch pathway include many enzymes and exhibit 769 many HCDE profiles (Table1, Figs. 4, 11, and 12, Suppl. Figs. 8, 12, and 13). The other 770 possible meaning of variable expression is dosage compensation, due to the limited space for 771 the distribution of extracellular, membrane, and cytoplasmic factors for signaling-pathway 772 related genes after genome duplication. This contrasts with genes encoding transcription

factors, in which homeologs are more similarly expressed (Watanabe et al., in press) possibly
because their working space, cis-regulatory modules, was also duplicated.

Here we observed many cases of temporally and spatially subfunctionalized homeologous genes (mainly NCSE profiles). The underlying mechanism must be changes of stage/tissue-specific cis-regulatory regions. Epigenetic studies on each stage and tissue should provide more useful information about different uses of various enhancers for homeologs. How variable expression patterns, achieved by changes in transcriptional regulation, led to functional diversification will be addressed in the future.

781

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#### 982 <Figure legends>

#### 983 Fig. 1. Criteria and examples of transcriptome correlation analysis

984 (A) Criteria for categorization of homeologous gene expression. See Materials and Methods 985 for details. All results are presented in Suppl. Data3. (B-E) Examples of four groups. 986 Group names are presented in each graph. In case of inconsistencies, group names in 987 different clutches are presented separately. (B) ctnnb1.L ( $\beta$ -catenin.L) and ctnnb1.S ( $\beta$ -988 *catenin.S*) showed quite similar expression patterns (HCSE). (C) *maml1.L* showed highly 989 correlated, but stronger expression than *maml1.S* throughout developmental stages (st8-12) 990 (HCDE). (D) sdc4.L and sdc4.S showed different expression patterns during development 991 (NCSE). (E) *numbl.L* showed stronger expression than *numbl.S* and the two expression 992 patterns are quite different throughout developmental stages. (F) An example of inconsistent 993 categories between clutches. *frat1.S* was expressed at higher levels than *frat1.L* during 994 development in Clutch T (HCDE), but both showed similar expression levels in Clutch U 995 (HCSE). Line graphs show expression levels of genes during oogenesis and embryogenesis. 996 Magenta, L genes; Blue, S genes; circles, Clutch T; triangles, Clutch U.

997

998 Fig. 2. Syntenic analyses of Wnt signaling-related singletons in X. laevis and X. tropicalis. 999 (A) Schematic view of the Wnt signaling pathway. Categories based on subcellular 1000 localization are indicated at the right. (B) Synteny around *wnt2b*. XLA2L retains conserved 1001 synteny around wnt2b with X. tropicalis chromosome 2 (XTR2), but several rearrangements 1002 may have occurred in XLA2S. (C) Synteny around rspo3. Complicated rearrangements were 1003 observed on both L and S chromosomes. (D) Comparison of *sfrp4* loci. *sfrp4.S* was lost in 1004 a large deletion (~23 Mb) between *velo1* and *sept7* on XLA6S. (E) Comparison of genomic 1005 loci surrounding *ppp2ca* and *tcf7*. XLA3S retains conserved synteny with XTR3, even though 1006 LOC100489679 was deleted. On the other hand, XLA3L lost tcf7 and there was a large inversion close to *vdac1.L*. In addition, a pseudogene of *ppp2ca.L*, shown with a dashed box,
was found between *vdac1.L* and *LOC100488619.L*. Magenta boxes show singletons involved
in Wnt signaling, except *hey2* in (C), which is related to Notch signaling. Double diagonal
lines indicate a large gap between genes. Diagonal lines on the genome signify deletion of
genes. Dashed lines represent putative inversion events. In each panel, only representative
gene models are shown for comparison.

1013

## Fig. 3. Frequent loss of *wnt11b* genes in vertebrate lineages and variable expression patterns of *wnt11a* homeologs.

1016 (A) Synteny around the wntllb gene in vertebrates. wntllb.S was deleted from X. laevis 1017 chromosome 8S (XLA8S) together with neighboring genes. Orthologs of wnt11b were also 1018 deleted in humans (HSAX) and medaka (OLA10). After the divergence of Xenopus and 1019 Nanorana, a large inversion seems to have occured between *igbp1* and *stard10-like*, as 1020 indicated by dashed lines. (B) Synteny around the wntlla gene in vertebrates. Although a 1021 genomic rearrangement was found in XLA2L, wnt11a orthologs and synteny are highly 1022 conserved among vertebrates. HSA, Homo sapiens; GGA, Gallus gallus (chicken); NPA, 1023 Nanorana parkeri (Tibetan frog), XTR, Xenopus tropicalis; XLA, Xenopus laevis; LOC, 1024 Lepisosteus oculatus (spotted gar); DRE, Danio rerio (zebrafish); OLA, Oryzias latipes 1025 (medaka). (C) Expression profiles of wntlla.L, wntlla.S and wntllb.L. Data are shown in 1026 graphs similar to those in Fig. 1. See text for detailed explanations of variable expression 1027 profiles.

1028

# Fig. 4. Variable expression profiles of Wnt signaling-components (Wnt ligands, Frizzled receptors, other extracellular/membrane factors, and cytoplasmic factors).

1031 (A-K) Variable expression profiles of Wnt signaling components. Data are shown in graphs

1032 similar to those in Fig. 1. See text for detailed explanations of variable expression profiles.

1033

#### 1034 Fig. 5. Correlations of epigenetic states and variable expression profiles

1035 (A-C) Genome browser representations of ChIP-seq and DNA methylation data using X. 1036 laevis gastrula embryos (st10.5) demonstrated biased enrichment of H3K4me3 and p300 1037 between homeologous genomic regions near axin2, cer1, and sfrp1. ChIP-seq results from 1038 biological replicates are shown separately. Green, H3K4me3; yellow, p300; gray, DNA 1039 methylation; bracket, strong enrichment of H3K4me3 on the promoter of the more strongly 1040 expressed homeolog; arrowhead, strong enrichment of p300 on enhancers of the more strongly 1041 expressed homeolog. (D) A vista plot represents sequence conservation in the genomic region 1042 around *sfrp1* in X. *laevis* and X. *tropicalis*. The sequence of *sfrp1*.L was used as a reference. 1043 Light blue, UTR; dark blue, coding sequences; orange, conserved non-coding sequences. 1044 Dashed lines and magenta boxes in (C) and (D) correspond to each other.

1045

#### 1046 Fig. 6. Variable expression patterns of Tcf/Lefgenes.

1047 (A) Schematic drawing of transcriptional regulation for Wnt target genes by Tcf/Lef. The Tcf 1048 family has a β-catenin-binding domain and a TLE/Groucho-binding domain in addition to the 1049 HMG box DNA-binding domain. When canonical Wnt signaling is off, Tcf protein represses 1050 target genes by forming a complex with TLE transcriptional corepressors. When canonical 1051 What signaling is activated,  $\beta$ -catenin accumulates in the nucleus, Tcf forms a complex with  $\beta$ -1052 catenin, and recruits other coactivators for transcription of target genes. (B-E) Expression 1053 profiles of *tcf/lef* genes. Data are shown in graphs similar to those in Fig. 1. See text for 1054 detailed explanations of variable expression profiles.

1055

#### 1056 Fig. 7. Schematic view of Hh signaling and syntenic analyses of its singletons

(A) Overview of the Hedgehog (Hh) signaling pathway. Categories based on subcellular
localization are indicated at the right. (B-C) A schematic comparison of syntenies around *kif*7
(B) and *stk36* (C) in *X. tropicalis* and *X. laevis*. Only representative gene models are listed for
comparison. Regions where corresponding gene models are missing on S chromosomes are
outlined in grey.

1062

#### 1063 Fig. 8. Variable expression profiles of Hh ligands and Ptch receptors.

1064 (A) Expression profiles of Hh ligands. (B) Expression profiles of Ptch receptors.
1065 Transcriptomic data are shown in graphs similar to those in Fig. 1. See text for detailed
1066 explanations of differential expression.

1067

## Fig. 9. Genes involved in heparan sulfate proteoglycans also showed variable expression profiles

(A) Schematic diagram of Glypican (Gpc) and Syndecan (Sdc). Solid lines and branches show
core protein and glycosaminoglycan chains, respectively. N-deacetylase/N-sulfotransferase
(NDST) removes N-acetyl groups from GlcNAc of nascent sugar chains (N-acetyl heparosan)
and substitutes the free amino group with sulfate (N-sulfo HS). (B-D) Expression profiles of *gpc1*, *gpc2*, *sdc4*, and *ndst1*. Transcriptomic data are shown in graphs similar to those in Fig.
See text for detailed explanations of variable expression.

1076

#### 1077 Fig. 10. Syntenic analyses of Notch signaling-related singletons

1078 (A) Schematic view of the Notch signaling pathway. Categories based on subcellular 1079 localization are indicated at the right. (B-H) Syntenies around singletons, shown in magenta 1080 boxes, involved in Notch signaling. Pseudogenes are shown with dashed boxes (*pofut1.S* and 1081 *rfng.S*). (C) A pseudogene of *rfng.S* and syntenic genes of *rfng* are located in scaffold 27 in

1082 the X. laevis genome. (D) In the X. tropicalis genome, dtx3l-like is located at the end of 1083 scaffold 734, together with syntenic genes. Syntenic genes of dtx31-like are located in 1084 scaffold 27 in the X. laevis genome, but dtx3l-like is deleted. Taken together with rfng.S(C), 1085 scaffold 27 seems to belong to XLA9 10S. (E) dtx3-like1.S was removed from XLA8S by a 1086 large deletion. (F) dtx4.S was deleted together with neighboring genes from XLA7S. (G) 1087 Together with the loss of *neurl2.S* in XLA9 10S, many syntenic genes became singletons via 1088 pseudogenization. (H) In the X. tropicalis genome, neurl4 is located at the end of scaffold 393 1089 together with syntenic genes. In XLA3L, neurl4.L and acap1.L are deleted, but their 1090 homeologs are located with syntenic genes in scaffold 20. Together with the observation of 1091 dvl2.S (see text), scaffold 20 seems to belong to XLA3S.

1092

#### 1093 Fig. 11. Variable expression of Notch signaling factors and its epigenetic basis

1094 (A) Genome browser representations of ChIP-seq and DNA methylation data using X. laevis 1095 gastrula embryos (st10.5) demonstrated biased enrichment of H3K4me3 and p300 between 1096 homeologous genomic regions of *dlc*. A blue box shows highly demethylated region of the 1097 *dlc.L* promoter. (B) A Vista plot shows conservation of p300 binding cis-regulatory regions 1098 around *dlc* genes in *Xenopus*. See Fig. 5 for explanations of genome browser representations 1099 and Vista plots. (C-H) Expression profiles of Notch signaling-related genes. Data are shown 1100 in graphs similar to those in Fig. 1. See text for detailed explanations of variable expression 1101 profiles.

1102

#### 1103 Fig. 12. Syntenic and transcriptomic analyses of Hippo signaling-related genes

(A) Schematic view of the Hippo signaling pathway. Categories based on subcellular
localization are indicated at the right. (B-E) Syntenies around singleton genes, which are
shown in magenta boxes, involved in Hippo signaling. A pseudogene, *rassf4.S*, is shown in a

dashed box. (F-J) Expression profiles of Hippo pathway factors. Data are shown in graphssimilar to those in Fig. 1. See text for detailed explanations of variable expression profiles.

1109

#### 1110 Fig.13. Syntenic and transcriptomic analysis of TLE/Groucho genes

- 1111 (A) Genomic organization of TLE/Groucho-related genes on XTR1, XLA1L, and XLA1S.
- 1112 The homeolog with dominant expression is indicated at the bottom (L or S gene). (B-E)
- 1113 Expression profiles of TLE-related genes. Data are shown in graphs similar to those in Fig. 1.
- 1114 See text for detailed explanations of variable expression profiles.





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#### Table 1. Results of transcriptome correlation analysis

	Developmental stages					Adult tissues			
	HCSE	HCDE	NCSE	NCDE	HCSE	HCDE	NCSE	NCDE	
Signaling pathway components									
Wnt signaling									
Wnt ligands	1	4	2	1	7	2	2	0	
Fzd receptors	0	5	1	1	4	3	0	1	
Extracellular-Membrane Positive	2	2	2	0	1	3	1	0	
Extracellular-Membrane Negative	6	8	2	2	7	4	2	0	
Cytoplasmic	3	8	1	3	4	13	0	0	
Nuclear	0	2	1	0	2	1	0	0	
total	12	29	9	7	25	26	5	1	
Hh signaling									
Ligands	2	0	0	0	0	3	0	0	
Receptor-Membrane	0	3	0	0	2	2	0	0	
Cytoplasmic-Cilia-Nuclear	2	1	0	0	2	3	0	0	
total	4	4	0	0	4	8	0	0	
HSPG									
Core protein	0	3	2	0	5	3	0	0	
Enzyme	0	1	0	0	4	1	0	0	
total	0	4	2	0	9	4	0	0	
Notch signaling									
Ligands-Receptors	1	1	1	0	1	2	0	0	
Extracellular-Membrane	2	4	0	2	2	8	0	0	
Cytoplasmic	1	4	2	1	7	4	0	0	
Nuclear	0	1	1	0	3	1	0	0	
total	4	10	4	3	13	15	0	0	
Hippo signaling									
Membrane	1	1	0	0	1	4	0	0	
Cytoplasmic	7	9	3	2	5	13	1	0	
Nuclear	0	2	0	0	1	2	0	0	
total	8	12	3	2	7	19	1	0	
TLE	0	3	0	0	0	3	0	0	
total	28	62	18	12	58	75	6	1	
total (%)	23.3	51.7	15.0	10.0	41.4	53.6	4.3	0.7	
Transcription factors									
(Watanabe et al., submitted)									
total	56	48	10	7	100	12	8	3	
total (%)	45.5	39.0	8.1	5.7	81.3	9.8	6.5	2.4	
All annotated homeologous pairs									
(Session et al., submitted)									
total	1,061	1,960	480	674	2,263	2,655	307	369	
total (%)	25.4	46.9	11.5	16.1	40.5	47.5	5.5	6.6	

#### Highlights

- 1. Genes of several signaling pathways are thoroughly characterized in Xenopus laevis.
- 2. Conservation rate of homeologs is much higher than that of all genes in the X. laevis genome.
- 3. Most homeologs show variable expression patterns, in contrast to transcription factors.
- 4. Homeologs with variable expression profiles are probably subfunctionalized, enhancing environmental adaptability.











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Suppl. Fig. 7 (continued)



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## Suppl. Fig. 8 (continued)




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Suppl. Fig. 9 (continued)









Suppl. Fig. 12 (continued)



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Suppl. Fig. 13 (continued)





## <Notes of Supplementary Data>

#### **Supplementary Data 1**

Suppl. Data 1 represents all transcriptome data of *X. laevis* analyzed in this study. Tpm values of each gene in developmental stages and adult tissues of two clutches (T and U) are listed.

#### **Supplementary Data 2**

Suppl. Data 2 represents all transcriptome data of *X. tropicalis* analyzed in this study. The average tpm values of RNA-seq data from biological replicates, which were sequenced in Tan et al., 2013, are listed. Gene names and IDs are based on *X. tropicalis* genome assembly v9.

#### **Supplementary Data 3**

Suppl. Data 3 represents all gene names, IDs, and results of the transcriptome correlation analysis. In columns D and G, newly annotated genes and manually corrected gene models in this study are shown in yellow. Some gene names used in this study are different from names in v1.8.3 annotation, which are shown in orange. In columns from I to N, results of the transcriptome correlation analysis are indicated. n/a means that a homeolog is not expressed in TPM>0.5 throughout all stages/tissues. inc. means that categorized groups in Clutch T and U are inconsistent.

#### <Supplemental figure legends>

#### Suppl. Fig. 1. Syntenic analyses of singleton genes involved in Wnt signaling

(A) Comparison of genomic loci around *porcn*. In *X. tropicalis*, *porcn* is located in scaffold\_5369 where there is no other gene model. In *X. laevis*, *porcn*.*S* is eliminated from XLA8S by a single gene deletion. Syntenic genes of *porcn* (*ebp* and *tbc1d25*) are also located in scaffolds but not in chromosome assemblies in *X. tropicalis*. Especially, *ebp* was found in genome assembly v4.1 but not found in v9. (B) Syntenic analysis of *csnk1g2*. *csnk1g2*.*S* is deleted by a large deleteion (~100 kb) together with surrounding genes. (C) Pseudogenes. BLAT search revealed pseudogenes for *dkkx.S*,

*notum2.S*, *shisa4.L*, and *trabd2a.S* (*tiki1.S*). Dashed line boxes indicate pseudogenes. Magenta boxes are genes involved in the Wnt signaling.

#### Suppl. Fig. 2. Analyses on *wnt11* genes

(A) A phylogenic tree of *wnt11* genes using amino acid sequences. Alignments of sequences were performed with MAFFT (v7.221) (Katoh et al., 2002) using the auto strategy. Unaligned regions were trimmed with TrimAl (v1.2rev59) (Capella-Gutiérrez et al., 2009) using the gappyout option. The maximum likelihood method with PROTGAMMAAUTO was used to construct phylogenetic trees with RAxML (v8.2.0) (Stamatakis, 2014). Bootstrap support values for nodes are indicated (n=100). Wnt11 of amphioxus (Bfl\_wnt11) was used as an outgroup. Vertebrate Wnt11 genes were separated into two clades, Wnt11a and Wnt11b. A scale bar of branch length indicates substitutions per site. Hsa, *Homo sapiens*; Gga, *Gallus gallus* (chicken); Npa, *Nanorana parkeri* (Tibetan frog), Xtr, *Xenopus tropicalis*; Xla, *Xenopus laevis*; Loc, *Lepisosteus oculatus* (spotted gar); Dre, *Danio rerio* (zebrafish); Bfl, *Branchiostoma floridae* (amphioxus). (B) Expression profiles of *wnt11* genes (*wnt11a*, *wnt11b.1*, and *wnt11b.2*) in *X. tropicalis* are represented in line graphs. See text for detailed explanations. References:

Capella-Gutierrez, S., Silla-Martinez, J.M., Gabaldon, T., 2009. trimAl: a tool for automated alignment trimming in large-scale phylogenetic analyses. Bioinformatics (Oxford, England) 25, 1972-1973.
Katoh, K., Misawa, K., Kuma, K., Miyata, T., 2002. MAFFT: a novel method for rapid multiple sequence alignment based on fast Fourier transform. Nucleic acids research 30, 3059-3066.
Stamatakis, A., 2014. RAxML version 8: a tool for phylogenetic analysis and post-analysis of large phylogenies. Bioinformatics (Oxford, England) 30, 1312-1313.

#### Suppl. Fig. 3. Variability of gene expression patterns in Wnt signaling genes.

(A-D) The distribution of Pearson's correlation coefficient scores was shown by box-whisker plots separately for stages and tissues of each clutch. Genes are categorized into their subcellular localizations

according to Fig. 2A. The statistical significance of the difference between categories was examined by 2x2 Fisher's exact test.

#### Suppl. Fig. 4. Transcriptomic analyses of Wnt ligands

Expression profiles of homeologs of *wnt2* (A), *wnt4* (B), *wnt6* (C), *wnt7a* (D), *wnt7c* (E), *wnt8a* (F), *wnt9b* (G), *wnt10a* (H). (A) *wnt2.L* shows slightly strong expression around st.25. (B) Expression patterns of *wnt4* homeologs are categorized as HCDE and L gene is dominant in both embryos and adult tissues. (C) Expression patterns of *wnt6* homeologs are categorized as NCSE in both embryos and adult tissues. (D) *wnt7a* is categorized as NCDE at developmental stages but HCSE in the adult. (E) Expression levels of *wnt7c* homeologs are very low at developmental stages, while they are high in brain, eye and skin of the adult. (F) *wnt8a* shows HCDE pattern in embryos but low expression in adults. *wnt8a.L* is more strongly expressed during gastrulation. (G) *wnt9b* is categorized as HCDE in embryos and as NCSE and HCSE in adult tissues of Clutch T and U. *wnt9b.S* is highly expressed during tailbud stage and in kidney. (H) L gene of *wnt10a* shows slightly higher expression especially after neurulation stage and in lung.

#### Suppl. Fig. 5. Transcriptomic analyses of Fzd receptors

(A) Expression profiles of fzd2 homeologs are categorized as HCDE in both embryos and adult tissues. As well as in embryonic stages, fzd2.S is more strongly expressed in adult tissues. (B) Expression profiles of fzd4 homeologs are also categorized as HCDE. fzd4.S is dominantly expressed in embryos and in some adult tissues such as lung, ovary, stomach, and testis. (C) fzd8.S has around 2-fold expression levels to fzd8.L in embryonic stages from st10 to 30, categorized as HCDE. In adult tissues, fzd8.S showed slightly higher expression in heart, intestine, spleen, and stomach and categorized as DE in both clutches. (D) fzd9.L showed stronger expression in adult tissues and its expression levels are not correlated with fzd9.S (NCDE). fzd9.L is also more heavily expressed throughout developmental stages in Clutch T but not in Clutch U. (E) fzd10.L tends to be expressed at higher levels, although categories were inconsistent between clutches.

#### Suppl. Fig. 6. Transcriptomic analyses of Wnt signaling related genes categorized in EC/M-pos

(A) lgr4.S shows higher expression through developmental stages, categorized as HCDE, and it also shows slightly higher expression in heart and intestine of the adult. (B) Expression profiles of lgr5homeologs show NC patterns in embryos and in adult tissues of Clutch U. lgr5.L is more strongly expressed in testis. (C) lrp6.L is more strongly expressed in egg to blastula (st8, 9), but lrp6.S is more strongly expressed in adult tissues (about 2-fold in many cases), resulting in NCSE (stages) and HCDE (tissues). (D) ndp homeologs show high expression after gastrulation stage, but their expression levels are not highly correlated especially in Clutch U. ndp.L is dominantly expressed in brain, eye, intestine, and lung, whereas ndp.S predominates in ovary, resulting in NCSE. (E) Expression levels of rspolhomeologs are very low during embryogenesis (TPM <1) but rspol.L appears to be dominant. Similarly, rspol.L is more strongly expressed in adult tissues such as brain, intestine, and spleen, showing DE patterns. (F) Expression profiles of ryk homeologs are categorized as HCDE in both embryos and adult tissues, in which the S gene is dominant.

