# Identification and Expression Analysis of Zebrafish Glypicans during Embryonic Development

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#### Abstract

Heparan sulfate Proteoglycans (HSPG) are ubiquitous molecules with indispensable functions in various biological processes. Glypicans are a family of HSPG's, characterized by a Gpi-anchor which directs them to the cell surface and/or extracellular matrix where they regulate growth factor signaling during development and disease. We report the identification and expression pattern of glypican genes from zebrafish. The zebrafish genome contains 10 glypican homologs, as opposed to six in mammals, which are highly conserved and are phylogenetically related to the mammalian genes. Some of the fish glypicans like Gpc1a, Gpc3, Gpc4, Gpc6a and Gpc6b show conserved synteny with their mammalian cognate genes. Many glypicans are expressed during the gastrulation stage, but their expression becomes more tissue specific and defined during somitogenesis stages, particularly in the developing central nervous system. Existence of multiple glypican orthologs in fish with diverse expression pattern suggests highly specialized and/or redundant function of these genes during embryonic development.

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#### Introduction

The members of the glypican family are extracellular matrix components which play essential roles in various biological processes. They are Heparan Sulfate Proteoglycans, composed of a cysteine-rich protein core to which heparan sulfate (HS) sugar chains are covalently attached at the Cterminal end. They usually mediate their function anchored on the exoplasmic cell membrane via a GPI-linkage, but can also be cleaved off the membrane and in some cases enter the circulation [1].

The HS sugar chains, being highly sulfated, attract a number of growth factors, due to their negative surface charge. Consequently, glypicans are known to modulate the activity of various growth factors like Wnt, Hedgehog (HH), Fibroblast growth factors (Fgfs) and BMP [2-5]. However not all functions of glypicans are mediated by their HS chains [6]. There are 6 glypican genes in humans (*GPC1-6*) and two in Drosophila (*dally* and *dally-like*), which code for the protein core [7]. Among glypicans, *dally* was the first mutant to be isolated in Drosophila displaying developmental defects in the eye, brain and wing [1]. This was attributed to a reduction in DPP signaling. Since then, various genetic and biochemical studies have associated glypicans to different developmental processes, growth and disease progression. They can function as low affinity co-receptors for growth factors or assist in their transport across cells [8]. In rodents, Gpc1 regulates brain size via the modulation of Fgf signaling [4]. It is over-expressed in tumors from different organs [9] and was recently associated with the pathogenesis of a liver disorder, biliary artresia [10]. GPC3 mutations in humans and mice result in Simpson-Golabi Behmel syndrome, characterized by pre- and postnatal skeletal anomalies and craniofacial malformations [11]. There is also a very high occurrence of GPC3 over-expression in hepatocellular carcinoma where it is considered as a serum marker and potential therapeutic target [12]. Gpc5 is a very specific enhancer of HH signaling and stabilizes the interaction between HH and its receptor Patched1 [3]. Gpc5 knockdown was seen in patients with neural tube defects [13] and this gene has also been implicated in nephrotic syndrome [14].

Among all glypicans, Gpc4 influences extremely diverse development processes. In *Xenopus* and zebrafish, Gpc4 regulates the convergent extension movements during gastrulation [2,15]. Its interaction with Fgf2 is also important for proper forebrain patterning in *Xenopus* [16]. Astrocytes secrete Gpc4 and Gpc6 which guide the formation of excitatory

synapses [17]. Gpc4 also regulates insulin signaling via its interaction with the insulin receptor, and its levels in circulation correlate with an increased BMI [1]. Finally mutations in Gpc6 result in omodysplasia, characterized by shortened limbs and facial dysmorphism [18].

In contrast to humans and mice, the study of glypican function in zebrafish has so far been limited to *gpc3* and *gpc4*. A *gpc4* mutant in fish (*knypek*) displays defective convergent extension movements during gastrulation resulting in a reduced body length [2]. Gpc4 is directly involved in mediating non-canonical Wnt signaling in the embryos. Rescued *knypek* mutants also display defects in craniofacial cartilage development in larval and adult stages [19]. Gpc3 inhibits canonical Wnt  $\beta$ -catenin signaling after getting cleaved from the surface by Notum hydrolase and this regulation is also necessary for proper gastrulation [20].

We have previously found by single molecule analysis that extracellular matrix composition influences the mobility of Fgf8 forming a morphogen gradient in the extracellular matrix [21,22] Due to a lack of detailed information on fish glypicans as extracellular matrix components, we began to systematically characterize these genes. Firstly we identified and isolated 10 glypican genes from the fish. We studied their phylogeny with respect to humans and analyzed their expression pattern at various stages of embryonic development. Our findings indicate that glypicans are overall conserved between mammals and zebrafish, and may serve both generalized and highly tissue-specific functions in developing tissues.

### **Materials and Methods**

#### **Ethics Statement**

All animal experiments were carried out in strict accordance with European Union and German laws (Tierschutzgesetz). All experimental procedures were approved by the animal ethics committee of the TU Dresden and the Landesdirektion Sachsen (approval number: AZ 24D-9168.11-1/2008-4). This institutional review board specifically approved this study.