#### Suppl. Fig. 7. Transcriptomic analyses of Wnt signaling-related genes categorized in EC/M-neg

(A) Expression profiles of *apcdd1* show dominant expression of *apcdd1.L* during early embryogenesis (eggs to st10) and in ovary. (B) Expression profiles of *dkk3* homeologs show DE patterns in both embryos and adult tissues. *dkk3.L* is dominantly expressed in embryos and many tissues. However, it should be noted that *dkk3.S* is more strongly expressed in heart. (C) Expression profiles of *frzb* homeologs show HCSE patterns in both embryos (Clutch U) and adult tissues (two clutches). However, *frzb.L* shows higher expression in brain and heart, and *frzb.S* shows higher expression in spleen. (D) Expression profiles of *kremen1* homeologs in adult tissues are categorized as HCDE, in which *kremen1.L* is more strongly expressed in many adult tissues such as brain and testis. (E) *notum1.S* is more strongly expressed during development, resulting in HCDE. However, *notum1.L* is

more strongly expressed in brain, eye, and testis. Interestingly, expression levels of *notum1* homeologs in lung show a high inter-clutch variation. (F) Expression profiles of rnf43 homeologs in embryos and adult tissues show HCDE and NCSE profiles. *rnf43.S* is more strongly expressed in embryos and in intestine, ovary, and skin. However, rnf43.L is more strongly expressed in heart. (G) Expression profiles of sfrp5 homeologs show NCSE patterns with changing the dominant homeolog from S to L around st30 during development, but HCSE patterns in adult tissues. (H) Expression profiles of sfrpx homeologs are categorized as DE in both embryos and adult tissues. *sfrpxS* is more strongly expressed, especially in oocytes, blastula to gastrula stages (st8-10), and ovary. (I) Expression profiles of shisal homeologs show that *shisal* L has stronger expression from oogenesis stage (0012) to blastula stage (st9) and in ovary (HCDE in embryos). (J) Expression profiles of *shisa2* homeologs show L-dominant HCDE patterns in both embryos and adult tissues. (K) Expression profiles of sostdc1 homeologs in embryos are categorized as NCSE at developmental stages. sostdc1.S is dominantly expressed in gastrula stages (st10, 12), while *sostdc1.L* expression increases from st15 and, at the same time, sostdc1.S expression starts to decrease. In adult tissues, sostdc1 homeologs show HCDE (Clutch T) and HCSE (Clutch U) profilles. (L) Expression levels of trabd2b (tiki2) homeologs are very low especially in Clutch U, although they show a HCDE profile with stronger expression of the L gene in Clutch T. In adult tissues. *trabd2b* homeologs show NCSE profiles. (M) Expression profiles of *tpbg* homeologs in embryos are HCDE, in which tpbg.S show higher expression from eggs to st10. tpbg.S is also more strongly expressed in ovary and testis (Clutch T), although tpbg is categorized as HCSE in adult tissues. (N) Expression profiles of wifl homeologs are HCDE in adult tissues. wifl L show dominant expression in some adult tissues, intestine, kidney, ovary, and spleen. (O) Expression profiles of *znrf3* homeologs are categorized as NCDE at developmental stages but HCSE (Clutch T) or HCDE (Clutch U) in adult tissues. *znfr3.L* has stronger expression from egg to blastula (st9).

# Suppl. Fig. 8. Transcriptomic analyses of Wnt signaling-related genes categorized in CP

(A) Expression profiles of axin1 show L gene-dominant HCDE patterns in adult tissues, whereas they

show a S gene-dominant HCDE pattern in embryos of Clutch U. (B) ccdc88c.L is dominantly expressed in embryos and adult tissues, resulting in DE profiles. (C) csnklal homeologs also show L gene dominant expression profiles in embryos and adult tissues. (D) Expression profiles of csnkld homeologs are also HCDE in embryos with stronger expression of the L gene. In adult tissues, they are similarly expressed (especially in Clutch U). (E) Conversely, csnk2al homeologs show S gene-dominant DE profiles in embryos and adult tissues. (F) Expression profiles of csnk2b homeologs also show S gene-dominant patterns in embryos and adult tissues, categorized as DE. (G) ctnnb1  $(\beta$ -catenin) homeologs are similarly expressed in embryos (also shown in Fig. 1B; HCSE), but differently expressed in adult tissues (HCDE). (H) ctnnbl1 ( $\beta$ -catenin-like 1) homeologs are also expressed during development and in adult tissues, but their expression levels are much weaker than those of *ctnnb1*. Similar to *ctnnb1*, *ctnnbl1*. S has slightly stronger expression. (I) Expression profiles of cxxc4 homeologs show L gene-dominant HCDE patterns in adult tissues and embryos of Clutch U. In embryos of Clutch T, cxxc4 homeologs show quite similar expression profiles (HCSE). (J) dvl1.L is dominantly expressed during development (NCDE) and in adult tissues (HCDE). However, dvl1.S has strong expression in some tissues such as brain, intestine, and lung. (K) dvl3.L is also dominantly expressed during development and in adult tissues (HCDE). Expression of *dvl3* homeologs is mainly in ovary and in eggs to st10 (maternal expression). (L) gsk3.L is more strongly expressed in embryos and all tissues, resulting in HCDE.

#### Suppl. Fig. 9. Transcriptomic analyses of genes involved in the Hh signaling

Expression profiles of *smo* (A), *hhip* (B), *gli1* (C), *gli2* (D), *gli3* (E), *prkaca* (F), *kif7* (G), *stk36* (H), *sufu* (I), *arl13b* (J) and *foxj1* (K). (A)in *smo* is categorized as HCDE in both embryos and adult tissues. The expression level of *smo.L* increases from blastula (st8) to tailbud stage (st25), consistent with the essential role of Hh signaling for neural patterning. L gene of *smo* is also dominant in many tissues, such as eye, heart, kidney, lung ovary and testis. Epigenetic analysis of *smo* is in Suppl. Fig. 10A. (B) *hhip.L* is dominantly expressed in both embryos and adult tissues. (C-E) Expression patterns of *gli* 

genes are highly correlated but in many developmental stages and adult tissues. During embryogenesis, all *gli* genes shows higher expression from gastrula stage, consistent with the importance of Hh signaling in neural patterning. The difference in their expression level of homeologs is detected in *gli2* (in both clutches). The S gene shows higher expression. In adult tissues, their expression levels are categorized as DE in *gli1* and *gli2*, but SE in *gli3*. (F) Expression patterns of *prkaca* homeologs are highly correlated (HC) in both embryos and adult tissues but expression levels are inconsistent between clutches. (G-H) *kif7.L* and *stk36.L* are singletons. These two genes are highly expressed during oogenesis and/or early embryonic stages. In adult, *kif7.L* is high in testis, *stk36.L* is high in ovary and testis. *sufu* homeologs are similarly expressed in both embryos and adult tissues, especially they are highly expressed in blastula stages (st8-9), ovary and testis. (I) *sufu* homeologs show correlated expression, categorized as HCSE. (J-K) Expression profiles of genes involved in ciliogenesis. *arl13b.L* is dominantly expressed during embryogenesis, especially around gastrula stages (st9-12) (J), while *foxj1.S* shows slightly higher expression during neurula stages (st12-15) (K).

#### Suppl. Fig. 10. Epigenetic analyses of smoothened gene

(A) ChIP-seq data at st10.5 showed stronger enrichment of H3K4me3 and p300 at the promoter and enhancer of *smo.L* than of *smo.S*. (B) Enhancer sequences are globally conserved between *smo.L*, *smo.S*, and *X. tropicalis smo*.

#### Suppl. Fig. 11. Transcriptomic analyses of HSPG-related genes

(A-E) Expression profiles of *glypicans*. Expression levels of *glypican* genes during embryogenesis are similar between homeologs (A-D and Fig. 9B), except for *gpc4* during neurulation stages, at which the L gene predominated (Suppl. Fig. 11C). In adult tissues, *glypicans* are highly expressed in brain, including *gpc3* and *gpc6*, which are not highly expressed during embryogenesis (B,E). Comparing each homeologous gene pair, L gene expression levels of *gpc1*, *gpc2*, and *gpc4* are higher in many tissues, categorized as HCDE, except *gpc4* in clutch U.

(F-I) Expression profiles of *ndst* and *sulf* genes. (F) *ndst1* shows HCSE pattern in adult tissues(G) L gene of *ndst2* is dominantly expressed in embryonic stages and adult tissues, categorized as HCDE. (H) During embryonic stages, *sulf1.L* is more highly expressed. Especially, *sulf1.L* was highly expressed at around the early neurula stage (st12). (I) Homeologous genes of *sulf2* show not highly correlated patterns (HC) but slightly similar expression patterns during embryogenesis. The expression levels are slightly different at tailbud stage. In the adult tissues, the gene shows HCSE pattern.

#### Suppl. Fig. 12. Transcriptomic analyses of Notch signaling genes

Expression profiles of dlc (A), notch1 (B), notch2 (C), notch3 (D), psen2 (E), psenen (F), furin (G), pofut2 (H), dtx5 (I), skp1 (J), nedd4 (K), mib1 (L), numb (M), hey1 (N), maml2 (O) and maml3 (P). (A) Expression levels of *dlc* homeologs are categorized as SE in both clutches. (B-D) Expressions of *notch1*, notch2, notch3 genes show highly correlated patterns in the adult tissues and the expression level was categorized as DE, except for notch2. During embryogenesis, notch3 homeologs show no-significant correlated expression patterns (NC). Expression of the S gene is a little bit high at st8 and st15-30, while that of the L gene is high at st10-15. (E-G) psen2, psenen and furin are categorized as HCDE in both embryos and adult tissues. Particularly, L gene of psen2 is dominant from oogenesis stage to st9 (E). (H) *pofut2* shows NCDE pattern during embryogenesis (L gene is dominant from egg stage to st12), but HCDE pattern in the adult tissues. (I-M) Expressions of cytoplasmic genes are categorized as HCDE (*dtx5* (I), *mib1* (L), *numb* (M)) or NCDE (*skp1* (J)), except for a gene categorized different group between clutches (nedd4 (K)). In both clutches, nedd4 shows different expression levels (DE). These results suggest that cytoplasmic factors also have been changed their expression pattern between each homeolog after genome duplication. (N-P) heyl shows NCSE pattern in developmental stages (N), and maml3 shows HCDE pattern in adult tissues (P). maml2 (O) shows inconsistent pattern between clutches but in both clutches the gene shows different expression levels between homeologs (DE).

## Suppl. Fig. 13. Transcriptomic analyses of Hippo signaling-related genes

(A-C) Expression profiles of transmembrane factors. (A) crb2 is categorized as HCSE during embryogenesis but HCDE in adult tissues. crb2.L is highly expressed in adult eye and heart. (B-C) fat1 and *fat2* show different expression levels between each homeolog in both embryos and adult tissues. In particular, expression level of *fat1.S* is higher than *fat1.L* in intestine (B) and expression level of fat2.S is higher than fat2.L during early neurula to late tailbad stage (st15-40) (C). (D-W) Expression profiles of cytoplasmic factors. (D) Although statistical results were not consistent between clutches, amot1.L is high during oogenesis and early embryogenesis stages and amot1.S is high after gastrulation (from st12) in developmental stages. In adult tissues, *amot1.S* is highly expressed in ovary and testis, categorized as NCSE. (E) ctnnal homeologs show HCDE pattern in both embryos and adult tissues. Expression level of *ctnnal*.S is higher than *ctnnal*.L during gastrula to early neurula (st10-15). The S gene is also dominant in many tissues, including heart, intestine, kidney, lung and skin. (F) frmd6 homeologs show no-significant correlated expression pattern (NC). frmd6.L is highly expressed during blastula (st8-9). (G-H) Expression level of *llgl1* (G) and *llgl2* (H) is particularly high during blastula (st8-9). *llgl2* is also highly expressed in ovary. Particularly, *llgl1* is categorized as NCSE. (I) Both L and S gene of *mobla* is maternally expressed. They show highly correlated expression patterns (HC). (J) mob1b shows NCSE pattern. (K-O) Homeologs of nf2 (K), prkci (L), ptpn14 (M), rassf2 (N) shows different expression levels (DE), and homeologs of sav1 (O) show NCSE pattern at least in one clutch. nf2 (K), prkci (L), ptpn14 (M), rassf2 (N) and sav1 (O) are highly expressed during blastula (st8-9) and early gastrula (st10). (P) scrib shows HCDE pattern in embryos and adult tissues. Especially, scrib.L is highly expressed in ovary. (Q-R) stk3 (Q) and stk4 (R) shows HCDE pattern at least in one clutch. (S) Homeologs of *tjp2* show different expression levels (DE). *tjp2.L* is highly expressed during neurula (st12-20). (T) Expression levels of tjp3homeologs are different (DE). (U) wwc1.S is highly expressed during blastula (st8-9), categorized as NCDE. (V-W) Genes of wwc2 and wwc3 are categorized as HCDE. Expression level of wwc2.S is higher than wwc2.L during blastula and neurula (st8-15) and many adult tissues such as lung, heart and kidney (V). Expression level of wwc3.L is higher than wwc3.S in heart and lung (W).

(X-Z) Expression profiles of nuclear factors. (X) *taz.L*, a singleton, is strongly expressed throughout oogenesis to early embryogenesis (oo12-st40) and in ovary. (Y-Z) *tead1* and *vgll4* show different expression level at least in one clutch. *tead1.S* (Y) and *vgll4.L* (Z) are highly expressed compared to each homeolog during blastula to early gastrula (st8-10).

# Suppl. Fig. 14. Expression profiles of yap1 and taz in X. tropicalis

In contrast to *X. laevis* (Suppl. Fig. 13X), expression of *X. tropicalis taz* is highly specific in early embryonic stages and greatly decreases at the early neurula stage (st13). On the other hand, *yap1* is continuously expressed during *X. tropicalis* development similarly to that in *X. laevis* (Fig. 12J).

# Suppl. Fig. 15. Comparison of expression profiles of TLE/Groucho genes between *Xenopus tropicalis* genome and *Xenopus laevis* L and S subgenomes

Expression profiles of TLE genes during embryonic development are compared between *X. tropicalis* genes (A), *X. laevis* L genes (B), and *X. laevis* S genes (C). For comparison, all examined stages are aligned and the same abscissa is used for each species. For *X. laevis* genes, averages of tpm values in Clutch T and U are shown in graphs.

Wnt	Fzd	Extracellular/	Extracellular/		
ligands	receptors	Membrane,	Membrane,	Cytoplasmic (28)	Nuclear (4)
(21)	(10)	Positive (13)	Negative (32)		
wnt1	fzd1	lrp5*	frzb	dvl1	lefl
wnt2	fzd2	lrp6	frzb2	dvl2**	tcf7l1 (tcf3)
wnt2b*	fzd3	ror1	sfrp1	dvl3	tcf7l2 (tcf4)
wnt3	fzd4	ror2	sfrp2	frat1(GBP)	tcf7 (tcf1)*
wnt3b	fzd5	ryk	sfrp4*	gsk3a	
wnt4	fzd6	porcn*	sfrp5	gsk3b	
wnt5a	fzd7	wls	sfrpx	apc	
wnt5b	fzd8	rspo1	dkk1	apc2	
wnt6	fzd9	rspo2	dkk2	axin l	
wnt7a	fzd10	rspo3*	dkk3	axin2	
wnt7b		ndp	dkkx*	ctnnb (β-catenin)	
wnt7c		lgr4	wif	ctnnbl (β-catenin-like)	
wnt8a		lgr5	cer	cxxc4 (Idax)	
wnt8b			sostdc1	ccdc88c (xDal)	
wnt9a			igfbp4	nkd1	
wnt9b			shisa1	dact1 (dapper/frodo)	
wnt10a			shisa2	nxn	
wnt10b			shisa4*	ppp2ca*	
wnt11a			shisa6	ppp2cb	
wnt11b*			shisa7	csnk1a1	
wnt16			shisa9	csnk2a1	
			apcdd1	csnk2a2	
			kremen1	csnk2b	
			kremen2	csnk1d	
			tpbg	csnk1e	
			tpbgl	csnk1g1	
			trabd2a (tiki1)*	csnk1g2*	
			trabd2b (tiki2)	csnk1g3	
			znrf3		
			rnf43		
			notum l		
			notum2*		

Supplementary	Table 1.	Wnt si	gnaling	pathway	related	genes	analyze	d in	this	study
				p		<b></b>			****	

\*Singletons (12/108). \*\*RNAseq data was not found in a homeologue due to the loss of gene model.

Liganda (2)	Receptor/Membrane	Cytoplasmic/Cilia/Nuclear
Ligands (3)	factors (4)	factors (11)
shh	ptch1	gli1
dhh	ptch2	gli2
ihh	smo	gli3
	hhat*	stk36 (fu)*
	hhatl	sufu
	hhip	prkaca
		kif7*
		arl13b
		foxj1

Supplementary Table 2. Hh signaling pathway related genes analyzed in this study.

\*Singletons (3/18)

Core protein (10)	Enzyme (6)
gpc1	ndst1
gpc2	ndst2
gpc3	ndst3
gpc4	ndst4
gpc5	sulf1
gpc6	sulf2
sdc1	
sdc2	
sdc3	
sdc4	

Supplementary Table 3. HSPG related genes analyzed in this study.

Ligands/Receptors	Extracellular/Membrane	Cytoplasmic	Nuclear factors
(8)	factors (12)	factors (22)	(6)
dlc (dll2)	psen1	cull	rbpj (Su(H))
dll1	psen2	dtx l	maml1
dll4**	psenen	dtx2	maml2
jagl	aphla	dtx3	maml3
jag2	ncstn	dtx3-like1*	hey1
notch1	adam10	dtx31-like*	hey2*
notch2	adam17	dtx4*	
notch3	pofut1*	dtx5	
	pofut2	fbxw7	
	furin	itch	
	lfng	skp1	
	rfng*	nedd4	
		nedd4l	
		mib1	
		mib2	
		neurl1	
		neurl1b	
		nrurl2*	
		neurl3	
		neurl4*	
		numb	
		numbl	

Supplementary Table 4. Notch signaling pathway related genes analyzed in this study

\*Singletons (8/48). \*\* RNAseq data was not found in a homeologue due to the loss of gene model.

Membrane factors (7)	Cytoplasmic factors (36)	Nuclear factors (5)
dchs1	amot	yap1
dchs2	amotl1	taz*
crb1*	amotl2	tead1
crb2	ctnna1	tead4
crb3	ctnna2	vgll4
fat1	dlg1	_
fat2	dlg4	
	scrib	
	llgl1	
	llgl2	
	ptpn14	
	<i>stk3 (mst2)</i>	
	stk4 (mst1)	
	savl	
	lats1*	
	lats2	
	mobla	
	moblb	
	limd1 (aiuba)*	
	nf2	
	frmd6	
	wwc1	
	wwc2	
	wwc3	
	pard6b	
	pard6g	
	prkci (aPKC)	
	rassfl	
	rassf2	
	rassf3	
	rassf4*	
	rassf5	
	rassf6	
	tjpl (zol)	
	tjp2 (zo2)	
	tjp3 (zo3)	

Supplementary Table 5. Genes in the Hippo signaling pathway analyzed in this study

\*Singletons (5/48).

 
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 1.97 5.85 2.06 3.32 st35.U2 6.25 0.76 1.12 7.27 1.31 1.81 7.85 0.63 0.01 0.63 0.01 0.63 0.01 0.63 0.01 1.41 st35.U2 1.53 1.52 1.53 1.52 1.53 1.54 1.52 1.54 1.52 1.55 1.54 1.55 0.31 0 140.U 0.82 0.5 0.41 13.12 13.42 0.04 23.31 3 3 HSPG\_Care protein HSPG\_Enzyme HSPG\_Enzyme HSPG\_Enzyme HSPG\_Enzyme HSPG\_Enzyme xt30.U 4.01 0.49 0.11 7.91 1.63 0.02 0.33 10.56 0.89 14.34 14.1 0.61 0.02 1.15 12.23 xt30.U 4.32 13.79 0 114.91 5.56 2.17 0.08 0.1 1.24 st40.U 73.51 60.02 5.34 9.34 egg.T st08.T 0 0.48 0.16 0.66 0.59 4.05 31.03 0.66 st15.U 154.66 53.44 0.38 gene n dic.L di1.L di4.L Notch signaling\_Ligands-Receptors Notch signaling\_Ligands-Receptors Notch signaling\_Ligands-Receptors 4 18

Alexis by a lange is a part of the second of	picli         0.03         0.77         1.28         0.64         0.62         1.03         1.77         0.24         0.25         0.24         0.24         0.24         0.24         0.24         0.24         0.24         0.24         0.24         0.24         0.24         0.27         0.24         0.27         0.24 <th0.24< th="">         0.24         0.24         <th< th=""><th><math display="block"> \begin{array}{cccccccccccccccccccccccccccccccccccc</math></th><th><math display="block"> \begin{array}{cccccccccccccccccccccccccccccccccccc</math></th><th><math display="block"> \begin{array}{cccccccccccccccccccccccccccccccccccc</math></th></th<></th0.24<>	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$
Higos Signita, C. Acquisance Higos	dgil         25.6         6.6.0         8.6.0         22.8.0         4.8.0         15.8.0         4.8.0         23.3.2         4.8.0         15.8.0         4.8.0         15.8.0	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	0.07         0.05         0.77         21.19         21.4         3.11         9.10         2.27         4.64         3.17         3.18         1.0         0.0           26.07         0.05         0.77         21.19         21.4         3.11         9.10         2.27         4.64         3.17         3.18         1.0         0.0           26.07         106         11.4         11.6         0.07         21.19         2.21         2.06         3.01         3.01         1.0         0.0           26.07         106         11.26         0.17         0.17         0.11         0.61         0.62         0.00	0         0

Wat signaling Wat ligands	gene name brail wrt1 I 0	in.T eye.T he	art.T intestine. kidney.T	iver.T lung.T m	uscle.T ovary.T par	Acreas skin.T spleer	en.T stomach. testis.T gene nam	brain.T eye.T he 12.08 6.62	art.T intestine. kidney.T 793 4.82 11.93	T liver.T lung.T	muscle.T ovary.T pa 1.55 1.62	ancreas skin.T sple 0.71 3.87 10	en.T stomach. testis.T gene 47 3.2 7.42 wnt11	ame brain.U eye.U	heart.U intestine.I k	idney.U liver.U lung.U 0.02 0.02	muscle.U ovary.U	pancreas skin.U	spleen.U stomach. tes	its.U gene name br 0.14 wrt1 S	rain.U eye.U heart.U 7.52 3.57 2.83	intestine: kidney.U	liver.U lung.U 1.28 3.59	muscle.U ovary.U pan 1.57 0.15	reas skin.U sple	en.U stomach.U 4.19 1.52	testis.U 1.38
Wnt signaling_Wnt ligands	wnt2.L 3	3.09 0	0 0 0	0 0	0 0.05	0 0	0 0 4.07 wnt2.S	4.75 0	0 0.11 0.09	0 0.05	0.13 0.08	0 0.11	0 0.08 0.33 wnt2.	2.56 0	0 0.05	0 0	0 0 0	0 0.05	o o	0.17 wnt2.S	4.04 0.09 0	0 0.07	0 0	0 0.08	0 0	0.08 0.06	0.07
Wnt signaling_Wnt ligands Wnt signaling_Wnt ligands	wnt2b.L 1 wnt3.L 3	1.73 2.9 3.07 0.07	1.74 7.76 0.72	0.59 13.19	0 0.05	0.07 0 0.5	0.52 2.94 1.21 0.15 0 0 wnt3.S	0.26 0	0 0 0.14	0 0	0 0	0 0	0 0 0 wnt31	L 1.17 2.15 6.42 0	0.59 2.73	0.3 0.18 20.	1 0 0	0.38 0.16	1.23 1.99	0.08 0.09 wnt3.S	0.35 0 0	0 0.2	0 0	0 0	0 0	0 0	0
Wnt signaling_Wnt ligands	wnt3a.L 2	2.08 1.86	0.02 0 0.03	0.05 1.31	0.04 0	0 3.71	0 0.01 0.11 wnt3a.S	0 0.17	0 0 0	0 0.1	0 0	0 1.83	0 0 0.18 wnt3a	L 0.49 0.2	0.01 0	0.01 0 0.	6 0.01 0	0.01 2.63	0 0	0 wnt3a.S	0.19 0 0	0 0	0 0.09	0 0	0 1.2	0 0	0
Wnt signaling_Wnt ligands Wnt signaling_Wnt ligands	wnt4.L 3 wnt5a.L 2	3.76 6.07 2.38 4.49	0.81 0.89 9.27 4.8 7.85 10.78	0 2.1	0.49 0.12	0 6.33	0 5.51 7.51 wnt4.S 2.45 1.1 0.45 wnt5a.S	3.49 4.05 3.15 4.93	1.35 0 2.18 1.11 1.22 3.51	0.32 9.76	1.03 0.09 0.72 2.8	0.07 4.11 0	13 1.19 0.85 wnt4. 64 1.3 1.61 wnt5a	. 4.27 4 L 1.2 1.78	0.46 0.85	7.17 0 1.2 5.18 0.25 2.8	3 0.06 0.11 9 0.43 0.08	0.11 12.38 0.35 0.2	0 5.6	3.58 wnt4.S 0.22 wnt5a.S	1.57 3.24 1.18 1.16 1.29 0.57	0.45 1.98	0 0.11	0.28 0 0	1.27 7.33 1.18 0.37	0.09 0.88	0.24
Wnt signaling_Wnt ligands	wnt5b.L 14	4.64 6.09	8.58 1.65 10.2	0.07 98.61	0.47 4.16	0.02 0.37 0.5	0.57 15.18 1.54 wnt5b.S	2.04 0.92	0 11.89 0.71	0.43 52.03	1.55 1.12	0.49 0.27 0	42 46.34 1.18 wnt5b	L 15.87 9.97	15.01 1.23	9.89 0.03 78.1	9 0.3 3.23	0.02 0.09	1.35 3.49	3.98 wnt5b.S	2.57 0.63 0.14	6.02 0.77	0.12 45.73	1.37 1.33 0	0.25 0.18	0.61 3.15	0.51
Writ signaling_Writ ligands	writ7a.L 14	4.67 6.4	0.16 0 3.44	1.12 3.28	0 0.14	0 5.02 7.	7.46 0 0.14 write.s	13.88 8.64	0.29 0.38 0.45	0.21 0.29	0.09 0.57	0.04 4.55 0	85 0.14 0.99 wnt7a	L 37.14 12.8	0.58 0.08	4.95 0.74 1.7	6 0.04 0	0.13 1.91	23.22 0	0.47 wnt7a.S	16.15 9.31 0.27	0.15 0.38	0.21 0.16	0.22 0.51 0	0.09 3.48	0.54 0.06	0.81
Writ signaling_Writ ligands	wnt7b.L 16	3.87 7.08	0.82 0.07 0.19	0 49.7	0.27 0	0.04 4.01	0 0.03 1.42 wnt7b.S	3.67 4.4	0 0.15 0.37	0 37.69	0 0	0 2.79	0 0 0 wnt7b	L 7.76 1.14	0.06 0	0.14 0 18.1	3 0 0	0.13 3.31	0.05 0.04	0 wnt7b.S	2.79 1.16 0	0 0 0	0 19.35	0 0 0	0 2.47	0 0 22	0 57
Wnt signaling_Wnt ligands	wnt8a.L 0	0.18 0	0 0 0	0 0	0.41 0	0 0	0 0 1.24 wnt8a.S	0 0	0 0 0	0 0	0 0	0 0	0 0 0.34 wnt8a	L 0 0.18	0 0	0 0	0 0.35 0	0 0	0 0	0.22 wnt8a.S	0 0 0	0 0	0 0	0.06 0	0 0	0 0	0.06
Writ signaling_Writ ligands Writ signaling_Writ ligands	writ9a.L 2	2.27 3.13	0.11 0.61 0.19	0.99 2.26	0.85 0.08	0.54 0.31 0.	0.1 0.05 0.03 Writsb.S 0.65 1.47 1.1 writ9a.S	1.06 4.05	6.05 0.82 12.43	1.2 6.02	0.98 0	0.4 0.44 0	47 1.8 1.63 wnt9a	L 3.76 0.03 L 0.68 1.03	2.28 0.35	7.59 0.22 2.5	7 1.28 0	0.33 0.13	0.12 0.02 0.52 0.29	0.05 wnt9a.S	12.16 1.53 U 0.47 1.16 0.89	0.19 0	0.2 0.67	0.58 0 0	1.13 0.1	0.27 0.17	0.1
Writ signaling_Writ ligands	writ9b.L	0 1.18	0.14 0.26 0.44	0 0.07	0.16 0	0 0 0.1	0.14 0 0 wnt9b.S	0.28 0.2	0.68 0.26 18.77	0 0.26	0.16 0.03	0.1 0.08 0	24 0.16 0.53 wnt9b	L 0 2.38	0.1 0	1.68 0	0 0.1 0.09	0 0	0 0.13	0.51 wnt9b.S	0.09 0.71 0.67	0.27 52.1	0.06 0.04	0.07 0.03 0	0.04 0.09	0.06 0.02	0.17
Wnt signaling_Wnt ligands	wnt10b.L 0	0.1 2.15	0 0 0.04	0 0	0.25 0	0 26.64	0 0 0 wnt10b.S	2.96 3.55	0.62 0.28 0.45	0.44 0.17	0.24 1.21	0.02 20.48 0	45 0.08 0.23 wnt10	o.L 0.66 0.13	0 0	0 0	0 0.16 0	0.02 38.5	0 0	0 wnt10b.S	1.09 0.45 0.3	0.11 0.41	0.1 0.24	0.13 0.06 0	0.06 31.57	0.08 0.09	0.02
Wnt signaling_Wnt ligands Wnt signaling_Wnt ligands	wnt11a.L 9 wnt11b.L 0	9.75 8.18 0.31 0	1.95 2.74 22.41 0.07 0.32 6.3	0.11 1.01	4.47 0 0 134.58	0.06 16.18 4.8 0.03 0.12 0.4	4.81 1.45 1.12 wnt11a.S 0.69 0 0.38	1.82 1.99	0.96 0.58 0.98	0 0.78	0.35 0	0 1.8 2	93 0.21 0 wnt11 wnt11	a.L 8.39 5.27 b.L 0.34 0.21	1.33 4.18 0.1 0.11	16.07 0.3 2.8 5.71 0.14 0.1	3 2.76 0 2 0.05 168.46	0.08 6.69	3.04 1.66 0.37 0.03	0.43 wnt11a.S 0.71	1.08 2.43 0.35	2.21 2.33	0 0.81	1.32 0 0	0.05 0.76	5.61 0.51	0.09
Writ signaling_Writ ligands Writ signaling_End receptors	wnt16.L 2	2.94 3.17	0 0.13 0.45	0 0.14	0 0	0 0 0.1	0.14 0 0.13 wnt16.S	0.84 6.47	0 0 0	0 0.07	0 0.1	0 0.13	0 0 1.32 wnt16	L 0.14 1.49	0 0.07	0 0	0 0 0	0 0	10.05 2.2	0 wnt16.S	0.14 0.75 0	2 60 19 10	0 0	0 0	0 0	0 0	0.09
Wnt signaling_Ezd receptors	fzd2.L 3	3.11 3.68	1.13 0.25 0.94	0.82 5.66	6.26 0	0.05 0.24 0.7	0.37 0.77 0.94 fzd2.S	2.73 4.19	3.87 1.52 3.68	0.3 8.64	6.19 0.65	0.15 0.95 2	03 0.55 2.35 fzd2.L	3.46 5.27	0.76 0.56	1.17 0.87 3.2	8 3.2 0.12	0.11 0.51	0.37 0.39	1.62 fzd2.S	2.51 5.85 4.16	0.82 4.25	0.33 5.61	6.76 0.95	0.3 0.54	2.85 0.86	5.98
Whit signaling_Fzd receptors	fzd4.L 1	1.01 1.56	3.98 0.85 2.34	0.1 1.2	0.13 1.37	0.06 0.31 0.7	0.34 0.34 0.74 fzd4.S	5.33 3.3	7.23 1.33 2.82	0.5 5.41	2.65 9.33	0.27 0.62 1	47 4.91 3 fzd4.L	1.47 2.64	6.24 0.17	2.57 0.31 0.	1 0.32 0.3	0.33 0.72	0.69 0.24	0.76 fzd4.S	4.85 5.12 5.98	1.15 3.14	0.83 2.27	2.13 3.55 0	0.61 0.56	2.22 4.57	5.34
Writ signaling_Fzd receptors Writ signaling_Fzd receptors	fzd5.L 3 fzd6.L 3	3.59 5.15 3.88 11.93	1.81 38.95 12.5 3.73 3.85 8.92	12.67 1.36 2.06 10.57	0.06 1.75 0.7 5.47	0.33 9.36 0.1 0.89 20.04 1	0.11 22.69 5.15 fzd5.S 1.7 9.85 7.99 fzd6.S	1.74 2.46 3.27 10.52 1	0.13 20.91 2.8 11.05 5.67 9.6	9.18 9.32 0.62 6.81	0 0.8	0.76 0.29 0.67 15.99 1	0 8.05 0.64 fzd5.L 93 2.71 20.73 fzd6.L	2.08 3.75 4.55 8.96	0.49 30.26 2.74 1.79	4.82 1.86 1.3 8.98 2.21 5.	8 0 0.28 1 0.84 4.42	0.48 10.35	0.04 8.57 2.25 9.82	0.68 fzd5.S 6.7 fzd6.S	1.05 1.6 0.06 4.26 9.83 8.37	8.13 2.87 2.97 9.34	1.48 5.34 0.8 3.32	0.05 0.29 0	0.38 0.62 .23 13.5	0.01 3.3 2.01 5.63	0.57
Wnt signaling_Fzd receptors	fzd7.L 5	5.35 2.63	3.62 0.36 9.72	0.32 13.44	0.16 41.39	0.15 0.92 4.1	4.14 0.49 3.27 fzd7.S	3.27 1.32	4.4 0.16 0.55	0 6.8	0.07 1.55	0.19 0.34 0	12 0.13 4.72 fzd7.L	5.8 5.47	1.51 0.27	8.33 0.66 5.1	1 0.44 28.35	0.07 0.26	6.72 0.6	1.49 fzd7.S	4.2 2.68 1.82	0.15 0.81	0.08 2.37	0.04 0.97 0	0.08 0.25	0.53 0.1	2.45
Whit signaling_Fzd receptors	fzd9.L 3	3.07 4.02	15.65 1.99 2.35	0.88 1.51	0.72 0.48	0.19 0.14 0.3	5.47 1.53 3.17 fzd9.S	0.98 0.47	0.62 1.52 0.17	0.1 0.87	0.05 0.04	0.08 0 0	27 1.72 1.49 fzd91	7.43 8.07	11.04 0.94	3.54 0.52 2	4 0.78 0.06	0.6 0.26	13.58 1.47	1.1 fzd9.S	3.07 1.61 0.7	0.93 0.83	0.49 1.59	0.2 0.04 0	1.49 2.23	0.3 1.5	0.57
Writ signaling_Fzd receptors Writ signaling_Extracellular-Membrane Positive	fzd10.L 6 lrp5.L 11	5.32 3.07 1.74 15.82	0.3 0.19 4.57	20.33 0.82 9.93 28.46	0.85 0.28 6.14 49.7	9.25 21.62 0. 1.74 15.7 11.	0.8 16.74 3.55 fzd10.S 1.14 5.64 5.33	6.01 1.43	0 0.4 0.64	15.35 0.73	0.05 0.73	9.34 1.19 3	24 1.1 0.8 fzd10. lrp5.L	L 8.87 3.29 5.55 10.22	0.16 0.32 8.44 4.46	5.79 25.34 0.7 13.66 3.06 9.6	4 0.3 0.36 6 3.67 1.89	3.87 17.83 2.05 12.07	0.86 14.99 10.83 3.93	4.49 fzd10.5 3.3	5.47 1.25 0.07	0.1 0.44	16.2 0.38	0.07 0.25 3	1.98 0.7	3.13 0.77	0.44
Writ signaling_Extracelular-Membrane Positive Writ signaling_Extracelular Membrane Positive	Irp6.L 3	3.86 3.17	2.96 3.65 3.21	0.63 4.14	0.45 4.13	0.21 1.66 2.1	2.13 1.48 6.77 Irp6.S	9.31 7.79	5.35 6.94 7.18	2.83 8.72	0.59 5.47	0.4 3.61	7.8 2.75 11.73 lrp6.L	6.14 5.64	2.75 2.6	4.1 1.56 1.2	3 0.67 4.34	0.36 1.17	3.5 1.52	5.15 lrp6.S	14.64 12.47 5.62	9.51 12.3	5.89 2.59	0.98 4.2 0	1.93 2.59 1	1.82 4.46	11.66
Wnt signaling_Extracellular-Membrane Positive	ror2.L 3	3.97 2.45	15.13 2.11 2.34	0.57 1.79	0.28 0.05	0.3 0.98 4./	4.03 1.03 4.14 ror2.S	5.52 0.9	2.24 4.1 2.02	0.57 0.94	0.31 3.16	0.21 0.54 3	16 3.17 1.92 ror2.L	2.1 1.46	4.17 0.68	1.28 0.09 1.	6 0.32 0.04	0.72 0.23	4.64 0.68	1.71 ror2.S	3.98 0.31 0.8	0.9 1.02	0.08 0.85	0.16 0.33 0	0.28 0.35	2.5 1.05	0.63
Writ signaling_Extracellular-Membrane Positive Writ signaling_Extracellular-Membrane Positive	ryk.L 7 porcn.L 55	7.15 7.37 5.09 29.61	7.59 8.3 10.02 8.71 9.03 18.7	4.55 12.04 6.17 13.8	3.13 38.42 5.4 45.61	1.03 4.44 9.8 1.91 6.85 15.	9.89 3.58 4.93 ryk.S 5.33 5.51 19.37	18.21 13.96	12.9 10.81 15.96	3.4 19.95	3.78 109	1.64 5.87 16	47 5.83 12.46 ryk.L porcn	10.6 9.06 L 118.8 50.3	6.53 7.65 18.9 11	13.55 5 9.1 32.71 26.26 11.6	2 4.26 17.66 8 7.91 257.23	1.25 3.53 2.31 8.35	10.3 3.42 24.06 9.16 8	3.78 ryk.S 19.29	32.22 22.14 12.67	8.3 20.09	6.17 12.37	2.96 98.82 1	.39 4.15 2	0.65 5.65	18.04
Writ signaling_Extracellular-Membrane Positive	wis.L 29	9.71 19.7 7.75 4.05	4.56 5.21 11.64	1.49 16.7	2.2 38.82	0.86 9.59 3.7	3.31 4.65 15.94 wis.S	19.02 15.76 2	24.36 3.23 9.68	1.1 22.44	0.93 17.8	0.3 8.1 6	18 2.7 4.53 Ws.L	25.31 20.99	10.43 2.82	13.36 0.66 7.8	5 1.41 14.12	0.78 6.14	2.05 2.54 1	4.11 wis.S	15.04 12.45 11.82	1.23 8.31	0.63 9.39	0.75 6.89 0	1.58 3.12	5.85 1.38	5.71
Writ signaling_Extracelular-Membrane Positive	rspo2.L 12	2.01 4.47	0.69 0.11 0.53	0.06 6.79	0 0.29	0.03 0.44 0.4	0.61 0.29 0.23 rspo2.S	4.04 1.51	0.33 0.07 0.13	0 2.32	0 2.95	0.04 0.5	0 0 0.07 rspo2	14.93 7.97	0.42 0.22	0.61 0 4.	9 0.09 0.64	0.08 0.23	0.75 0.47	0.04 rspo2.S	6.72 1.87 0.35	0 0.7	0 2.39	0 5.09	0.4 0.4	0 0.04	0.15
Writ signaling_Extracelular-Membrane Positive Writ signaling_Extracelular-Membrane Positive	Igr4.L 3	18.9 2.33 3.46 4.28	4.19 8.86 3.55	1.14 1.09 3.28 0.17	0.08 21.77	0.44 2.67 1.1 0.85 3.51 0.*	1.13 4.93 1.18 0.72 15.59 4.92 lgr4.S	4.12 6.7 1	14.24 13.05 6.04	1.9 2.85	0.63 5.49	0.58 6.99	rspos 1.4 10.58 7.36 lgr4.L	5.57 6.13	2.9 4.59	5.36 3.76 0.0	4 0.29 0 7 0.12 4.53	1.36 3.44	0.04 1.78	1.97 lgr4.S	5.85 8.72 9.87	16.46 8.28	2.93 1.75	1.13 3.42 1	.75 5.21	2 9.49	5.83
Writ signaling_Extracelular-Membrane Positive Writ signaling_Extracelular-Membrane Positive	Igr5.L 2 ndo.l 4	2.95 5.52	0.75 3.43 2.65	0.13 0.17	0.12 0.46	0.12 0.74 0.8	0.84 1.7 10.85 lgr5.S 0.2 1.39 1.63 ndo.S	1.78 7.16	0.55 2.41 0.72	0 0.98	0.26 0.04	0.01 1.22	0.1 3.26 1.59 lgr5.L 0 0.17 6.57 ndo.l	1.32 2.02	0.5 0.66	1.79 0.02 0.2	8 0.08 0.05	0.17 0.17	0.87 0.43	3.71 lgr5.S 1.07 ndn S	0.43 1.94 0.17	0.37 0.45	0 0.53	0.01 0 0	0.03 0.64	0.03 1.07	0.22
Wnt signaling_Extracellular-Membrane Negative	frzb.L 51	1.69 25.41	96.97 2.31 0.79	3.14 1.25	5.38 1	0 30.95 17.0	7.08 8.64 1.21 frzb.S	13.19 23.44	2.92 3.06 0.75	0.43 0.55	0.44 0.11	0.36 37.92 137	76 3.71 0.74 frzb.L	52.62 22.38	41.59 1.48	0.81 1.23 2.6	2 5.13 0.26	0.62 21.78	9.17 4.52	1.71 frzb.S	9.67 12.54 0.65	0.97 0.64	1.13 0.35	1.64 0.15 0	.36 31.13 8	13.93 1.62	0.39
Writ signaling_Extracelular-Membrane Negative	sfrp1.L 31	1.36 72.79	33.28 6.63 4.03	0.32 38.5	1 4.48	0.68 7.27 7.4	7.16 8.9 2.33 strp1.S	16.1 36.7 1	11.64 1.85 7.86	0 3.72	5.76 0	0.21 2.53 0	84 2.68 1.17 strp1.	40.1 80.19	30.41 9.47	7.89 1.1 80.6	5 1.02 9.88	1.96 4.73	14.25 7.34 5	57.99 strp1.S	33.27 54.53 9.13	1.02 8.81	0.71 3.48	8.15 0.14 0	1.26 1.54	1.55 1.25	1.41
Writ signaling_Extracellular-Membrane Negative Writ signaling_Extracellular-Membrane Negative	sfrp2.L 3 sfrp4.L 1	3.82 47.15 13.2 2.28	0.68 6.15 3.73 52 5.95 1.14	0 0.19	4.49 0.05 1.35 0	0.22 6.24 0.8	0.86 0.72 0.58 strp2.S 4.23 3.58 0	12.62 27.75	5.21 1.12 19.49	0.03 4.57	12.89 0.05	0.78 8.96 1	81 4.89 2.21 strp2. strp4.	. 2.61 66.46 6.37 0.45	1.47 7.35 13.24 7.04	1.41 0 0.4 0.35 0.25 2.4	6 4.17 0 2 1.38 0	0.91 4.61 0.4 0.74	0.84 0.59 3.5 1.44	0.38 strp2.S	10.98 30.14 5.65	0.7 11.22	0.22 5.45	6.45 0.02	1.6 6.16	1.42 3.1	0.83
Writ signaling_Extracellular-Membrane Negative	strp5.L 8	3.99 7.08	28.21 1.2 3.35	0.17 7.61	1.19 0	1.35 0.21 0.5	0.58 1.68 0.36 strp5.S	16.79 2.67 2	24.12 4.38 1.64	0 1.29	1.25 0.1	0.9 0 0	22 1.57 0.69 strp5.	4.94 3.97	10.59 0.71	2.07 0.1 4.0	5 0.55 0	2.01 0.09	0.39 0.51	0.03 strp5.S	7.31 0.72 7.53	1.33 0.69	0 1.23	0.21 0 1	.13 0	0.1 1.06	0.14
Wnt signaling_Extracelular-Membrane Negative	dkk1.L 0	0.75 12.81	0.91 0.59 1.3	0 4.95	0 0	0.58 2.04	0 0.43 0.35 dkk1.S	2.6 4.42	3.76 0 2.48	0 0.06	0 0	0.06 1.69	0.5 0 0 dkk1.i	1.51 17.44	2.28 1.04	2.05 0.09 2.9	6 0.09 0.08	0.73 1.87	0.09 0.96	0.54 dkk1.S	2.63 5.55 1.89	0.32 2.7	0 0	0 0.08	0 1.47	0.17 0.3	0.31
Writ signaling_Extracellular-Membrane Negative Writ signaling_Extracellular-Membrane Negative	dkk2.L 11 dkk3.L 16	1.37 18.66 5.79 51.51	8.54 2.68 10.91 26.36 12.16 12.37	0.06 1.48 1.14 25.75	3.69 0.04 1.29 2.93	0.69 2.99 10.5 1.08 4.84 6.	0.58 1.43 1.08 dkk2.S 5.19 5.98 4.45 dkk3.S	6.16 17.63 1 4.53 4.97 4	10.05 1.36 5.78 44.13 1.84 1.47	0 5.08	1.81 2.55 0.8 0.09	0.27 4.18 0 0.12 1.16 2	47 1.98 3.5 dkk2.1 41 1.03 0.69 dkk3.1	5.66 9.29 24.77 71.77	4.13 0.79 36.29 13.7	8.77 0.4 0.5 16.23 1.25 33.9	7 3.88 0 8 2.7 3.29	0.93 0.32 3.73 3.16	5.02 0.46 8.6 8.2	0.24 dkk2.S 6.11 dkk3.S	2.07 8.55 2.27 6.65 7.6 62.28	0.24 3.08 2.07 1.58	0 0.59	1.01 0.13 0 1.89 0.04 0	0.47 0.25 0.32 1.21	0.23 0.96 2.43 1.33	0.08
Writ signaling_Extracellular-Membrane Negative Writ signaling_Extracellular Membrane Negative	dkkx.L 0	0.85 0	0 0 0	0 0	0 0.2	0 0	0 0 0 0 dikkorp.S	0 0	0 0 0	0 0	0 0	0 0	0 0 0 dkkx.	6.73 0	0 0	0.17 0	0 0 0.77	0 0	0.2 0.14	0 dikkxp.S	0 0 0	0 0	0 0	0 0	0 0	0 0	20.94
Wnt signaling_Extracellular-Membrane Negative	cer1.L 0	0.12 0.07	0 0 0	0 0	0 0	0 0.14	0 0 0.15 cer1.S	2.07 1.03 3	32.97 0 0	0 0.1	0 0.54	0.1 0	0 0.07 0.47 cer1.L	0.08 0	0 0	0.05 0	0 0 0	0 0	0.05 0	0 cer1.S	1.1 0.3 5.12	0.2 0.23	0 0	0.07 0 0	0 1.50	0 0.05	0
Writ signaling_Extracellular-Membrane Negative Writ signaling_Extracellular-Membrane Negative	sostdc1.L 11 igfbp4.L 7	1.52 17.17 7.91 21.62 :	9.91 2.54 3.55 21.81 27.84 56.1	0.48 13.53 43.34 30.46	0.83 0.04 14.09 2.09	0.34 56.61 1.6 5.62 8.53 26.	1.61 5.59 3.19 sostdc1.S 5.12 19.93 12.75 igfbp4.S	15.52 7.71 9.09 47.04 5	9.96 2.27 2.11 54.13 23.49 517.66	0.19 12.2 698.53 63.01	1.66 0 5.96 1.11	0.29 27.27 0 2.99 11.18 18	07 3.43 0.52 sostdi 34 20.25 13.38 igfbp4	1.L 6.42 8.05 L 13.13 33.15	3.18 0.69 29.31 21.63	1.36 0.14 4. 90.09 174.96 36.7	7 0.34 0 '8 9.68 5.37	0.42 13.24 11.66 5.13	0.63 6.24 28.5 23.83 1	0.53 sostdc1.S 18.31 igfbp4.S	6.8 3.64 3.12 12.73 56.54 81.15	3.49 1.43 35.19 169.18	0.05 1.6 1457.75 63.01	1.41 0 1 5.57 0.92 5	1.16 5.71 1.03 5.05 1	0.33 4.56 4.74 20.22	0.04
Writ signaling_Extracellular-Membrane Negative Writ signaling_Extracellular-Membrane Negative	shisa1.L 0 shisa21 26	0.52 0.4	0 0.05 3.63	1.01 0.12	0 99.82	0.33 0 0.4	0.41 0 7.32 shisa1.S 2.08 2.71 4.78 shisa2.S	0.25 0.05	0 0 0	0 0	0 0.23	0.12 0	0 0 1.65 shisa 33 0.5 0.54 shisa	L 0.41 0.8	0.18 0	3.15 2.3 0.4	1 0.08 140.82 7 117.54 0.18	0.1 0.15	0.12 0.03	4.54 shisa1.S 1.69 shisa2.S	0.96 0.26 0.09	0 0.03	0 0	0 0.97 0 6.28 0.05 0	0.05 0.03	0 0	1.04
Writ signaling_Extracelular-Membrane Negative	shisa4p.L	0 0	0 0 0	0 0	0 0	0 0	0 0 0 shisa4.S	31 8.76 1	14.64 9.49 13.53	4.99 15.88	5.9 0.31	1.23 5.87 18	91 5.57 10.68 shisa-	pL 0 0	0 0	0 0	0 0 0	0.15 0.5	0 0	0 shisa4.S	40.27 12.62 22.47	11.75 16.3	13.05 13.68	9.89 0.72 1	.31 5.9 2	0.99 5.63	11.94
Writ signaling_Extracellular-Membrane Negative Writ signaling_Extracellular-Membrane Negative	shisa6.L 9 shisa7.L 4	9.95 0.89 4.11 0.72	0 0 0	0 0	0 0	0 0	0 0.02 0 shisa6.S 0 0 0.24 shisa7.S	35.46 4.86 3.65 0.38	0.27 0.12 0.69 0 0 0	0.55 1.37	0.05 0.03	0.02 0.07 0.04 0.07	0.1 0.42 0.31 shisai 0 0 0.21 shisai	L 11.55 0.17 L 2.85 0.06	0 0	0 0	0 0 0 0 0 0	0 0	0 0	0.05 shisa6.S 0.15 shisa7.S	26.26 1.84 0.23 4.39 0.22 0	0.04 0.39	0.01 0.94	0.05 0 0	1.03 0.26 1.03 0	0.08 0.11	0.05
Writ signaling_Extracellular-Membrane Negative Writ signaling_Extracellular-Membrane Negative	shisa9.L 15 kremen11	5.79 1.96 7.8 5.59	0 0 0.14	0 0	0 0	0 0 0.3	0.35 0 0.49 shisa9.S	4 0.34	0 0 0.82	0 0	0 0	0.03 0.05	0 0 0.11 shisas 05 0.05 2.27 kreme	L 5.25 0.39	0 0 578 018	0.2 0 4.2 0.57 8.3	0 0 0.11	0.07 0	0 0	0 shisa9.S	4.35 0.04 0	0 0.37	0 0	0 0	0 0	0 0.03	0
Wnt signaling_Extracellular-Membrane Negative	kremen2.L	0 2	0.12 0.16 0.18	0.1 0.06	0 0.04	0 8.21	0 0.02 0.44 kremen2.1	0.18 8.58	0.13 0 0.1	0 0	0 0	0 20.19 0	06 0 3.02 kreme	n2.L 0.06 1.58	0.04 0.05	0.1 0.16	0 0 0.04	0.02 11.38	0.08 0.06	0.18 kremen2.S	0.25 4.86 0	0 0.07	0 0	0 0	0 15.59	0 0.18	0.27
Writ signaling_Extracelular-Membrane Negative	tpbg.L 15	5.23 5	1.14 2.89 3.11	0.16 2.49	0.08 32.93	0.08 1.34 1.7	1.51 2.24 8.98 tpbg.S	10.77 6.89	2.37 1.47 5.74	0.29 1.47	0.22 79.91	0.09 2.72 0	1.4 1.12 58.63 tpbg.L	5.43 1.99	0.36 0.19	1.38 0.05 1.3	4 0.08 25.37	0.08 0.45	0.8 0.96	3.18 tpbg.S	5.09 2.55 0.57	0.25 2.65	0.14 1.12	0.17 8.43 0	1.02 2.05	0.35 0.29	3.64
Writ signaling_Extracellular-Membrane Negative Writ signaling_Extracellular-Membrane Negative	tpbgl.L 5 trabd2a.L (t# 3	5.53 3.32 3.65 3.03	0 0.54 5.14 2.85 0.64 0.95	0 0.86	0 0	0 0	0 1.13 1.49 tpbgl.S 1.26 1.06 8.84	19.39 5.77	0 2.57 3.26	0 0.85	0.34 0.1	0 0 7	49 0.72 0.71 tpbgLl trabd2	. 8.11 4.45 a.L.(t) 2.71 2.04	0 1.94	3.74 0 1.8 0.59 0.48 2.9	5 0 0 9 0.23 0.04	0.22 0	0 1.8	0 tpbgl.S 2.43	18.87 2.75 0.23	0.78 2.13	0 1.33	0.33 0 0	0.13	3.91 0.8	0
Writ signaling_Extracellular-Membrane Negative	trabd2b.L (t# 4	4.82 6.62	5.75 0.84 4.66	7.86 7.94	1.8 0	0.57 1.16 1.0	1.06 0.64 1.33 trabd2b.S	11 1.94 5.39	1.17 3.51 1.34	0.03 3.81	2.05 0.02	0.51 0.93 0	23 5.09 2.17 trabd2	b.L.(81 1.15 1.48	1.99 0.19	3.55 0.71 1.6	8 0.54 0	0.83 1.14	0.78 0.26	0.15 trabd2b.S (til	0.36 1.1 0.57	2.02 0.82	0.02 1.38	0.96 0.02 0	.97 0.52	0.07 0.81	0.06
Writ signaling_Extracelular-Membrane Negative	mf43.L 2	2.51 2.1	7.35 7.65 5.96	0.96 3.13	0.07 0.34	0.61 1.9 1.4	1.63 2.09 1.35 mf43.S	3.72 1.93	0.62 0.23 1.47 0.71 9.42 6.34	1.79 7.26	0.43 4.24	0.35 7.19 1	21 1.3 1.99 mf43.	3.32 1.41	4.35 6.66	5.95 0.3 3.6	9 0.04 0.04	1.17 2.32	1.44 2.55	0.35 mf43.S	6.59 2.46 0.54	10.51 6.55	3.44 3.39	0.61 2.16 0	1.48 3.67	1.11 1.43	1.48
Writ signaling_Extracellular-Membrane Negative Writ signaling_Extracellular-Membrane Negative	notum1.L 5 notum2.L 2	5.34 5.2 2.84 0.71	1.44 0.25 3.18 0.52 0.77 0.61	0.05 9.96 0.29 0.57	1.24 16.73 0.14 0.47	0.06 0.83 2.7 0 0.11 €	2.73 0.19 4.76 notum1.S 6.7 0.02 1.96	0.47 0.37	0.42 0.25 2.93	0.53 17.18	0.05 23.01	0.08 0.3 0	55 0.05 0.19 notum notum	1.L 2.18 1.64 2.L 3.18 0.81	0.9 0.14	2.21 0.23 7.3 0.67 0.31	2 1.18 1.22 0 1.28 0.13	0.06 0.18	1.87 0.11 3.49 0.18	0.35 notum1.S 0.47	0.07 0.1 0.29	0.07 1.42	0.38 3.07	0.03 2.83 0	1.09 1.03	0.31 0.04	0.07
Writ signaling_Cytoplasmic Writ signaling_Cytoplasmic	dvl1.L 41	1.45 10.55	5.36 13.63 4.73	0.93 25.71	1.36 0.05	1.51 7.54 0.7	0.75 6.4 8.33 dvl1.S	36.97 6.77	3.69 18.06 3.62	0.79 17.35	1.35 0.33	0.47 4.96 1	04 2.11 2.65 dvl1.L	49.53 12.39	4.25 18.84	5.37 0.61 15.8	7 1.48 0.09	2.79 5.16	2.2 9.67	7.35 dvl1.S	55.82 11.88 2.76	16.07 6.09	1.42 8.09	1.29 0.18 0	1.95 2.72	2.58 3.96	3.04
Writ signaling_Cytoplasmic Writ signaling_Cytoplasmic	dvl3.L 12	2.31 9.4	7.4 6.26 11.54	3 13.02	4.69 77.73	0.78 8.07 10.1	0.18 4.33 16.91 dvl3.S	10.42 7.36 1	11.13 4.19 7.19	2.07 9.82	6.93 37.51	0.84 5.27 7	68 2.63 16.28 dvl3.L	14.28 10.63	10.03 5.2	11.41 3.53 9.0	6 5.76 43.99	0.97 8.52	11.31 4.78 1	14.97 dvl3.S	10.75 6.63 11.01	3.61 7.25	2.53 7.51	7.59 12.86 1	.03 5	7.32 3.28	11.82
Wnt signaling_Cytoplasmic Wnt signaling_Cytoplasmic	frat1_L 6 ctnnbl1.L 17	5.22 11.39 7.65 10.94	2.44 5.23 7.93 10.29 9.2 12.7	0.7 5.2 4.87 13.41	1.32 37.59 4.15 50.14	1.16 2.47 3.4 1.36 6.49 14.	3.49 4.63 44.07 frat1.S 4.82 5.88 33.45 ctnnbi1.S	9.82 8.48 25.8 14.16 1	1.81 4.84 8.74 14.35 13.65 17.24	0.69 4.39 5.75 15.65	3.88 99.02 3.22 63.72	0.21 11.03 4 2.34 9.42 16	02 4.53 47.5 frat1.1 11 7.68 31.9 ctnnbl	18.85 17.89 I.L 13.53 8.53	10.92 10.07 5.35 6.91	14.69 3.1 4.9 9.91 2.83 11.3	7 17.69 57.53 5 3.93 24.83	2.2 15.35 1.15 9.34	10.82 11.19 9 8.85 4.8 1	8.35 frat1.S 10.11 ctnnbi1.S	10.71 9.96 2.33 24.97 14.77 8.21	9.44 14.73	2.35 3.77 4.57 13.7	5.64 61.33 0 4.97 38.1 1	1.98 9.85 1.44 10.84 1	7.46 9.55 5.48 5.46	69.86 19.43
Writ signaling_Cytoplasmic Writ signaling_Cytoplasmic	ctnnb1.L 171 csok1d1 93	1.99 76.93 2 3.15 52.41	52.69 104.61 73.88 35.8 37.63 48.2	25.33 102.24 14.89 48.79	10.08 69.24	8.65 70.29 68.6	8.66 70.35 54.82 ctnnb1.S 1.76 25.92 111.19 csnk1d.S	321.88 147.68 1 51.6 22.25 2	160.2 174.65 171.46 21.15 22.93 33.1	43.21 243.44	33.27 226.47 11.71 159.17	19.05 112.91 115	54 82.6 92.1 ctnnb 31 12.82 257.83 csnk1	L 201.24 94.26	218.68 61.18 22.33 22.44	72.56 17.48 40.9	3 10.65 26.78 7 13.23 11.15	6.92 49.25 3.74 57.18	73.83 67.09 3	3.62 ctnnb1.S 3	30.23 154.12 100.53 51.56 23.66 18.75	89.99 156.14	28.87 71.27 5.43 9.36	23.59 75.97 23	1.99 97.4 1 1.69 9.73 1	29.9 74.92 9.71 11.12	59.39 32.75
Wnt signaling_Cytoplasmic	csnk1e.L 39	9.87 44.75	11.25 10.95 18.8	4.87 11.51	3.98 83.04	1.76 12.12 13.1	3.19 7.05 17.1 csnk1e.S	41.59 21.41	7.69 12.54 16.09	5.02 16.65	9.66 77.33	1.49 17.82 19	69 7.04 15.1 csnk1	aL 55.24 54.68	13.08 6.82	17.15 8.04 9.2	5 3.67 29.45	1.61 10.38	17.39 6.55 1	13.07 csnk1e.S	58.19 26.87 6.71	9.76 16.85	7.35 18.54	21.47 44.71 1	.57 30.26 2	9.83 6.66	13.83
Wnt signaling_Cytoplasmic Wnt signaling_Cytoplasmic	csnk1g1.L 25 csnk1g2.L 31	5.59 16.45 1.61 17.56	6.46 14.65 15.96 13.91 15.98 26.41	3.17 11.37 4.7 17.3	3.5 30.8 6.75 255.95	1.42 5.94 14.9 1.34 12.48 24.0	4.98 7.28 40.95 csnk1g1.5 4.05 7.89 34.32	31.17 20.71	8.73 14.81 17.53	6.26 14.04	3.9 36.36	1.66 8.01 21	48 8.81 22.95 csnk1 csnk1	1.L 18.55 14.46 2.L 18.58 9.5	3.18 9.66 6.49 6.82	11.81 1.99 5.9 13.32 1.81 6.1	3 3.71 11.58 7 5.98 39.43	1.06 6.87 1.56 11.3	11.38 3.45 1 13.45 3.17	10.69 csnk1g1.S . 6.1	22.82 14.96 4.04	9.07 12.71	2.48 5.07	2.84 11.68 1	.32 10.45 1	4.73 4.45	7.45
Writ signaling_Cytoplasmic Writ signaling_Cytoplasmic	csnk1g3.L 19 csnk2a11 15	3.45 12.11 5.27 11.34	5.71 8.82 10.2 9.41 11.85 13.2	3 13.18 5.3 8.43	4.1 30.44 6.08 23.69	1.31 7.8 15.4	5.47 4.13 9.75 csnk1g3.5 2.02 5.91 10.62 csnk2a1.5	19.64 15.24 16.67 18.78 1	5.82 11.25 11.46 18.42 20.34 26.9	3.55 10.38	3.15 66.27 20.22 73.74	1.18 8.11 14	32 5.08 25.23 csnk1 65 13.73 136.88 csnk2	3L 6.14 1.9 11 31.49 17.2	1.86 2.02	2.74 0.37 4.0	1 2.83 1.04 6 10.55 37.6	0.76 8.47	4.02 1.09	0.51 csnk1g3.S 9.38 csnk2a1.S	4.04 1.8 1.39	1.92 2.72 45.71 37.63	0.21 2.98	1.52 2.04 0 26 186 72 F	1.55 9.2 1.26 12.12 3	3.05 0.98 8.33 18.71	0.85
Wnt signaling_Cytoplasmic	csnk2a2.L 42	2.81 31.08	2.77 19.66 29.24	15.74 36.4	40.62 54.02	6.24 26.16 41.4	1.45 18.01 128.8 csnk2a2.5	35.81 29.2 3	33.03 18.62 24.39	14.76 29.68	34.42 55.66	5.48 23.52	42 15.4 86.12 csnk2	12.L 44.65 40.14	27.49 15.86	30.51 14.65 31.7	9 31.58 43.26	5.18 24.96	37.59 17.63 12	26.58 csnk2a2.S	41.32 35.38 24.2	14.74 27.36	18.95 25.83	29.32 55.3 4	13 25.16 3	9.84 12.61	100.83
Writ signaling_Cytoplasmic Writ signaling_Cytoplasmic	codc88c.L 3	3.35 5	1.51 9.84 5.45	17.65 1.35	0.64 8.51	0.4 0.98 32.1	2.97 3.13 5.07 codc88c.5	0.24 0.18	0.47 0.85 1.3	0.77 0.14	0.47 0.08	0.01 0.27 23	47 43.73 335.78 csilik2 43 0.14 0.43 ccdc8	3c.L 0.81 0.66	0.11 1.69	0.98 1.25 0.2	4 23.26 36.5 16 0.1 0.29	0.45 0.97	4.23 0.71	0.17 codc88c.S	0.05 0.03 0.02	0.43 0.22	0 0	0.17 0 0	1.03 0.24	2.42 0.08	0.07
Wnt signaling_Cytoplasmic Wnt signaling_Cytoplasmic	axin1.L 8 axin2.L 34	3.62 3.35 4.37 12.6	2.61 3.48 3.65 5.4 13.16 2.14	1.27 4.84 0.2 36.77	0.94 18.42 1.37 0.45	0.33 3.2 4.2 4.54 6.64 1.	4.21 1.97 6.42 axin1.S 1.06 1.82 6.98 axin2.S	6.24 2 27.19 4.28	1.72 4.54 1.9 2.35 3.13 0.75	0.89 2.45 0.03 12.88	0.04 4.89 0.62 2.07	0.35 2.28 3 0.02 3.17 2	29 1.26 3.79 axin1. 55 0.57 0.73 axin2.	5.47 2.42 44.36 14.85	1.65 3.61 4.05 8.73	2.58 0.68 1.6 2.88 0.33 21.9	6 0.79 3.08 3 1.04 0.21	0.28 2.67 4.16 2.4	3.39 1.08 4.05 2.34	2.56 axin1.S 4.09 axin2.S	4.38 1.66 1.15 27.41 4.67 3.78	2.7 1.89 3.35 1.24	0.5 0.5 0.02 6.99	0.41 1.08 0	1.14 1.18 1.31 1.39	2.38 0.77 5.16 0.86	1.05
Writ signaling_Cytoplasmic Writ signaling_Cytoplasmic	gsk3a.L 28 ork3b.L 23	3.73 17.61	11.34 29.68 18.48	5.78 15.55	5.89 32.34	2.15 10.36 18.8	8.85 8.96 35.45 gsk3a.S	10.88 7.53	4.6 8.06 10.76	1.71 6.47	3.17 6.69	0.78 4.82 6	75 4.13 21.52 gsk3a 23 11.57 34.33 ork3b	L 41.81 23.6	11.65 17.23	21.26 13.38 10.5	6 8.65 32.26	2.77 6.91	21.47 7.4 4	13.04 gsk3a.S	15.15 11.22 5.18	6.35 10.82 10.72 20.82	3.3 2.98	4.03 5.93 1	1.03 3.98	9.44 4.17	17.37
Wnt signaling Cytoplasmic	apc.L 46	3.57 12.04	15.71 2.87 6.04	1.89 2.87	1.1 25.55	0.35 3.31 11.2	1.27 2.7 16.93 apc.S	36.14 12.46	5.11 3.21 5.38	1.65 3.2	1.74 21.2	0.39 4.33 9	95 2.42 7.38 apc.L	7.1 1.1	2.19 0.5	1.16 0.13 0.6	3 0.63 0.48	0.28 3.01	1.09 0.33	0.69 apc.S	6.05 0.98 0.61	0.74 1.34	0.2 1.53	0.64 0.52 0	.63 5.45	1.01 0.32	0.54
Writ signaling_Cytoplasmic Writ signaling_Cytoplasmic	csnk1a1.L 140	0.01 155.78	5.69 125.52 88.77	27.48 90.3	33.55 180.78	9.58 250.37 98	2.65 0.72 2.19 apt2.8 38.1 51.35 56.94 csnk1a1.5	92.52 97.18 4	49.21 72.77 64.88	20.73 51.53	19.26 114.05	7.78 116.07 57	84 27.6 107.53 csnk1	a1.L 113.78 112.35	47.77 70.7	77.81 20.51 59.7	9 33.9 34.77	9.32 356.66	82.13 52.87 2	21.93 csnk1a1.S	60.14 56.03 27.14	29.35 45.41	15.9 28.74	20.37 14.88	6.7 150.2 4	0.28 23.18	33.5
Wnt signaling_Cytoplasmic Wnt signaling_Cytoplasmic	cxxc4.L 7 nkd1.L 0	7.42 2.26 0.68 0.29	0.16 0.19 0.88 3.04 0.58 2.3	0.05 0.21 0.31 1.05	0.12 0.35 0.96 6.73	0.03 0.14 0.8 0.32 2.03 4.	0.84 0.04 2.41 cxxo4.S 4.11 0.96 1.76 nkd1.S	0.84 0.53 5.2 2.4	0.19 0.09 0.67 2.12 0.96 3.6	0 0.02	0.21 0.09 0.33 19.25	0 0.25 0	09 0.06 0.27 cxxc4 47 0.79 2.46 nkd1.1	L 3.99 1.5 2.44 0.04	0.12 0 1.2 0.26	0.92 0 0.0 1.05 0.08 0.9	9 0 0.17 5 0.24 0.48	0.07 0.1 0.28 0.63	0.25 0.08 1.81 0.46	2.45 cxxx04.S 0.28 nkd1.S	0.57 0.18 0 1.32 0.77 0.44	0.02 0.14	0 0	0 0.03 0	0.04 0.03 2.05 1.53	0.1 0	0.09
Writ signaling_Cytoplasmic Writ signaling_Cytoplasmic	dact1.L 68	3.58 14.5	16.24 7.2 17.85	0.61 37.55	1.9 194.52	0.49 7.03 9	9.6 6.54 6.83 dact1.S	18.41 5.23	3.89 3.88 18.47	0.21 17.05	1.49 271.49	0.51 2.66 3	79 3.83 5.62 dact1.	53.26 9.8	8.29 4.55	10.55 0.46 18.8	5 1.03 14.8	0.82 1.53	9.19 9.16	1.16 dact1.S	14.88 5.01 1.5	2.85 12.02	0.36 11.23	0.41 106.2 0	1.45 0.44	2.44 5.05	5.1
Wnt signaling_Otoplasmic	ppp2cb.L 95	5.37 23.83	21.78 25.7 29.76	8.58 33.46	16.02 49.79	4.75 23.71 27.2	7.33 16.79 83.02 ppp2cb.S	93.65 25.53 3	32.39 32.51 39.15	20.7 52.4	20.81 25.92	8.18 29.9 46	71 29.4 95.09 ppp2c	b.L. 120.24 35.3	21.65 30.1	35.72 9.68 24.2	8 15.97 40.58	4.26 34.77	29.45 25.34	57.7 ppp2cb.S	97.22 32.23 27.55	44.76 41.93	21.89 46.42	15.61 18.4	7.2 29.57 4	7.47 38.57	63.52
Writ signaling_Nuclear	lef1.L 5	5.95 0.87	0.59 0.4 0.46	0 2.53	0 0	0.15 1.68 3./	3.46 0.39 6.16 lef1.S	4.04 1.24	0.15 0.81 0.34	0.26 5.43	0 0	0.07 0.52 3	75 0.1 3.48 lef1.L	5.17 1.83	0.54 0.52	0.75 0.98 0.2	5 0.21 0	0.24 0.53	3.78 0.14	2.28 lef1.S	2.58 0.97 0.54	0.37 0.25	0.78 1.38	0 0 0	1.25 72.99	4.07 0.48	0.79
Writ signaling_Nuclear Writ signaling_Nuclear	tcf7i1.L tcf7i2.L 1	5 7.19 19.5 2.05	4.26 4.95 5.89 5.61 9.45 1.89	1.21 8.55 4.61 6.07	1.84 48.34 1.6 1.55	0.46 3.28 3.5 0.12 3.86 18.	3.52 2.63 8.39 tcf7i1.S 8.74 3.06 6.91 tcf7i2.S	7.62 5.63 28.29 2.54	6.3 3.66 9.48 3.83 9.46 1.88	1.15 12.99 4.01 4.52	4.46 51.42 0.91 0.03	0.28 4.22 4 0.32 4.27 13	22 2.31 11.48 tcf7i1. 35 3.04 3.85 tcf7i2.	6.84 9.9 14.93 1.03	3.52 7.66 2.1 6.82	7.83 3.02 4.8 2.28 1.21 1.8	2 2.35 38.42 5 2.61 0.37	0.95 1.89 0.4 1.61	5.4 4.62 1 11.98 1.41	12.34 tcf711.S 1.67 tcf712.S	13.06 10.16 6.18 17.79 0.83 1.38	5.45 13.33 6.09 1.61	3.25 8.01 1.11 2.54	6.8 51.8 1 1.49 0.03 0	.29 3.75 .44 3.09	8.25 5.28 7.8 1.2	15.42
Wnt signaling_Nuclear	case name brai	nT eve T by	art T intertine kidney T i	wert weat m	uncle T over T par	norman skin T solar	tof7.S	2.14 0.29	2.26 6.3 11.7	3.96 8.44	0.54 44.29	0.31 2.27 244	78 0.95 13.23	ama brain II eva II	heart II intertine I k	ideeu III Ikuer II - kuee II	mutcle II ovan II	papersas skin II	coloon II stomach ter	td7.S	1.44 1.19 0.93	2.12 6.08	4.9 3.02	0.1 14.01	0.4 1.36 17	6.21 0.79	11.28 testis II
Hh signaling_Ligands	shh.L 9	9.15 0.45	0.11 4.47 5.47	0 24.18	0 0	0 0.66 0.1	0.21 7.48 0 shh.S	1.6 0.4	0 0.6 0	0 0	0.05 0	0 0.04	0 1.75 0.04 shh.L	10.21 1.19	0.08 11.27	7.58 0.04 21.1	6 0 0	0.02 0.23	0 27.85	0.03 shh.S	2.06 0.42 0.04	1.08 0	0 0.04	0 0	0 0	0 3.63	0
Hh signaling_Ligands Hh signaling_Ligands	dhh.L 2 ihh.L 1	2.12 35.24 1.89 35.33	0.1 22.06 11.48 0.99 24.53 13.89	0.06 14.51 1.15 17.47	0 0.38	0.02 1.67 0.	0.1 11.23 7.75 dhh.S 1.43 8.68 7.95 lhh.S	0.41 18.88 0.19 16.81	0.02 1.91 2.18 0 8.04 3.16	0.06 0.08	0.07 0.03 0 0.09	0.1 0.21 0	02 0.95 17.23 dhh.L 26 0.09 7.43 lhh.L	1.61 25.43 1.37 31.54	0.07 2.78 0.52 12.47	10.83 0.04 5.2 10 0.44 11.	2 0.18 0.08 8 0.13 0.02	0.11 0.66 0.21 0.71	0.11 3.22 2.82 8.95	2.19 dhh.S 5.76 lhh.S	0.23 12.92 0.02 0.51 24.34 0	0.02 2.71 3.69 2.84	0 0.02	0.03 0.03 0	0.05 0.09 0.11 0	0 1.11 0.52 0.37	3.99
Hh signaling_Receptor-Membrane Hh signaling_Receptor-Membrane	ptch1.L	7.4 6.58	2.39 4.44 5.38 0.14 3.12 2.83	0.32 4.21	0.41 4.1	0.17 3.35 1.9	1.96 2.87 3.79 ptch1.S 3.32 1.66 1 ptch2.S	4.07 3.08	1.07 3.31 1.81	0.18 4.48	0.1 1.11	0.07 2.53 1	29 1.66 2.23 ptch1 23 1.2 2.46 ptch2	L 5.13 4.42	1.22 1.9	2.63 0.05 2.1	2 0.08 0.09	0.34 1.23	1.34 1.78 2.39 1.93	0.66 ptch1.S 0.64 ptch2.S	2.09 2.74 0.39	1.31 1.17	0.08 2.74	0 0.1 0	1.25 1.03	1.01 1.13 0.52 2.01	0.44
Hh signaling_Receptor-Membrane	smo.L 5	5.71 5.47	1.67 1.97 5.61	0.26 4.72	0.93 13.31	0.33 1.59 3./	3.51 0.99 9.5 smo.S	5.66 3.18	5.52 2.42 2.65	0.23 2.78	0.69 2.81	0.13 1.53 3	02 1.26 7.09 smol	1.76 1.28	4.09 0.62	1.94 0.15 3.0	7 0.51 0.63	0.61 0.63	1.85 0.5	0.92 smo.S	0.99 0.51 1.53	0.43 0.96	0.08 1.16	0.3 0.06 0	0.42	1.04 0.47	0.65
Hh signaling_Receptor-Membrane	hhatL 12	2.17 5.05	0.71 2.45 2.38	1.4 2.19	0 6.67	0.18 0.67 0.0	0.64 1.81 9.77	0.17 1.47	0.29 0.55 1.49	0.05 0.6	0 0.34	0.06 0.41 1	b3 0.71 8.7 http:// hhat.l	12.22 6.12	0.35 2.01	2.59 1.23 0.8	6 0 8.02	0.07 1.03	0.67 0.77	7.78	0.34 1.5 0.04	0.44 4.55	0.12 0.3	0 0.26 0		1.74 0.57	3.39
Hh signaling_Receptor-Membrane Hh signaling_Cvtoplasmic-Cilia-Nuclear	hhati.L 2 di1.L 0	2.65 0.54	0 0 0.07	0 0	8.57 0 0.23 0.04	0 0.72	0 0 0.25 hhati.S 0.13 0.7 1.08 gli1.S	0.92 5.17 3.85 4.3	5.94 0 0 2.18 2.72 6.27	0 0.02	62.78 0 0.39 0.12	0 0.04 0	05 0.05 0.04 hhatil 48 2.01 8.02 dli1.L	. 4.92 1.41 0.21 0.28	0.2 0	2.09 0 0.62 0.04 1.3	0 18.22 0 7 0.05 0.01	0 1.32	0 0	0.05 hhad.S 0.35 gli1.S	0.67 7.84 2.38 1.32 0.85 0.68	0.07 0.03	0 0.04	74.6 0.03 0.13 0.03 0	0 0.12	0.06 0.07	0.03
Hh signaling_Cytoplasmic-Cilia-Nuclear	gli2L 4	4.25 4.51	3.31 1.62 2.83	0.46 9.45	1.4 0.59	0.14 2.57 2.8	2.87 1.27 10.19 gli2.S	1.78 2.72	0.97 1.1 0.84	0.18 0.83	0.45 0.48	0.11 1.82 1	86 0.64 3.55 gli2.L	6.11 5.2	2.2 1.03	2.91 0.62 2.0	9 0.79 0.13	0.65 1.29	4.48 1.42	6.84 gli2.S	1.15 1.82 0.38	0.27 0.6	0.02 0.53	0.1 0.15 0	0.44	0.78 0.2	1.8
Hh signaling_cytoplasmic-Cilia-Nuclear	stk36.L	5.2 5.53	2.48 1.34 9.18	1.79 3.59	0.63 52.06	0.19 0.86 2	2.48 0.79 66.55	4.04		4.0	0.04	0.00		10.55 8.9	3.17 0.94	12.95 1.61 2.1	3 1.02 144.07	0.66 1.39	3.58 1.53 13	0.82		0.52	4.00 1.42			0.2/	0.13
Hi signaling_Cytoplasmic-Cilla-Nuclear Hh signaling_Cytoplasmic-Cilla-Nuclear	prkaca.L 16	5.cd 6.24 5.24 17.8	0.00 3.33 8.9 28.3 21.29 24.63	3.93 2.81 6.14 16.57	u.d/ 23.53 5.01 18.15	0.3d 2.51 6.2 1.55 8.73 16./	9.∠1 1.8 29.21 sufu.S 5.85 6.53 9.83 prkaca.S	4.84 5.07 47.9 27.82 2	0.00 1.91 7.5 20.23 21.02 33.1	1.8 2.27 7.53 25.45	0.61 15.04 11.84 33.55	0.29 3.24 8 2.87 13.28 25	10 1.17 9.13 suful. 23 9.28 15.78 prkac	8.03 10.19 L 27.32 45.57	8.69 4.77 62.39 13.53	39.87 14.2 10.	9 1.25 34.64 8 6.84 35.26	1.24 3.64 1.55 8.55	8.39 4.07 2 25.88 8.22	19.6 prkaca.S	7.9 7.31 3.91 80 50.59 23.93	2.04 8.22 19.94 40.05	1.88 1.95 8.86 6.5	0.63 9.48 0		0.+/ 1.7 16.79 10.46	5.52 14.71
Hh signaling_Cytoplasmic-Cilia-Nuclear Hh signaling_Cytoplasmic-Cilia-Nuclear	kif7.L 9 ari13b.L 19	9.85 7.31 3.28 21.15	7.24 5.37 8.17 9.21 5.31 9.95	3.19 8.46 4.46 10.75	1.94 22.01 3.09 6.19	0.78 6.97 12.8	2.84 3.79 39.2 8.1 2.83 83.23 pri13h S	9.22 2.83	3.99 1.82 4.95	0.74 0.28	0 8.81	0.27 3.21 0	kif7.L 55 0.46 59.01 ari13t	6.67 2.73 L 16.61 14.92	3.15 2.5 7.04 5.35	3.81 1.25 3.6 11.06 5.64 10	1 0.69 1.06 6 5.68 2.83	1.13 5.66 1.75 5.17	7.42 2.02	7.08 17.53 art13b.S	9.78 6.12 2.45	0.56 5.04	1.29 0.71	2.13 6.75	.22 1.5	0.55 0.39	71.12
Hh signaling_Cytoplasmic-Cilia-Nuclear	foxj1.L 12	2.81 0.09	0.28 0.15 13.19	0.35 0.19	0 0	0.06 0	0 0.65 0.51 foxj1.S	5.16 0.25	0.77 0 10.6	0.63 0	0 0	0.06 0	0 0.78 2.33 foxj1.	17.23 0.25	0.17 0	11.2 0.53 0.2	4 0 0	0.23 0	0.11 0.84	0.2 foxj1.S	6.01 0.04 0.13	0.06 11.3	0.08 0.05	0.08 0 0	.14 0.07	0.04 2.58	0.39
HSPG_Core protein	gene name brai gpc1.L 4	11.1 eye.T he 48.6 20.36	arc.i intestine: kidney.T I 1.14 9.56 5.02	wei.1 iung.T m 36.78 10.39	uscle.1 ovary.T pai 0.8 0.79	4.46 9.67 6.1	ren.i stomacn. testis.T gene nam 5.99 7.24 68.83 gpc1.S	an.i eye.T he 30.64 13.96	unci intestine.' kidney.1 0.85 0.95 1.12	i iiver.i lung.T 1.63 1.44	0.35 1.77	enureas skin.T sple 0.21 13.08 4	87 0.46 25.79 gpc1.	same brain.U eye.U . 59.48 20.9	2.15 5.38	4.13 39.72 6.3	muscie.U ovary.U 7 0.77 0.52	pancreas skin.U 1.74 3.1	spieen.u stomach. tes 5.75 6.76 6	era.u gene name br 99.57 gpc1.S	ram.U eye.U heart.U 29.13 10.97 0.65	intestne: kidney.U 0.76 0.87	wer.u lung.U 0.69 1.89	0.2 1.11 0	areas skin.U sple 1.19 4.95	en.U stomach.U 3.19 0.29	vestis.U 14.89
HSPG_Core protein HSPG_Core protein	gpc2.L 12 gpc3.L 29	2.98 2.99 3.15 10.57	0.79 0.82 1.14 7.33 0.26 0.82	0.5 1.06 0 20.5	1 0.19 0 0.37	0.13 0.56 1.1	1.11 0.39 2.35 gpc2.8 5.31 1.03 4.01 cpc3.8	1.14 0.07 22.62 4.12	0 0.08 0 0.21 0.19 2.37	0 0 7.99	0 0.06	0 0	0 0 0.56 gpc2. 35 0.14 0.33 nnc3	11.44 2.25	0.98 0.81 1.41 0.18	1.32 0.3 0.7 1.05 0 15.3	3 0.92 0.13 1 0 0.05	0.19 0.84 0.14 0.09	1.03 0.39 3.52 0.23	2.23 gpc2.S 0.47 gpc3.S	3.23 0.13 0.19 22.31 3.92 0.16	0.29 0.85	0 0 0 3.67	0 0.11	0 0.13	0 0.04 0.19 P	0.42
HSPG_Core protein HSPG_Core protein	gpo4.L 23	3.98 41.35 7.59 17.32	27.31 27.51 22.91	5.31 22.94 0.12 19.42	3.72 19.28	1.5 15.62 14.7	4.37 15.95 18.76 gpo4.8	13.98 19.58 1 30.58 26.3 3	10.54 17.82 13.13	4.56 14.16	2.73 7.41	1.47 5.19 7	07 7.74 26.5 gpc4.	7.64 14.76	6.75 11.27 5.68 1.29	9.08 0.56 13.0	9 1.88 1.91	1.72 8.04	7.47 4.31	1.6 gpc4.S	5.26 12.12 3.49	9.94 9	1.95 8	1.83 0.84 1	48 2.33	5.22 4.39 2.27 6.07	2.36
HSPG_Core protein	gpc6.L 3	3.36 1.26	0 0 0.03	0 0.17	0 0.42	0 0.14	0 0.14 0.54 gpc6.S	3.08 0.65	0.11 0.05 0.1	0 0.14	0 0.39	0 0.09	0 0.05 0.53 gpc6.	1.47 0.21	0 0	0.05 0 0.1	4 0 0.1	0 0.09	0 0.02	0 gpc6.S	0.75 0.12 0.03	0.02 0.05	0 0.03	0 0.12 0	0.01 0.01	0 0.01	0.03
HSPG_Core protein HSPG_Core protein	sdc1.L 9 sdc2.L 183	#.63 9.38 3.07 190.53 2	2.75 56.48 43.54 57.13 35.1 87.74	4./8 28.16 169.84 109.32	0.85 14.63 31.15 25.24	5.57 40.37 2.5 7.75 68.99 25	2.57 21.38 7.71 sdc1.S 5.46 29.95 79.63 sdc2.S	9.98 15.08 140.52 189.13 17	0.58 73.25 8.49 76.27 35.51 62.27	2.15 9.02 98.77 97.03	u.24 67.19 63.67 21.69	1.5/ 114.06 7 13.22 97.13 30	rz 24.12 73.06 sdc1.1 23 38.38 55.2 sdc2.1	4.55 4.63 109.45 101.54	1.59 30.01 130.8 21.23	21.46 4.21 17.2 81.97 87.38 116.7	9 0.73 3.2 2 32.47 2.44	4.56 55.13 10.19 30.77	2.54 19.69 26.3 25.59 1	8.6 sdc1.S 11.16 sdc2.S	65.59 71.18 100.7	37.43 4.53 15.78 42.43	0.91 0.98 29.74 84.03	0.05 10.42 1 73.29 1.17 16	1.86 101.64 1.63 71.59 3	3.94 14.54 0.32 25.59	16.72 9.11
HSPG_Core protein HSPG_Core protein	sdc3.L 223 sdc4.L 30	3.39 48.02 3.55 75.54	28.23 20.75 10.69 54.68 86.44 121.91	11.48 50.66 54.37 183.5	4.1 0.37 17.32 8.09	1.07 9.59 48.7 7.19 89.28 127	8.75 14.58 5.78 sdc3.S 23.8 86.98 20.69 srin4 S	122.23 19.92 5 11.29 62.11 1	56.09 6.58 3.29 10.31 67.57 75.07	2.31 15.69 20.09 70.19	1.2 0.1 3.35 11.64	1.1 3.59 14 4.99 64.65 46	18 8.17 3.24 sdc3.1 11 32.61 14.89 sdc4.1	68.29 9.78 14.71 23.56	7.11 4.02 26.7 58.21	6.58 2.89 36.3 91.16 26.41 67.8	4 1.56 0 5 10.8 2.34	1.52 2.39 10.72 263 18	26.86 4.41 66.9 65.3	1.23 sdc3.5 3.09 sdc4.5	30.08 2.64 8.28 10.36 40.56 10.74	0.7 1.38	0.16 7.38 21.07 32.37	0.25 0 0	0.59 0.92 0.21 148.67 R	1.96 1.75	0.49
HSPG_Enzyme HSPG_Enzyme	ndst1.L 10	0.77 9.28	4.2 5.11 6.68	5.39 3.25 16.73 24.9	3.02 21.24	0.57 4.64 4/	4.47 2.45 4.79 ndst1.8	20.78 11.5	6.45 4.59 8.22 1.44 2.03	4.94 9.48	1.8 7.75	1.22 6.41 8	64 4.08 6.37 ndst1.	L 17.38 17.48	2.85 7.86	6.94 7.06 2.3 19.67 20.05	9 2.25 29.04	0.62 3.08	4.77 2.52	5.55 ndst1.8	25.05 15.74 4.9	6.85 8.63	6.54 9.25	1.67 8.27 1	.17 4.28 0.3 1.72	9.4 5.44	5.58
HSPG_Enzyme	ndst3.L 24	40.23	0 0.05 0.04	0 0.07	0 0.16	0 0.09 0.1	0.15 0.03 1.52 ndst3.8	27.38 6.27	0 0 0.17	0 0	0 0	0.02 0	0 0.01 0.95 ndst3	L 127.42 64.61 L 9.96 1.15	0 0.03	0.03 0 0.0	9 0 0	2.20 13.51	0.03 0	0.03 ndst3.S	10.84 1.41 0.03	2.49 3.04	0 0	0.03 0	0 0.03	0 0.02	0.23
HSPG_Enzyme HSPG_Enzyme	ndst4.L 3 sulf1.L 5	3.85 0.52 5.14 19.62	0 0 0 0	0 0 0.37 5.03	0 0 0 0 0.75 4.8	0 0 0 0.66 2.14 1.1	0 0 0.17 ndst4.S 1.75 2.56 3.24 sulf1.S	6.05 1.54 4.97 9.61	0.03 0 0 0 5.17 0.74 2.35	0 0 0 0 0.34 16.6	0 0.91 1.14 1.02	0.09 0 0 2.87 0	0 0.01 0.1 ndst4. 59 0.51 3.41 sulf1.	L 1.04 0.11 1.35 4.99	0 0 3.07 0.87	0 0 4.74 0.04 2.1	0 0.03 0 7 0.6 0.24	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0 0	0.02 ndst4.S 0.37 sulf1.S	2 0.38 0.03 1.65 1.24 1.34	0.22 0.76	0 0	0 0.07 0	0.04 0 0.14 0.86	0 0	0.02
HSPG_Enzyme	sulf2.L 110 gene name hrak	0.68 44 In.T. eve.T. hv	6.39 13.02 35.04 art.T intestine, kidney T	33.99 71.85 iver.T lung.T m	2.02 21.08 uscle.T.ovary.T nav	1 1.97 15.5 Increas skin.T soler	5.55 3.47 40.11 sulf2.S ten.T stomach, testis.T _ cene nam	106.59 46.95 1 brain.T eve.T he	12.92 12.56 31.78 sart.T intestine, kidney 1	7.46 75.6 T liver.T lung T	3.16 19.85 muscle.T ovary.T na	2.16 27.25 33 ancreas skin.T snie	77 2.74 16.07 sult2.1 an.T stomach, testis.T	173.23 96.31 ame brain.U evell	4.12 9.38 heart.U intestine Lki	32.6 25.71 6.9 idney.U liver.U king I	5 1.29 23.26 muscle.U ovarv 1	2.7 0.65 pancreas skin !!	19.95 2.61 2 spleen.U stomach teo	19.23 sulf2.S 1 dis.U gene name he	162.97 80.72 11.78 rain.U eve.U heart I	10.05 29.18 intestine: kidney 11	6.13 27.94 liver.U lung.11	2.49 16.91 3 muscle.U ovarv.U nan	1.97 29.06 3 creas_skin.U snle	17.56 3.33 en.U stomach I I	18.21 testis.U
Notch signaling_Ligands-Receptors	dic.L 1	1.75 0.28 5.42 2.61	0.19 0.83 0.37	0.04 3.71	0.11 0	0.05 1.01 0.7	0.05 0.16 1.23 dlc.S	1.25 0.13 7.27 2.54	0 0.21 0.3	0 0.08	0 0 128 0.29	0.08 0 0	84 0.03 0.07 dlc.L	1.41 0.67	0.57 0.48	0.16 0.19 0.5	4 0.2 0 6 111	0 0.17	0 0.16	0.26 dlc.S	1.07 0.23 0	0 0.27	0.05 0	0 0 0	1.03 0 14 0.77 7	0.47 0.04	0
Notch signaling_Ligands-Receptors	di4.L 11	1.71 7.31	9.57 22.29 17.45	4.43 122.56	6.35 2.29	0.95 12.45 22.7	2.82 4.38 5.73 dll4.S	1.47 2.01	a	5.00 1.9	1.20 0.20	0.04 40	1.00 dil1L di4L	3.89 1.92	3.61 15.27	11.59 1.97 10.3	6 1.76 0.3	1.48 4.35	12.64 2.29	0.54 dl4.S		5.20 0.39	1.20	1.01 0.06 1		2.40	0.4

Notch signaling, Liganda Receptors Notch signaling, Extracellular Membrane Notch signaling, Extracellular Membrane Notch signaling, Extracellular Membrane	jupili         3.9         14.04         6.09         10.7         9.31         0.9         11.09         1.40         0.6         0.6         8.9         7.74         102         2.73           modell         2.4         8.8         7.74         102         2.73         100         2.21         100         10.0         1.00         1.00         2.74         100         2.74         100         2.74         100         2.74         100         2.74         100         2.74         100         2.74         100         2.74         100         2.74         100         2.74         100         2.74         100         2.74         100         2.74         100         2.74         100         2.74         100         2.74         100         2.74         100         2.74         100         2.74         100         100         1.04         100         100         1.06         100         1.06         1.06         1.06         100         100         1.06         100         100         100         100         1.06         100         1.06         100         100         1.06         100         100         100         100         100         100         1	15         179         7.27         159         7.16         7.14         0.37         7.16         0.54         2.26         0.37         5.01         5.20         0.34         3.73         jegili           1.5         1.79         7.18         7.17         7.18         7.18         7.19<	44         1674         344         101         927         127         368         141         022         142         1206         1032         043         pp15         244         1183         112         359         818         0.02         2.17         0.52         2.00         0.72         107         12.13         0.25         2.62           1.00         1.00         2.00         0.02         2.14         10.22         1.02         0.02         2.17         0.52         2.00         0.72         10.7         12.13         0.25         2.62           1.00         1.00         2.00         0.02         2.14         10.2         2.00         1.02         2.00         0.72         10.7         12.13         0.25         2.62           2.20         0.27         1.01         0.02         2.24         1.00         2.00         0.27         1.02         0.20         0.25         0.24         0.04 <t< th=""></t<>
Nech signaling, Extracultura-Membane Nech signaling, Caracultura-Membane Nech signaling, Caracultura-Membane Nech signaling, Cytopiasmic Nech signaling, Cytopiasmic	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	minia 111 2 2020 1029 1029 1019 1019 1029 102	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$
Noch signaling. Cyclopiannic Noch signaling. Cyclopiannic	Schlam, 1         44.8         19.9         26.9         14.8         27.9         64.9         14.9         12.9         11.1         11.1         12.9           Schlam, 1         45.9         19.0         27.9         14.8         27.9         64.9	AS         T/T6         A.77         Z1         O.31         T/T6         A.77         Z1         O.31         D.71         O.31         D.71         O.31         D.71         O.31         D.71         D.71 <thd.71< th=""> <thd.71< th=""> <thd.71< th="" th<=""><th><math display="block"> \begin{array}{cccccccccccccccccccccccccccccccccccc</math></th></thd.71<></thd.71<></thd.71<>	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$
Nech signaling_Cybpissmic Nech signaling_Cybpissmic Nech signaling_Cybpissmic Nech signaling_Cybpissmic Nech signaling_Cybpissmic Nech signaling_Nechar Nech signaling_Nechar Nech signaling_Nechar Nech signaling_Nechar Nech signaling_Nechar Nech signaling_Nechar	mediti         318         644         41.58         359         151         150         171         350         150         151         151         150         151         151         150         151         151         150         151         151         150         151         151         150         151         151         150         151         15	Juffis         2,429         6.11         4.7         6.49         3.0         1.3         2.64         1.6         0.66         0.55         6.26         1.87         2.22         7.68         mentlik           set         5         0         0.64         2.71         1.06         2.44         1.66         2.45         1.67         2.55         1.64         2.24         7.68         mentlik         1.66         2.44         1.66         2.44         1.66         2.44         1.67         2.45         1.66         2.24         1.66         2.44         1.66         2.44         1.66         2.44         1.66         2.44         1.66         2.44         1.66         2.44         1.66         2.44         1.66         2.44         1.66         2.44         1.66         2.44         1.66         2.44         1.66         2.44         1.66         2.44         2.45         1.66         2.45         1.66         2.45         1.66         2.45         1.66         2.46         1.66         2.45         1.66         2.45         1.66         2.45         1.66         2.45         1.66         2.45         1.66         2.45         1.66         2.45         1.67         1.66	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$
Hippo signalita, Membane Hippo signalita, Membane Hippo signalita, Membane Hippo signalita, Membane Hippo signalita, Membane Hippo signalita, Membane Hippo signalita, Cytoplasmic Hippo signalita, Cytoplasmic Hippo signalita, Cytoplasmic Hippo signalita, Cytoplasmic Hippo signalita, Cytoplasmic		heris         B.44         6.8         164         0.91         164         0.06         3.42         0.37         11         0.56         0.52         1.49         0.42         6.44         devel           26.5         7.77         11.19         0.49         0.02         0         0.03         0.02         0         0.03         0.02         0         0.03         0.02         0         0.01         0.08         0.02         0         0.01         0.08         0.02         0         0.01         0.08         0.02         0         0.01         0.08         0.02         0         0.01         0.08         0.02         0         0.01         0.08         0.02         0         0.01         0.08         0.02         0         0.01         0.08         0.02         0         0.01         0.08         0.02         0.01         0.08         0.02         0         0.01         0.01         0.01         0.01         0.01         0.01         0.01         0.01         0.01         0.01         0.01         0.01         0.02         0.01         0.02         0.01         0.01         0.01         0.01         0.01         0.01         0.01         0.01 <td< th=""><th>14         80         254         071         20.0         23         24         0.85         2.2         0.81         0.82         0.82         0.82         0.82         0.82         0.82         0.82         0.82         0.82         0.82         0.85         0.82         0.85         0.82         0.85         0.82         0.85         0.82         0.85         0.82         0.85         0.82         0.85         0.1         0.08         0.04         0.08         0.04         0.08         0.05</th></td<>	14         80         254         071         20.0         23         24         0.85         2.2         0.81         0.82         0.82         0.82         0.82         0.82         0.82         0.82         0.82         0.82         0.82         0.85         0.82         0.85         0.82         0.85         0.82         0.85         0.82         0.85         0.82         0.85         0.82         0.85         0.1         0.08         0.04         0.08         0.04         0.08         0.05
Hippo signalité, Cytopisamic Hippo signalité, Cytopisamic		$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Mage         Mage <th< th=""></th<>
Higos algolarling_C/polptamic Higos algolarling_C/polptamic	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	25         11.34         11.06         10.26         0.67         0.91         0.80         21.1         16.27         81.1         25.46         65.3         21.6         7.4         0.86         model           web         2.52         6.40         5.23         6.40         5.24         6.40         6.24         6.40         6.24         6.40         6.24         6.40         6.40         6.24         6.40         6.41         6.40         6.41	555         477         165         526         432         168         138         148         139         147         117         118         148         139         147         117         118         148         147         117         118         348         117         118         348         117         118         348         117         117         118         348         117         118         348         117         118         348         117         117         118         348         117         118         348         117         118         348         117         118         348         117         118         348         117         118         348         117         118         348         117         118         348         117         118         348         117         118         348         118
Hippo signaling_Cytoplasmic Hippo signaling_Cytoplasmic Hippo signaling_Cytoplasmic Hippo signaling_Cytoplasmic Hippo signaling_Nuclear Hippo signaling_Nuclear Hippo signaling_Nuclear Hippo signaling_Nuclear Hippo signaling_Nuclear TLE_Nuclear	member         0         22         273         141         818         414         418         829         070         0.66         0.4         158         65.05         0.12         0.14         0.12         0.12         0.14         0.12         0.12         0.14         0.14         0.12         0.12         0.14         0.12 <th0.12< th=""> <th0.12< th=""> <th0.12< th=""></th0.12<></th0.12<></th0.12<>	Diff         0         0         4         25         36         4         26         27         16         4         26         4         26         17         16         16         17         16         16         17         16         16         17         16         16         16         17         16 <th16< th=""> <th16< th=""></th16<></th16<>	Constraint         Constraint <thconstraint< th="">         Constraint         Constrai</thconstraint<>
TLE_Nuclear TLE_Nuclear	961. 2134 666 2123 623 822 235 79 184 1276 054 617 1635 111 123 aesl. 103.49 4425 4452 2369 367 1289 6138 1786 4987 602 2776 3591 3739 64.4	43 1477 743 320 729 419 329 617 119 2634 039 374 1573 481 483 964 3 n.s. 14229 6726 7685 5244 14021 2639 8533 37268 96522 6,81 5639 7332 3832 12033 863.1 1	GME 736 22 636 761 164 362 211 325 68 445 1086 33 34 645 122 687 107 687 683 116 356 182 312 676 46 1133 364 181 068 6912 4322 3262 6258 2059 6024 245 6786 786 3831 6142 3929 7246 6455 1738 714 7264 6685 17174 3764 6527 6549 6251 681 7781 6736 3929 692

gene group	gene name	gnee ID	cell2	cell4	cell8	cell16	st06	st08	st09	st10	st11	st13	st15	st16	st19	st20	st22	st24	st28	st31	st33	st38	st40	st41 s	st44
Wnt signaling_liga	and: wnt1	Xetrov90006199r	1.47	1.92	1.1	1.94	2.18	1.01	0.35	0	1.227	2.785	10.46	13.47	10.07	8.24	10.91	6.02	6.69	3.505	2.43	1.81	0.605	1.42	1.36
	wnt2	Xetrov90008153r	0	0	0	0	0	0	0	0	0	0	0	0	0.157	1.125	1.605	1.453	1.73	0.42	0.31	0.55	0.185	0.575	0.41
	wnt2b	Xetrov90005248r	0	0	0	0	0	0	0.185	0.205	0.527	1.405	16.21	15.265	17.767	10.89	10.715	7.883	6.32	5.25	5.93	8.31	11.22	8.825	8.31
	wnt3	Xetrov90024857r	0	0	0	0	0	0	0	0	0	0	0.19	0.195	0.217	0.205	0.1	0.327	0	0.08	0.21	0.31	0.145	0.06	0.31
	wnt3a	Xetrov90015461r	0	0	0	0.25	0	0	0.135	0	4.073	8.695	10.96	12.39	10.92	10.62	8.245	6.883	5.795	5.255	5.24	3.72	3.35	4.615	3.36
	wnt4	Xetrov90018493r	0	0	0	0.3	0.34	0	0	1.055	3.777	7.865	21.85	24.92	22.177	19.545	14.875	10.703	8.48	5.655	5.715	3.34	3.515	4.805	5.85
	wnt5a	Xetrov90030795r	18.55	12.76	18.5	17.61	25.54	32.49	41.065	10.935	9.547	11.835	33.43	49.545	43.09	53.565	37.2	36.993	37.815	44.395	42.44	49.1	46.605	47.36	37.47
	wnt5b	Xetrov90030950r	0.45	0.59	0.45	0.2	0.3	0.48	10.265	42.865	76.577	122.165	64.37	80.43	59.683	48.1	37.82	23.137	18.765	16.39	13.69	17.15	14.685	13.445	10.26
	wnt6	Xetrov90024498r	0	0	0	0	0	0	0	0	0	0	1.16	0.88	0.79	1.5	1.315	1.8	1.53	1.975	1.285	1	1.78	0.93	1
	wnt7b	Xetrov90028160r	0.63	0	0	0.55	0	0	0.285	1.29	3.463	2.845	0	0.455	1.76	5.91	6.21	11.66	14.48	21.215	21.49	28.34	23.71	30.645	21.33
	wnt8a	Xetrov90007482r	0.25	0	0	0	0	2.55	115.01	276.94	242.3	141.15	70.42	61.105	47.87	32.155	26.85	11.753	4.955	0.86	0.135	0.16	0	0.135	0
	wnt8b	Xetrov90017928r	0	0	0	0	0	0	0.14	0.16	3.9	4.745	8.45	9.415	5.607	6.56	5.93	4.493	2.625	2.15	1.715	1.5	1.27	0.45	1.12
	wnt9a	Xetrov90015459r	0	0	0	0	0	0	0	0	0	0.575	0.8	0.85	0.76	3.385	3.455	3.543	5.07	3.065	3.36	2.81	4.585	3.55	3.5
	wnt9b	Xetrov90024859r	0	0	0	0	0	0	0	0	0.1	0	0.28	0.72	0.247	0.895	0.695	2.013	1.37	1.32	1.455	1.43	1.28	0.68	0.48
	wnt10a	Xetrov90024501r	0	0	0	0	0	0	0.17	0	0.58	0.555	28.86	28.895	31.433	27.965	28.97	31.95	26.675	24.15	22.045	21.64	14.495	14.055	11.94
	wnt10b	Xetrov90006200r	0	0	0	0	0.13	0.12	0.07	0	0.07	0.135	1.71	2.12	2.167	5.88	5.8	4.09	5.15	6.8	6.95	5.35	7.83	6.92	6.53
	wnt11a	Xetrov90007000r	3.84	3.97	2.99	4.49	5.19	9.25	5.56	1.475	3.89	5.555	21.08	23.975	27.693	49.92	52.495	48.397	40.215	40.275	31.045	37.89	32.55	37.185	33.37
	wnt11b.1 (wnt11	b.(Xetrov90020286r	23.91	24.3	18.75	20.24	18.81	13.67	20.035	16.935	17.627	14.275	8.06	6.335	5.943	3.675	3.16	3.02	3.075	2.155	1.56	1.93	1.565	0.91	0.71
	wnt11b.2 (wnt11	b.(Xetrov90020285r	3.05	5.03	5.31	3.87	3.56	3.1	17.75	13.39	16.863	13.83	8.43	6.425	5.95	3.51	3.255	2.143	1.63	1.19	0.86	0.55	0.475	0.385	0.14
	wnt16	Xetrov90008168r	0	0	0	0	0	0.33	0	0	0	0	0	0	0.08	0.55	0.91	0.82	0.34	1.34	1.005	0.67	2.03	2.19	1.56
HSPG_Core prote	ein sdc4	Xetrov90024779r	5.53	5.73	3.95	4.62	5.71	6.99	11.175	20.89	26.007	24.235	10.22	16.03	15.023	22.39	17.035	12.27	11.935	12.355	12.165	13.09	7.86	9.04	10.99
Hippo signaling N	luci taz	Xetrov90027507r	177.2	187.28	180.72	191.67	178.44	146.87	146.35	135.27	43.853	18.2	10.16	12.675	9.45	10.08	11.055	6.903	6.695	11.48	7.33	6.74	6.185	10.04	7.24
	yap1	Xetrov90006851r	378.32	410.91	422.25	404.69	393.27	384.87	304.995	214.11	213.9	315.805	154.73	240.425	156.263	136.775	94.685	79.287	83.39	86.36	71.67	78.99	64.695	70.56	62.17
TLE/Groucho	tle1	Xetrov90002301r	161.34	176.79	174.14	192.63	205.14	257.17	252.765	150.795	105.283	106.91	107.98	112.91	96.407	83.11	80.155	67.603	61.14	58.305	44.84	40.34	28.72	26.855	21.2
	tle2	Xetrov90002028r	637.22	645.39	639.88	589.49	556.19	510.9	524.8	514.95	392.903	294.665	248.23	272.28	198.85	208.82	187.335	156.207	127.81	100.03	74.58	63.82	69.77	54.185	57.62
	tle4	Xetrov90002299r	145.64	153.57	159.89	157.78	172.96	205.33	140.145	42.215	27.993	28.205	42.67	41.845	39.51	31.425	30.85	26.21	23.39	24.555	24.225	26.54	21.47	24.21	22.29
	aes	Xetrov90002031r	176.83	177.9	182.49	178.49	192.84	182.13	176.6	131.21	87.293	84.665	113.04	96.81	107.77	143.015	146.035	132.65	134.795	106.8	90.045	88.24	95.395	79.64	83.34

										Transcriptome correlation analysis							
								deve	lopmental	stages		adult tissu	Jes				
gene category	L gene	ID	annotation	S gene	ID	annotation	pair/singleton	Clutch T	Clutch U	consensus	Clutch T	Clutch U	consensus				
Wnt signaling_Wnt ligands	wnt1.L	Xelaev1801331	4 1.8.3	wnt1.S	Xelaev180158	1.8.3	pair	HCDE	NCDE	inc.	NCDE	n/a	inc.				
Wnt signaling_Wnt ligands	wnt2.L	Xelaev1801764	7 1.8.3	wnt2.S	Xelaev180210	1.8.3	pair	n/a	n/a	n/a	HCSE	HCSE	HCSE				
Wnt signaling_Wnt ligands	wnt2b.L	Xelaev1801234	9 1.8.3				singleton	n/a	n/a	n/a	n/a	n/a	n/a				
Wnt signaling_Wnt ligands	wnt3.L	Xelaev1804337	1 1.8.3	wnt3.S	Xelaev180461	1.8.3	pair	n/a	n/a	n/a	n/a	n/a	n/a				
Wnt signaling_Wnt ligands	wnt3a.L	Xelaev1803057	3 1.8.3	wnt3a.S	Xelaev180327	1.8.3	pair	HCDE	n/a	inc.	HCDE	HCSE	inc.				
Wnt signaling_Wnt ligands	wnt4.L	Xelaev1803568	3 1.8.3	wnt4.S	Xelaev180375	: 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE				
Wnt signaling_Wnt ligands	wnt5a.L	Xelaev1800178	3 1.8.3	wnt5a.S	Xelaev180030	(1.8.3	pair	HCDE	NCDE	inc.	HCSE	HCSE	HCSE				
Wnt signaling Wnt ligands	wnt5b.L	Xelaev18003003	3 1.8.3	wnt5b.S	Xelaev180198	1.8.3	pair	HCSE	HCDE	inc.	HCSE	HCSE	HCSE				
Wnt signaling Wnt ligands	wnt6.L	Xelaev1804450	6 1.8.3	wnt6.S	Xelaev180470	41.8.3	pair	NCSE	NCSE	NCSE	NCSE	NCSE	NCSE				
Wnt signaling_Wnt ligands	wnt7a.L	Xelaev1800181	7 1.8.3	wnt7a.S	Xelaev180025	1.8.3	pair	NCDE	NCDE	NCDE	HCSE	HCSE	HCSE				
Wnt signaling_Wnt ligands	wnt7b.L	Xelaev1801665	91.8.3	wnt7b.S	Xelaev180197	41.8.3	pair	NCSE	NCSE	NCSE	HCDE	HCSE	inc.				
Wnt signaling_Wnt ligands	wnt7c.L	Xelaev1800003	1 1.8.3	wnt7c.S	Xelaev180417	1.8.3	pair	n/a	n/a	n/a	HCSE	HCSE	HCSE				
Wnt signaling Wnt ligands	wnt8a.L	Xelaev1801710	9 1.8.3	wnt8a.S	Xelaev180215	1.8.3	pair	HCDE	HCDE	HCDE	n/a	n/a	n/a				
Wnt signaling Wnt ligands	wnt8b.L	Xelaev1803486	3 1.8.3	wnt8b.S	Xelaev180371	1.8.3	pair	HCDE	HCSE	inc.	HCSE	HCSE	HCSE				
Wnt signaling Wnt ligands	wnt9a.L	Xelaev1803057	6 1.8.3	wnt9a.S	Xelaev180327	1.8.3	pair	HCSE	HCSE	HCSE	HCSE	HCDE	inc.				
Wnt signaling Wnt ligands	wnt9b.L	Xelaev1804337	2 1.8.3	wnt9b.S	Xelaev180461	1.8.3	pair	HCDE	HCDE	HCDE	NCSE	HCSE	inc.				
Wnt signaling Wnt ligands	wnt10a.L	Xelaev1804450	3 1.8.3	wnt10a.S	Xelaev180470	41.8.3	pair	HCDE	HCSE	inc.	NCSE	NCSE	NCSE				
Wnt signaling Wnt ligands	wnt10b.L	Xelaev1801331	5 1.8.3	wnt10b.S	Xelaev180158	; 1.8.3	pair	NCSE	n/a	inc.	HCSE	HCSE	HCSE				
Wnt signaling Wnt ligands	wnt11a.L	Xelaev1801407	) 1.8.3*(wnt11.L)	wnt11a.S	Xelaev180163	1.8.3*(wnt11.S)	, pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE				
Wnt signaling Wnt ligands	wnt11b.L	Xelaev1803862	7 1.8.3				singleton	n/a	n/a	n/a	n/a	n/a	n/a				
Wnt signaling Wnt ligands	wnt16.L	Xelaev1801766	1 1.8.3	wnt16.S	Xelaev180210	1.8.3	pair	NCSE	n/a	inc.	HCSE	n/a	inc.				
Wnt signaling Fzd receptors	fzd1.L	Xelaev1803084	9 1.8.3	fzd1.S	Xelaev180329	1.8.3	, pair	HCDE	HCDE	HCDE	HCSE	HCSE	HCSE				
Wnt signaling Fzd receptors	fzd2.L	Xelaev1804327	4 1.8.3	fzd2.S	Xelaev180460	¥ 1.8.3	, pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE				
Wnt signaling Fzd receptors	fzd3.L	Xelaev1802825	5 1.8.3	fzd3.S	Xelaev180302	1.8.3	, pair	HCDE	HCSE	inc.	HCSE	HCSE	HCSE				
Wnt signaling Fzd receptors	fzd4.L	Xelaev1801389	3 1.8.3	fzd4.S	Xelaev180163	4 1.8.3	, pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE				
Wnt signaling Fzd receptors	fzd5.L	Xelaev1804497	- 4 1.8.3	fzd5.S	Xelaev180473	1.8.3	, pair	NCSE	NCSE	NCSE	HCSE	HCSE	HCSE				
Wnt signaling Fzd receptors	fzd6.L	Xelaev1803226	3 1.8.3	fzd6.S	Xelaev180339	r. 1.8.3	pair	HCDE	HCDE	HCDE	HCSE	HCSE	HCSE				
What signaling Ezd receptors	fzd7.L	Xelaev1804494	this study	fzd7.S	Xelaev180473	this study	pair	NCDE	NCDE	NCDE	HCDE	HCDE	HCDE				
Wnt signaling Fzd receptors	fzd8.L	Xelaev1803071	5 1.8.3	fzd8.S	Xelaev180328	1.8.3	pair	HCDE	HCDE	HCDE	NCDE	HCDE	inc.				
Wnt signaling Fzd receptors	fzd9.L	Xelaev1801179	3 1.8.3	fzd9.S	Xelaev180145	: 1.8.3	pair	HCDE	HCSE	inc.	NCDE	NCDE	NCDE				
Wnt signaling Fzd receptors	fzd10.L	Xelaev1800774	7 1.8.3	fzd10.S	Xelaev180105	1.8.3	pair	HCDE	HCSE	inc.	HCSE	HCDE	inc.				
Wnt signaling Extracellular-Membrane Po	s Irp5.L	Xelaev1802226	3 1.8.3				singleton	n/a	n/a	n/a	n/a	n/a	n/a				
Wnt signaling Extracellular-Membrane Po	s Irp6.L	Xelaev1800252	1 1.8.3	Irp6.S	Xelaev180198	41.8.3	pair	NCSE	NCSE	NCSE	HCDE	HCDE	HCDE				
Wnt signaling Extracellular-Membrane Po	s ror1.L	Xelaev1802299	3 1.8.3	ror1.S	Xelaev180251	: 1.8.3	pair	HCDE	NCDE	inc.	HCDE	HCDE	HCDE				
Wnt signaling Extracellular-Membrane Po	s ror2.L	Xelaev1800700	2 1.8.3	ror2.S	Xelaev180102	1.8.3	, pair	HCSE	HCSE	HCSE	NCSE	HCSE	inc.				
Wnt signaling Extracellular-Membrane Po	s ryk.L	Xelaev1802794	3 1.8.3	ryk.S	Xelaev180299	1.8.3	, pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE				
Wnt signaling Extracellular-Membrane Po	s porcn.L	Xelaev1803810	3 1.8.3				singleton	n/a	n/a	n/a	n/a	n/a	n/a				
Wnt signaling Extracellular-Membrane Po	swis.L	Xelaev1802296	) 1.8.3	wls.S	Xelaev180251	(1.8.3	pair	HCSE	HCSE	HCSE	HCSE	HCDE	inc.				
Wnt signaling Extracellular-Membrane Po	s rspo1.L	Xelaev1801251	1 1.8.3	rspo1.S	Xelaev180151	1.8.3	, pair	n/a	n/a	n/a	NCDE	HCDE	inc.				
Wnt signaling Extracellular-Membrane Po	s rspo2.L	Xelaev1803228	3 1.8.3	rspo2.S	Xelaev180339	1.8.3	, pair	NCSE	NCSE	NCSE	HCSE	HCSE	HCSE				
Wnt signaling Extracellular-Membrane Po	s rspo3.L	Xelaev1802699	4 1.8.3	•			singleton	n/a	n/a	n/a	n/a	n/a	n/a				
Wnt signaling Extracellular-Membrane Po	s lgr4.L	Xelaev1802198	7 1.8.3	lgr4.S	Xelaev180243	1.8.3	pair	HCDE	HCDE	HCDE	HCSE	HCDE	inc.				
Wnt signaling Extracellular-Membrane Po	s lgr5.L	Xelaev1801755	7 1.8.3	lgr5.S	Xelaev180211	1.8.3	, pair	NCDE	NCSE	inc.	HCSE	NCSE	inc.				
Wnt signaling Extracellular-Membrane Po	s ndp.L	Xelaev1801241	5 1.8.3	ndp.S	Xelaev180147	1.8.3	, pair	HCSE	NCSE	inc.	NCSE	NCSE	NCSE				
Wnt signaling Extracellular-Membrane Ne	er frzb.L	Xelaev1804478	7 1.8.3	frzb.S	Xelaev180472	1.8.3	, pair	HCDE	HCSE	inc.	HCSE	HCSE	HCSE				
Wnt signaling Extracellular-Membrane Ne	e frzb2.L	Xelaev1802402	1 1.8.3	frzb2.S	Xelaev180259	1.8.3	pair	HCDE	HCDE	HCDE	n/a	n/a	n/a				
Wnt signaling Extracellular-Membrane Ne	ecsfrp1.L	Xelaev1801865	3 1.8.3	sfrp1.S	Xelaev180202	41.8.3	pair	HCDE	HCDE	HCDE	HCDE	NCDE	inc.				
Wnt signaling Extracellular-Membrane Ne	e sfrp2.L	Xelaev1800547	1.8.3	sfrp2.S	Xelaev180092	1.8.3	pair	HCSE	HCSE	HCSE	HCDE	HCSE	inc.				
Wnt signaling Extracellular-Membrane Ne	e sfrp4.L	Xelaev1803127	5 1.8.3		/10/00/100002		singleton	n/a	n/a	n/a	n/a	n/a	n/a				
Wnt signaling Extracellular-Membrane Ne	sfrp5.L	Xelaev1803470	3 1.8.3	sfrp5.S	Xelaev180370	1.8.3	pair	NCSE	NCSE	NCSE	HCSE	HCSE	HCSE				
Wnt signaling Extracellular-Membrane Ne	e sfrpx.L	Xelaev1801391	5 1.8.3	sfrpx.S	Xelaev18016	1.8.3	pair	HCDE	HCDE	HCDE	HCDE	NCDE	inc.				
Wnt signaling Extracellular-Membrane Ne	edkk1.L	Xelaev1803445	1.8.3	dkk1.S	Xelaev180367	1.8.3	pair	HCSE	HCSE	HCSE	HCSE	HCDE	inc.				
Wnt signaling Extracellular-Membrane Ne	e dkk2.L	Xelaev1800569	5 1.8.3	dkk2.S	Xelaev180093	1.8.3	pair	HCDE	n/a	inc.	HCSE	HCDE	inc.				
Wnt signaling Extracellular-Membrane Ne	e dkk3.L	Xelaev1802177	7 1.8.3	dkk3.S	Xelaev18024	1.8.3	pair	NCDE	NCDE	NCDE	HCDE	HCDE	HCDE				
Wnt signaling Extracellular-Membrane Ne	dkkx.L	Xelaev1804318	5 1.8.3	dkkxp.S	Xelaev189004	this study	singleton	n/a	n/a	n/a	n/a	n/a	n/a				
Wnt signaling_Extracellular-Membrane Ne	eç wif1.L	Xelaev1801751	9 1.8.3	wif1.S	Xelaev180211	(1.8.3	pair	HCSE	HCSE	HCSE	HCDE	HCDE	HCDE				

Wnt signaling Extracellular-Membrane N	leccer1.L	Xelaev18006799 1.8.3	cer1.S	Xelaev180100; 1.8.3	pair	HCDE	HCSE	inc.	n/a	n/a	n/a
Wnt signaling Extracellular-Membrane N	le sostdc1.L	Xelaev18030924 1.8.3	sostdc1.S	Xelaev180330 1.8.3	pair	NCSE	NCSE	NCSE	HCDE	HCSE	inc.
Wht signaling Extracellular-Membrane N	leciafbn4 l	Xelaev18043135 1 8 3	iafbn4 S	Xelaev180459(1.8.3	pair	HCSE	HCSE	HCSE	HCSE	HCSE	HCSE
Wht signaling Extracellular-Membrane N	lershisa1 l	Xelaev18038736 this study	shisa1 S	Xelaev180420 this study	nair	HCDE	HCDE	HCDE	NCSE	HCSE	inc
Wht signaling Extracellular Membrane N	levenisa? I	Xelaev18013772.1.8.3	shisa2 S	Xelaev180162 1 8 3	nair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Wht signaling Extracellular Membrane N		Xelaev18013772 1.0.3	shisa2.0	Xelaev100102, 1.0.3	singleton	n/a	n/a	n/a	n/a	n/a	n/a
What signaling Extracellular Membrane N	let shisa4p.L	Xelaev18900650 tills study	shice S	Xelaev 180 150( 1.0.5	singleton	LICOE	n/a	ino		LICOE	ino
Whit signaling_Extracellular-Membrane N		Xelaev100441021.0.3	shise7 C	Xelaev180407 1.6.3	pali	ncoe	11/d	nic. n/e	HODE	HCOE	
Whit signaling_Extracellular-Membrane N	le(snisa7.L	Xelaev18035942 1.6.3	shisa7.5	Xelaev1803771.6.3	pair	n/a	n/a	n/a	HOOF	HOOF	HOOF
wht signaling_Extracellular-Membrane N	le(snisa9.L	Xelaev180451651.8.3	snisa9.5	Xelaev180474(1.8.3	pair	n/a	n/a	n/a	HUSE	HUSE	HUSE
wht signaling_Extracellular-Membrane N	le(kremen1.L	Xelaev18007911 1.8.3	kremen1.S	Xelaev180107(1.8.3	pair	HCDE	HUSE	INC.	HCDE	HCDE	HCDE
Wht signaling_Extracellular-Membrane N	le(kremen2.L	Xelaev18045673 1.8.3	kremen2.S	Xelaev18047811.8.3	pair	HCSE	HCSE	HCSE	HCSE	HCSE	HCSE
Wht signaling_Extracellular-Membrane N	le(apcdd1.L	Xelaev18031847 1.8.3	apcdd1.S	Xelaev180335(1.8.3	pair	HCDE	NCDE	inc.	NCSE	NCDE	inc.
Wnt signaling_Extracellular-Membrane N	le(tpbg.L	Xelaev18027329 1.8.3	tpbg.S	Xelaev180294;1.8.3	pair	HCDE	HCDE	HCDE	HCSE	HCSE	HCSE
Wnt signaling_Extracellular-Membrane N	le(tpbgl.L	Xelaev18004367 this study	tpbgl.S	Xelaev180164 <mark>(this study</mark>	pair	HCSE	HCSE	HCSE	HCSE	HCSE	HCSE
Wnt signaling_Extracellular-Membrane N	le(trabd2a.L (tik	ki1 Xelaev18006601 1.8.3			singleton	n/a	n/a	n/a	n/a	n/a	n/a
Wnt signaling_Extracellular-Membrane N	le(trabd2b.L (tik	i2 Xelaev18023146 1.8.3	trabd2b.S (tik	i2Xelaev180252; 1.8.3	pair	HCDE	n/a	inc.	NCSE	NCSE	NCSE
Wnt signaling_Extracellular-Membrane N	le( znrf3.L	Xelaev18007912 1.8.3	znrf3.S	Xelaev180107(1.8.3	pair	NCDE	NCDE	NCDE	HCSE	HCDE	inc.
Wnt signaling_Extracellular-Membrane N	le( rnf43.L	Xelaev18011819 1.8.3	rnf43.S	Xelaev180145: 1.8.3	pair	HCDE	HCDE	HCDE	NCSE	NCSE	NCSE
Wnt signaling_Extracellular-Membrane N	le(notum1.L	Suzuki00074 this study	notum1.S	Xelaev180464: 1.8.3*(notum.S)	pair	HCDE	HCDE	HCDE	HCDE	NCSE	inc.
Wnt signaling_Extracellular-Membrane N	le(notum2.L	Xelaev18045202 1.8.3			singleton	n/a	n/a	n/a	n/a	n/a	n/a
Wnt signaling Cytoplasmic	dvl1.L	Xelaev18035651 1.8.3	dvl1.S	Xelaev180375(1.8.3	pair	NCDE	NCDE	NCDE	HCDE	HCDE	HCDE
Wnt signaling Cytoplasmic	dvl2.L	Xelaev18019661 1.8.3	dvl2.S	no model	pair	n/a	n/a	n/a	n/a	n/a	n/a
Wnt signaling Cytoplasmic	dvl3.L	Xelaev18027442 1.8.3	dvl3.S	Xelaev180295; 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Wnt signaling Cytoplasmic	frat1.L	Xelaev18032205 1.8.3	frat1.S	Xelaev180338 1.8.3	pair	HCDE	HCSE	inc.	HCSE	HCDE	inc.
What signaling Cytoplasmic	ctnnbl1 I	Xelaev18003084 1 8 3	ctnnbl1 S	Xelaev180465/183	pair	HCDE	NCSE	inc	HCDE	HCDE	HCDE
What signaling Cytoplasmic	ctnnb11	Xelaev18031149 1 8 3	ctnnb1 S	Xelaev180332(1.8.3	nair	HCSE	HCSE	HCSE	HCDE	HCDE	HCDE
What signaling Cytoplasmic	cenk1d l	Xoloov19042776 1.8.3	cenk1d S	Xelaev180032(1.0.0	nair	NCDE	NCDE	NCDE	HCDE	HCSE	inc
Wht signaling Cytoplasmic	conk1e l	Xelaev10043770 1.0.3	conk1e S	Xelaev(180020; 1.0.3	pair	HCSE	HCDE	inc	HODE	HCSE	HCSE
What signaling Cytoplasmic	conk1g11	Xelaev10023099 1.0.3	conkigi S	Xelaev180257(1.0.5	pair	HCDE	HODE		HODE	LCOL	ino
What signaling Cytoplasmic	CSIRTYT.L	Xelaev18018082 1.6.3	CSIIK IYI.S	Xelaev18020741.6.3	pair	HCDE	node	nobe	node	ncoe	n/o.
What signaling_Cytoplasmic	CSRK 1g2.L	Xelaev18006348 1.6.3			singleton	n/a	n/a		n/a	n/a	11/a
Wat signaling_Cytoplasmic	CSRK1g3.L	Xelaev18007961 1.8.3	CSRK1g3.S	Xelaev18010741.8.3	pair	HCDE	HODE	HCDE	HUSE	HUSE	HCSE
Whit signaling_Cytoplasmic	csnk2a1.L	Xelaev18043651 this study	csnk2a1.S	Xelaev180463(this study	pair	NCDE	HCDE	inc.	HCDE	HCDE	HCDE
Whit signaling_Cytoplasmic	csnk2a2.L	Xelaev18022836 1.8.3	csnk2a2.S	Xelaev180249!1.8.3	pair	HCDE	HCSE	inc.	HCDE	HCSE	inc.
Wnt signaling_Cytoplasmic	csnk2b.L	Xelaev18039202 1.8.3	csnk2b.S	Xelaev180424(1.8.3	pair	NCDE	NCDE	NCDE	HCDE	HCDE	HCDE
Wnt signaling_Cytoplasmic	ccdc88c.L	Xelaev18039541 1.8.3	ccdc88c.S	Xelaev180413; 1.8.3	pair	HCDE	NCDE	inc.	HCDE	HCDE	HCDE
Wnt signaling_Cytoplasmic	axin1.L	Xelaev18045581 1.8.3	axin1.S	Xelaev180478(1.8.3	pair	HCSE	HCDE	inc.	HCDE	HCDE	HCDE
Wnt signaling_Cytoplasmic	axin2.L	Xelaev18044248 1.8.3	axin2.S	Xelaev180468; 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Wnt signaling_Cytoplasmic	gsk3a.L	Xelaev18035964 1.8.3	gsk3a.S	Xelaev180377; 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Wnt signaling_Cytoplasmic	gsk3b.L	Xelaev18011240 1.8.3	gsk3b.S	Xelaev180144(1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Wnt signaling_Cytoplasmic	apc.L	Xelaev18008006 1.8.3	apc.S	Xelaev180107 1.8.3	pair	HCDE	HCDE	HCDE	HCSE	HCSE	HCSE
Wnt signaling_Cytoplasmic	apc2.L	Xelaev18006224 1.8.3	apc2.S	Xelaev180097! 1.8.3	pair	NCDE	n/a	inc.	HCDE	HCSE	inc.
Wnt signaling_Cytoplasmic	csnk1a1.L	Xelaev18017218 1.8.3	csnk1a1.S	Xelaev180214; 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Wnt signaling_Cytoplasmic	cxxc4.L	Xelaev18005708 1.8.3	cxxc4.S	Xelaev180094(1.8.3	pair	HCSE	HCDE	inc.	HCDE	HCDE	HCDE
Wnt signaling_Cytoplasmic	nkd1.L	Xelaev18022467 1.8.3	nkd1.S	Xelaev180247; 1.8.3	pair	HCSE	HCSE	HCSE	HCSE	NCSE	inc.
Wnt signaling Cytoplasmic	dact1.L	Xelaev18039817 1.8.3	dact1.S	Xelaev180411; 1.8.3	pair	HCSE	HCSE	HCSE	HCDE	HCSE	inc.
Wnt signaling Cytoplasmic	nxn.L	Xelaev18012739 1.8.3	nxn.S	Xelaev180153; 1.8.3	pair	NCSE	NCSE	NCSE	HCSE	HCSE	HCSE
Wnt signaling Cytoplasmic	ppp2cb.L	Xelaev18006173 1.8.3	ppp2cb.S	Xelaev180097(1.8.3	pair	HCSE	HCDE	inc.	HCDE	HCSE	inc.
Wnt signaling Cytoplasmic			ppp2ca.S	Xelaev180199 this study	singleton	n/a	n/a	n/a	n/a	n/a	n/a
Wnt signaling Nuclear	lef1.L	Suzuki00098 this study	lef1.S	Suzuki00099 this study	pair	HCDE	HCDE	HCDE	HCSE	HCSE	HCSE
Wht signaling Nuclear	tcf7 1	Xelaev18018649183	tcf7l1 S	Xelaev180202/18/3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Wht signaling Nuclear	tcf7l2 l	Suzuki00005 this study	tcf7l2 S	Suzuki00096 this study	nair	NCSE	NCSE	NCSE	HCSE	HOSE	HCSE
What signaling Nuclear	COLLE		tcf7 S	Suzuki00090 this study	singleton	n/2	n/2	n/a	n/2	n/a	n/a
White signalling_inducted	shh l	Valae: (19020676 1 8 3	shh S	Suzukiuuug/ tiiis suuuy	nair		HCSE	inc	HCDE	HCDE	HCDE
Lin signalling_Liganda	dbb l		alli.a	Aeidev 180328, 1.0.3	pair	HODE	LCOL				
i in signaling_Liganda	UIIII.L	Aeidev 180 13326 1.0.3	unn.o	Aeidev 180 158, 1.0.3	pair	HOSE	HOSE	HOSE			
nn signalling_Ligands		Xelaev18044498 1.8.3	1111.5	Xelaev180470; 1.8.3	pair	HODE	HODE	HODE			HODE
nn signaling_keceptor-wembrane	ptch1.L	Xelaev18006956 1.8.3	ptcn1.5	Xelaev180101 1.8.3	pair	HUDE	HODE	HODE	HUDE	HUDE	HCDE
Hn signaling_Receptor-Membrane	ptcn2.L	Xelaev18023085 1.8.3	ptcn2.S	Xelaev180252(1.8.3	pair	HCDE	HCDE	HCDE	HUSE	HUSE	HUSE
Hn signaling_Receptor-Membrane	smo.L	Xelaev18017905 1.8.3	smo.S	Xelaev180208 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Hn signaling_Receptor-Membrane	hhip.L	Xelaev18005527 1.8.3	hhip.S	Xelaev180092; 1.8.3	pair	NCDE	n/a	inc.	NCDE	NCSE	inc.

Hh signaling_Receptor-Membrane	hhat.L	Xelaev18026180 1.8.3			singleton	n/a	n/a	n/a	n/a	n/a	n/a
Hh signaling_Receptor-Membrane	hhatl.L	Xelaev18030596 1.8.3	hhatl.S	Xelaev180327 1.8.3	pair	HCDE	HCSE	inc.	HCSE	HCSE	HCSE
Hh signaling_Cytoplasmic-Cilia-Nuclear	gli1.L	Xelaev18013435 1.8.3	gli1.S	Xelaev180159; 1.8.3	pair	HCDE	HCSE	inc.	HCDE	HCDE	HCDE
Hh signaling Cytoplasmic-Cilia-Nuclear	gli2.L	Xelaev18044365 1.8.3	gli2.S	Xelaev180469; 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Hh signaling Cytoplasmic-Cilia-Nuclear	gli3.L	Xelaev18031191 1.8.3	gli3.S	Xelaev18033241.8.3	pair	HCDE	NCSE	inc.	HCSE	HCSE	HCSE
Hh signaling Cytoplasmic-Cilia-Nuclear	stk36.L	Xelaev18045625 1.8.3	•		singleton	n/a	n/a	n/a	n/a	n/a	n/a
Hh signaling Cytoplasmic-Cilia-Nuclear	sufu.L	Xelaev18034640 1.8.3	sufu.S	Xelaev180369; 1.8.3	pair	HCSE	HCSE	HCSE	HCSE	HCDE	inc.
Hh signaling Cytoplasmic-Cilia-Nuclear	prkaca.L	Xelaev18018940 1.8.3	prkaca.S	Xelaev180201(1.8.3	pair	HCDE	HCSE	inc.	HCDE	HCSE	inc.
Hh signaling Cytoplasmic-Cilia-Nuclear	kif7 l	Xelaev18018352 1 8 3	p	100001002011	singleton	n/a	n/a	n/a	n/a	n/a	n/a
Hh signaling Cytoplasmic-Cilia-Nuclear	arl13b I	Xelaev18011556 1 8 3	arl13b S	Xelaev1801421183	nair	NCDE	HCDE	inc	HCDE	HCDE	HCDE
Hh signaling Cytoplasmic-Cilia-Nuclear	foxi1 I	Xelaev18044086 1 8 3	foxi1 S	Xelaev180467:18.3	pair	HCSE	HCSE	HCSE	HCSE	HCSE	HCSE
HSPG Core protein	anc1 L	Xelaev18027873 1 8 3	anc1 S	Xelaev180200 1 8 3	nair	HCSE	NCSE	inc	HCDE	HCDE	HCDE
HSPG Core protein	apc21	Xelaev180121013 1.8.3	apc2 S	Xelaev180008 1 8 3	nair	NCSE	NCSE	NCSE	HCDE	HCDE	HCDE
HSPG Core protein	gpc2.L	Xelaev18039001 1 8 3	apc3 S	Xelaev180008 1.0.3	pair	n/a	n/a	n/a	HCSE	HCSE	HCSE
HSPG Core protein	gpc0.L	Xelaev18039001 1.0.3	gpc0.0	Xelaev100423 1.0.3	pair				HCDE	HCSE	inc
HSPG_Core protein	gpc4.L	Xelaev18036999 1.0.3	gpc4.5	Xelaev180423 1.8.3	pair	HCOL	NCSE	incol	HCOL	LCSE	
HSPG_Core protein	gpc5.L	Xelaev18027874 1.6.3	gpc5.5	Xelaev180299 1.8.3	pair	ncse n/o	NC3E	n/o.	HCSE	HCSE	HCSE
	gpco.L	Xelaev18013153 1.6.3	gpco.S	Xelaev180156 1.8.3	pair				HCSE	HCSE	HCSE
	SUCT.L	Xelaev18028097 1.6.3	suci.s	Xelaev180301 1.8.3	pair	HODE	HODE	HCDE	HUGOE	HOOF	HOOF
HSPG_Core protein	SOC2.L	Xelaev18032236 1.8.3	sac2.5	Xelaev180339[1.8.3	pair	HCDE	HCDE	HCDE	HUSE	HUSE	HUSE
HSPG_Core protein	sdc3.L	Xelaev18012477 1.8.3	sdc3.S	Xelaev180151(1.8.3	pair	HCDE	HCSE	INC.	HCDE	HCDE	HCDE
HSPG_Core protein	sdc4.L	Xelaev18043244 1.8.3	sdc4.S	Xelaev180460(1.8.3	pair	NCSE	NCSE	NCSE	HCDE	HCSE	inc.
HSPG_Enzyme	ndst1.L	Xelaev18016917 1.8.3	ndst1.S	Xelaev180200+1.8.3	pair	NCDE	NCSE	inc.	HCSE	HCSE	HCSE
HSPG_Enzyme	ndst2.L	Xelaev18034893 1.8.3	ndst2.S	Xelaev180371, 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
HSPG_Enzyme	ndst3.L	Xelaev18005673 1.8.3	ndst3.S	Xelaev180093(1.8.3	pair	n/a	n/a	n/a	HCSE	HCSE	HCSE
HSPG_Enzyme	ndst4.L	Xelaev18005671 1.8.3	ndst4.S	Xelaev180093(1.8.3	pair	n/a	n/a	n/a	HCSE	HCSE	HCSE
HSPG_Enzyme	sulf1.L	Xelaev18032097 1.8.3	sulf1.S	Xelaev180337{ 1.8.3	pair	NCDE	HCDE	inc.	HCSE	HCDE	inc.
HSPG_Enzyme	sulf2.L	Xelaev18043428 1.8.3	sulf2.S	Xelaev180461: 1.8.3	pair	NCDE	NCSE	inc.	HCSE	HCSE	HCSE
Notch signaling_Ligands-Receptors	dlc.L	Xelaev18039430 1.8.3	dlc.S	Xelaev180413(1.8.3	pair	HCDE	HCDE	HCDE	NCSE	HCSE	inc.
Notch signaling_Ligands-Receptors	dll1.L	Xelaev18026769 1.8.3	dll1.S	Xelaev180290 <sup>,</sup> 1.8.3	pair	HCSE	HCDE	inc.	HCSE	HCDE	inc.
Notch signaling_Ligands-Receptors	dll4.L	Xelaev18040076 1.8.3	dll4.S	no model	pair	n/a	n/a	n/a	n/a	n/a	n/a
Notch signaling_Ligands-Receptors	jag1.L	Xelaev18026450 1.8.3	jag1.S	Xelaev180285; 1.8.3	pair	NCSE	NCSE	NCSE	HCDE	HCSE	inc.
Notch signaling_Ligands-Receptors	jag2.L	Xelaev18039762 1.8.3	jag2.S	Xelaev180411; 1.8.3	pair	HCSE	NCSE	inc.	HCSE	HCDE	inc.
Notch signaling_Ligands-Receptors	notch1.L	Xelaev18038316 1.8.3	notch1.S	Xelaev180415; 1.8.3	pair	HCSE	HCSE	HCSE	HCDE	HCDE	HCDE
Notch signaling_Ligands-Receptors	notch2.L	Xelaev18023583 1.8.3	notch2.S	Xelaev180255 <mark>(this study</mark>	pair	HCDE	HCSE	inc.	HCDE	HCDE	HCDE
Notch signaling_Ligands-Receptors	notch3.L	Xelaev18018885 1.8.3	notch3.S	Xelaev180201 1.8.3	pair	NCDE	NCSE	inc.	HCSE	HCSE	HCSE
Notch signaling Extracellular-Membrane	psen1.L	Xelaev18039884 1.8.3	psen1.S	Xelaev180410; 1.8.3	pair	HCSE	HCSE	HCSE	HCDE	HCDE	HCDE
Notch signaling Extracellular-Membrane	psen2.L	Xelaev18026786 1.8.3	psen2.S	Xelaev180290; 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Notch signaling Extracellular-Membrane	psenen.L	Xelaev18036462 1.8.3	psenen.S	Xelaev180380; 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Notch signaling Extracellular-Membrane	aph1a.L	Xelaev18040555 1.8.3	aph1a.S	Xelaev180427! 1.8.3	pair	NCDE	HCDE	inc.	HCDE	HCDE	HCDE
Notch signaling Extracellular-Membrane	ncstn.L	Xelaev18040642 1.8.3	ncstn.S	Xelaev180428(1.8.3	pair	NCDE	HCSE	inc.	HCDE	HCDE	HCDE
Notch signaling Extracellular-Membrane	adam10.L	Xelaev18018164 1.8.3	adam10.S	Xelaev180206 1.8.3	pair	HCDE	HCDE	HCDE	HCSE	HCSE	HCSE
Notch signaling Extracellular-Membrane	adam17.L	Xelaev18028032 1.8.3	adam17.S	Xelaev180300; 1.8.3	pair	NCDE	NCDE	NCDE	HCDE	HCDE	HCDE
Notch signaling Extracellular-Membrane	lfna.L	Xelaev18045227 1.8.3	lfna.S	Xelaev180475; 1.8.3	pair	HCSE	HCSE	HCSE	HCSE	HCSE	HCSE
Notch signaling Extracellular-Membrane	rfna.L	Xelaev18043769 1.8.3	5		singleton	n/a	n/a	n/a	n/a	n/a	n/a
Notch signaling Extracellular-Membrane	furin.L	Xelaev18018314 1.8.3	furin.S	Xelaev180205(1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Notch signaling Extracellular-Membrane	pofut1 I	Xelaev18043053 1 8 3		X61467 100200	singleton	n/a	n/a	n/a	n/a	n/a	n/a
Notch signaling Extracellular-Membrane	pofut2 I	Xelaev18044882183	nofut2 S	Yelsov180473'183	nair	NCDE	NCDE	NCDE	HCDE	HCDE	HCDE
Notch signaling_Extraceridial memorane	cul1 l	Xelaev18031160 this study	cul1 S	Xelaev180473, 1.0.0	nair	HCSE	HCDE	inc	HCDE	HCSE	inc
Notch signaling_Cytoplasmic	dtv1 I	Xelaev18031109 118 3009	dtv1 S	Xelaev1803322 till Study	nair	HCSE	HCSE	HCSE	HCSE	HCSE	HCSE
Notch signaling_Cytoplasmic	dtx21	Xelaev18007429 1.0.3	dtv2 S	Xelaev180103 1.0.3	pair	NCDE	HCDE	inc	HCDE	HCDE	HCDE
Notch signaling_Cytoplasmic	dtx3 I	Xelaev18012096 1.0.3	dtv3 S	Xelaev180155, 1.8.3	pair	HCSE	n/a	inc.	HCSE	HCSE	HCSE
Notch signaling_Cytoplasmic	dtv3_like 1 !	Acidev 100 13443 1.0.3	000.0	Acidev 100 1094 1.0.0	singleton	n/a	n/a	n/a	n/a	n/a	n/a
Notch signaling Cytoplasmic	dtv31 like 1	Aeidev 18040251 1.0.3			singleton	n/a	n/a	n/a	n/a	n/a	n/a
Notch signaling_Cytoplasmic	dtv4 l	Xelaev18044336 1.0.3			singleton	n/a	n/a	n/a n/o	n/a	n/a	n/a
Noton signaling_Cy(oplasmic	ULX4.L	Xelaev18035125 1.8.3	db/E C	V I 100105 this study	Singleton	n/a	n/a	n/a n/a			
Notch signaling_Cytoplasmic	UIX5.L	Xelaev18043843 this study		Xelaev180465 this study	pair		11/a		HCDE	HUDE	HUDE
Notch signaling_Cytoplasmic	IDXW/.L	Xelaev18005488 1.8.3 (IDXW7-IIKe.L)		Xelaev180092, 1.8.3 (fDxw7-like.S)	pair	HUDE	HUDE	HUDE	HUSE	HUSE	HUSE
Notch signaling_Cytoplasmic	ICR.L	Xelaev18043930 1.8.3	IICH.S	Xelaev180466 1.8.3	pair	HUDE	HUSE	INC.	HUSE	HUSE	HUSE
Noton signaling_Cytoplasmic	SKP1.L	Xelaev18016889 1.8.3	skp1.S	Xelaev180199(1.8.3	pair	NCSE	NCSE	NCSE	HUSE	HCDE	INC.
Notch signaling_Cytoplasmic	nedd4.L	Xelaev18018180 1.8.3	nedd4.S	Xelaev180206! 1.8.3	pair	n/a	n/a	n/a	HCDE	NCDE	inc.

Notch signaling Cytoplasmic	nedd4I.L	Xelaev18008410 1.8.3	nedd4I.S	Xelaev180110; 1.8.3	pair	HCDE	NCDE	inc.	HCDE	HCSE	inc.
Notch signaling Cytoplasmic	mib1.L	Xelaev18031901 1.8.3	mib1.S	Xelaev180336 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Notch signaling Cytoplasmic	mih2 I	Xelaev18035630 1 8 3	mih2 S	Xelaev180375;18.3	pair	HCDE	HCDE	HCDE	HCSE	NCSE	inc
Notch signaling Cytoplasmic	neurl1 l	Xelaev18034635 1 8 3	neurl1 S	Xelaev180360:1.8.3	nair	HCSE	NCSE	inc	HCSE	HCSE	HCSE
Notch signaling Cytoplasmic	neurl1h l	Xelacy19037035 1.0.0	neurl1h S	Xelacy190303 1.0.0	pair	NCSE	NCSE	NCSE	HCSE	HCSE	HCSE
Notch signaling_Cytoplasmic	neurl2 l	Xelaev18017233 1.0.3	ficultio.o	Xeldev 1002 14, 1.0.5	singleton	n/o	n/o	n/a	n/a	n/2	n/a
Noten signaling_Cytoplasmic	neurl2.L	Xeldev 16043670 1.0.3	no	V-I	Singleton	NODE	n/a	ina			ina
Noten signaling_Cytoplasmic	neuris.L	Xeldev 160 16562 1.6.5	neuris.s	Xelaev 180203(1.8.3	pair	NGDE	11/d	inic.		HUSE	IIIC.
Noten signaling_Cytoplasmic			neuri4.5	Xelaev180010(1.8.3	singleton	n/a	n/a	n/a	n/a	n/a	n/a
Notch signaling_Cytoplasmic	numb.L	Xelaev18039881 1.8.3	numb.S	Xelaev180410(1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Notch signaling_Cytoplasmic	numbl.L	Xelaev18039315 1.8.3	numbl.S	Xelaev180425; 1.8.3	pair	NCDE	NCDE	NCDE	HCSE	HCSE	HCSE
Notch signaling_Nuclear	hey1.L	Xelaev18032125 1.8.3	hey1.S	Xelaev180338; 1.8.3	pair	NCSE	NCSE	NCSE	HCSE	HCSE	HCSE
Notch signaling_Nuclear	hey2.L	Xelaev18027001 1.8.3			singleton	n/a	n/a	n/a	n/a	n/a	n/a
Notch signaling_Nuclear	maml1.L	Xelaev18016823 1.8.3	maml1.S	Xelaev180199(1.8.3	pair	HCDE	HCDE	HCDE	HCSE	HCSE	HCSE
Notch signaling_Nuclear	maml2.L	Xelaev18013849 1.8.3	maml2.S	Xelaev180163 1.8.3	pair	NCDE	HCDE	inc.	HCDE	HCSE	inc.
Notch signaling_Nuclear	maml3.L	Xelaev180055551.8.3 (maml3-like.1.	<mark>l</mark> maml3.S	Xelaev180092(1.8.3 (maml3-like.1.S	pair	n/a	n/a	n/a	HCDE	HCDE	HCDE
Notch signaling_Nuclear	rbpj.L	Xelaev18005188 1.8.3	rbpj.S	Xelaev180089 1.8.3	pair	HCDE	HCSE	inc.	HCSE	HCSE	HCSE
Hippo signaling_Membrane	dchs1.L	Xelaev18013988 1.8.3	dchs1.S	Xelaev180165(1.8.3	pair	HCDE	HCSE	inc.	HCDE	HCDE	HCDE
Hippo signaling_Membrane	dchs2.L	Xelaev18005469 1.8.3	dchs2.S	Xelaev180092 1.8.3	pair	n/a	n/a	n/a	HCSE	n/a	inc.
Hippo signaling Membrane	crb1.L	Xelaev18023448 1.8.3			singleton	n/a	n/a	n/a	n/a	n/a	n/a
Hippo signaling Membrane	crb2.L	Xelaev18038421 1.8.3	crb2.S	Xelaev180418, 1.8.3	pair	HCSE	HCSE	HCSE	HCDE	HCDE	HCDE
Hippo signaling Membrane	crb3.L	Xelaev18019125 1.8.3	crb3.S	Xelaev180008; 1.8.3	pair	HCDE	HCDE	HCDE	HCSE	HCSE	HCSE
Hippo signaling Membrane	fat1 I	Xelaev18005336 1 8 3	fat1 S	Xelaev180091(1.8.3	pair	NCDE	HCDE	inc	HCDE	HCDE	HCDE
Hippo signaling Membrane	fat21	Xelaev18016840 this study	fat2 S	Xelaev180100 this study	nair	HCDE	NCDE	inc	HCDE	HCDE	HCDE
Hippo signaling_Cytoplasmic	amot	Xelaev18038818183	amot S	Xelaev180121, 1.8.3	nair	HCDE	HCDE	HCDE	HOSE	HCDE	inc
Hippo signaling_Cytoplasmic	amoti 1	Xelaev18038616 1.0.3	amotil1 S	Xelaev180421 1.0.3	pair	HCSE	NCSE	inc	NCSE	NCSE	NCSE
Hippo signaling_Cytoplasmic	amoti? I	Xeldev 10013030 1.0.3	amoth2 S	Xelaev18020011.9.2	pair	LCOL		inc.	HCSE	HCSE	LCOL
Hippo signaling_Cytoplasmic	amouz.L	Xelaev 1802/945 1.8.3	amouz.S	Xelaev 180299(1.8.3	pair	HCOE	HODE		HODE	HODE	HCOE
Hippo signaling_Cytoplasmic	cunna I.L	Xelaev18016936 1.6.3	cuma 1.5	Xelaev180200 1.8.3	pair		HCDE	HCDE	HODE	HODE	HODE
Hippo signaling_Cytoplasmic	ctnna2.L	Xelaev18004810 1.8.3	ctnna2.5	Xelaev180088; 1.8.3	pair	n/a	n/a	n/a	HUSE	HUSE	HUSE
Hippo signaling_Cytoplasmic	dig1.L	Xelaev18027514 this study	dig1.S	Xelaev180296 this study	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Hippo signaling_Cytoplasmic	dlg4.L	Xelaev18019541 1.8.3	dlg4.S	Xelaev180010; 1.8.3	pair	HCSE	HCSE	HCSE	HCDE	HCDE	HCDE
Hippo signaling_Cytoplasmic	scrib.L	Xelaev18032547 1.8.3	scrib.S	Xelaev180341; 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Hippo signaling_Cytoplasmic	llgl1.L	Xelaev18045557 1.8.3	llgl1.S	Xelaev180477(1.8.3	pair	NCSE	NCSE	NCSE	HCSE	HCSE	HCSE
Hippo signaling_Cytoplasmic	llgl2.L	Xelaev18044062 1.8.3	llgl2.S	Xelaev180467(1.8.3	pair	HCDE	NCSE	inc.	HCDE	HCDE	HCDE
Hippo signaling_Cytoplasmic	ptpn14.L	Xelaev18026221 1.8.3	ptpn14.S	Xelaev180286(1.8.3	pair	NCDE	NCDE	NCDE	HCDE	HCSE	inc.
Hippo signaling_Cytoplasmic	stk3.L	Xelaev18032220 1.8.3	stk3.S	Xelaev180338(1.8.3	pair	HCDE	HCDE	HCDE	HCSE	HCDE	inc.
Hippo signaling_Cytoplasmic	stk4.L	Xelaev18043241 1.8.3	stk4.S	Xelaev180460( 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Hippo signaling_Cytoplasmic	sav1.L	Xelaev18039624 1.8.3	sav1.S	Xelaev180412, 1.8.3	pair	NCSE	NCSE	NCSE	HCDE	HCSE	inc.
Hippo signaling Cytoplasmic			lats1.S	Xelaev180291; 1.8.3	singleton	n/a	n/a	n/a	n/a	n/a	n/a
Hippo signaling Cytoplasmic	lats2.L	Xelaev18013789 1.8.3	lats2.S	Xelaev180162; 1.8.3	pair	HCSE	HCSE	HCSE	NCDE	HCDE	inc.
Hippo signaling Cytoplasmic	mob1a.L	Xelaev18018517 1.8.3	mob1a.S	Xelaev180203 1.8.3	pair	HCDE	HCSE	inc.	HCDE	HCDE	HCDE
Hippo signaling Cytoplasmic	mob1b.L	Xelaev18005794 1.8.3	mob1b.S	Xelaev180094 1.8.3	pair	NCSE	NCSE	NCSE	HCDE	HCSE	inc.
Hippo signaling Cytoplasmic	limd1.L	Xelaev18031309 1.8.3			singleton	n/a	n/a	n/a	n/a	n/a	n/a
Hippo signaling Cytoplasmic	nf2 I	Xelaev18007416 1 8 3	nf2 S	Xelaev180103(183	nair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Hippo signaling Cytoplasmic	frmd6 I	Xelaev18030672183	frmd6 S	Xelaev180/12:183	nair	NCDE	NCSE	inc	HCSE	HCSE	HCSE
Hippo signaling_Cytoplasmic	wwc1 l	Xelaev18033072 1.0.0	MMC1 S	Xelaev180215(1.8.3	pair	NCDE	NCDE	NCDE	NCSE	HCSE	inc
Hippo signaling_Cytoplasmic	www.c2.L	Xelaev18005288 1 8 3	wwc1.0	Xelaev180215(1.0.5	pair	HCDE	HCDE	HCDE	HCDE	HCDE	
Hippo signaling_Cytoplasmic	wwcz.L	Xelaev10005366 1.0.3	wwc2.3	Xelaev100091/1.0.3	pair	LICOL	LCOL	HCDL	HODE		
Hippo signaling_Cytoplasmic	wwco.L	Xelaev18012373 1.8.3	wwc3.3	Xelaev180147, 1.6.3	pair	HCSE	HOSE	HCSE	HODE	HODE	HODE
Hippo signaling_Cytoplasmic	pardob.L	Xelaev18043447 1.6.3	pardon.5	Xelaev180461, 1.6.3	pair	HUGOE	HUGDE	HUSE	HODE	HODE	INC.
Hippo signaling_Cytoplasmic	pardog.L	Xelaev18031741 1.8.3	pardog.S	Xelaev180335 1.8.3	pair	HUSE	HCDE	inc.	HUSE	HCDE	INC.
Hippo signaling_Cytoplasmic	prkci.L	Xelaev18027593 1.8.3	prkci.S	Xelaev180047; 1.8.3	pair	HCDE	NCDE	inc.	HCDE	HCSE	inc.
Hippo signaling_Cytoplasmic	rasst1.L	Xelaev18023842 1.8.3	rasst1.S	Xelaev180257(1.8.3	pair	HCSE	HCSE	HCSE	HCDE	HCSE	inc.
Hippo signaling_Cytoplasmic	rassf2.L	Xelaev18018561 1.8.3	rassf2.S	Xelaev180203; 1.8.3	pair	HCSE	HCDE	inc.	HCDE	HCDE	HCDE
Hippo signaling_Cytoplasmic	rassf3.L	Xelaev18017523 1.8.3	rassf3.S	Xelaev180211(1.8.3	pair	HCSE	HCSE	HCSE	HCDE	HCSE	inc.
Hippo signaling_Cytoplasmic	rassf4.L	Xelaev18035163 1.8.3			singleton	n/a	n/a	n/a	n/a	n/a	n/a
Hippo signaling_Cytoplasmic	rassf5.L	Xelaev18012202 1.8.3	rassf5.S	Xelaev180149 1.8.3	pair	NCSE	n/a	inc.	HCSE	HCDE	inc.
Hippo signaling_Cytoplasmic	rassf6.L	Xelaev18005832 1.8.3	rassf6.S	Xelaev180095( 1.8.3	pair	HCSE	NCSE	inc.	HCSE	HCSE	HCSE
Hippo signaling_Cytoplasmic	tjp1.L	Xelaev18018146 1.8.3	tjp1.S	Xelaev180206! 1.8.3	pair	HCSE	HCSE	HCSE	HCDE	HCDE	HCDE
Hippo signaling_Cytoplasmic	tjp2.L	Xelaev18006873 1.8.3	tjp2.S	Xelaev180100(1.8.3	pair	NCDE	HCDE	inc.	HCDE	HCSE	inc.
Hippo signaling_Cytoplasmic	tjp3.L	Xelaev18006094 1.8.3	tjp3.S	Xelaev180096 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE

Hippo signaling_Nuclear	taz.L	Xelaev18038086 1.8.3			singleton	n/a	n/a	n/a	n/a	n/a	n/a
Hippo signaling_Nuclear	tead1.L	Xelaev18021781 this study	tead1.S	Xelaev180245 <mark>(this study</mark>	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Hippo signaling_Nuclear	tead4.L	Xelaev18036091 this study	tead4.S	Xelaev180378 <sup>,</sup> this study	pair	HCDE	HCSE	inc.	HCSE	HCSE	HCSE
Hippo signaling_Nuclear	yap1.L	Xelaev18013813 1.8.3	yap1.S	Xelaev180162: 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
Hippo signaling_Nuclear	vgll4.L	Xelaev18001858 1.8.3	vgll4.S	Xelaev180025! 1.8.3	pair	HCSE	NCDE	inc.	HCSE	NCSE	inc.
TLE_Nuclear	tle1.L	Xelaev18006924 1.8.3	tle1.S	Xelaev180101, 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
TLE_Nuclear	tle2.L	Xelaev18006642 1.8.3	tle2.S	Xelaev180011; 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE
TLE_Nuclear	tle4.L	Suzuki00121 this study	tle4.S	Xelaev180101; 1.8.3	pair	HCSE	HCDE	inc.	HCSE	HCDE	inc.
TLE_Nuclear	aes.L	Xelaev18006647 1.8.3	aes.S	Xelaev180011; 1.8.3	pair	HCDE	HCDE	HCDE	HCDE	HCDE	HCDE