#### Zebrafish husbandry

Zebrafish were raised and maintained as described previously [23]. The wild-type line used was TL. Zebrafish embryos were obtained by natural spawning of adult fish and staged according to hours post fertilization (hpf) or standard criteria [24]

#### **Bioinformatics analysis**

Ensembl Zv9, GenBank and DFCI EST databases were used to identify zebrafish glypican sequences. Human glypican sequences were blasted against all three databases and the obtained fish sequences were confirmed for the presence of the glypican domain. Mega5.1 software was used for phylogenetic analysis. ClustalW and the Jalview software were used for generating and viewing the multiple sequence alignment, respectively. Protein sequence similarity and identities were obtained using NCBI BLASTp. Cinteny server (<u>http://cinteny.cchmc.org/</u>) and genomicus server were used for syntenic analysis.

## **Molecular Cloning**

Zebrafish mRNA was isolated from 24 and 48 hpf old embryos using the Trizol/Phenol-Chloroform method. cDNA was prepared from RNA using SuperScriptIII First-Strand Synthesis system (Invitrogen). The open reading frames of glypican genes were cloned into Topo vector using the primers given in Table 1. *gpc2* full length sequence was obtained by performing RACE using SMARTer RACE cDNA amplification kit (Clontech) with primer: CAGCCCTGAAACACCTTAGCAGAGA for 5' RACE and primer: AGACGCGCGGCAGGTACCTGCCAGCAG for 3' RACE.

## RT-PCR

cDNA was prepared from different developmental stages as mentioned above and used for RT-PCR. Full length primers (Table 1) were used to amplify *gpc1a*, *gpc1b*, *gpc4* and *gpc5c*. The primers used for *gpc2*, *gpc3*, *gpc5a*, *gpc5b*, *gpc6a* and *gpc6b* are also mentioned in Table 1. The PCR reaction was carried out using DreamTaq DNA polymerase (Fermentas) for 30-35 cycles.

## In Situ Hybridization

Embryos at the desired stage were fixed in 4% PFA and *in situ* hybridization was carried out according to the protocol described previously [25]. Full-length antisense probes were synthesized using T7/SP6 polymerase, Digoxigenin label (Roche) and linear Topo vectors. The color was developed using BM purple and used for imaging. Flat mounts were prepared after removing yolk sac and mounted in glycerol.

## Results

#### Identification of Fish Glypicans

There are 6 glypican genes in the human genome (*GPC1-6*). These sequences were blasted against Ensembl Zv9, GenBank and DFCI zebrafish EST databases to obtain the corresponding zebrafish glypicans. A previous study also reported 6 fish glypicans [10] but we identified 10 genes and named them according to their similarity to the human orthologs. The accession numbers of all genes from the different databases are shown in Table 2. New GenBank accession numbers were obtained for most sequences. Also indicated are the corresponding human orthologs and their peptide length.

Glypican gene family members can be grouped into two subfamilies, as reported previously [7]: *GPC1/2/4/6* and *GPC3/5* family (Figure 1). Phylogenetic comparison of fish, human and *Drosophila* sequences revealed that all fish genes cluster with their human orthologs. The two genes in Drosophila, *dally* and *dally-like protein* each belong to a different family. Multiple orthologs of human genes are commonly found in fish genome due to a duplication event which occurred before the radiation of teleosts [26]. Corresponding to *HsGPC2* we identified one

# Table 1. Primer list.

Gene Name	Forward Primer	Reverse Primer
Primers for clon	ing	
gpc1a	ATGGATCTGACAGCGGTCGC	TGATCTAGATTATCGTCTGAGCAATAGACTC
gpc1b	ATGGGTTTTGTCTCGCTGGT	GCATCTAGATTATCGCCTAAGCAAGACTGT
gpc2	ATGAAGATGATGAAGGTGGTGATGAAGAT	TTACAGACACAGACAGAGAGTAAAGC
gpc3	ATGATGCCTGGACTGAAGTTG	AGCTCGAGATCACTGAAGACCCAGTGTTATG
gpc4	CCTGGATCCATGAAGATGATCGTTGTGTT	GTGCTCGAGTTATCTTGTTTGGAGAGTGA
gpc5a	ACGGGATCCATGTCTCTCACCTAAAATC	GTCTCGAGTTCATTGTGTCTCCTTACTGG
gpc5b	AATGCTCCGCGGGACAGCA	TACTCGAGATCAAGGCCACAGGAGGAGCT
gpc5c	CGAATTCATGTCACGCGTGAATGTCAGCT	TCTCGAGTTCGACCCTTAGAGCTAAGGTATG
gpc6a	TAGGATCCATGGTGAAGACACCTGTCGT	CACTCGAGTTATCTCCAGCAGAGCAGCA
gpc6b	AAGGATCCATGTGGGCTGTGTGCGCGCT	GTCTCGAGCTATCTGCAGGTCAGTGCCA
Primers for RT-	PCR	
gpc2	CGA AGC TGC GCG GAG TCC CG	ACCAGTTGGTCCAGGTCCGTCC
дрс3	AGTGCGCTCATCCTTTCAGT	CATACGCAGAGCTCCCTTTC
gpc5a	GGATACTGCCTGAACGTGGT	TTTTCAGCCTGCGCTTTAAT
gpc5b	TCTACCTTCGAGGCGATGAT	CTCGCATCACGTTGAGACAT
gpc6a	CACCAAAGGCTTCAGTCTCC	CCATAAGTCCCTGGACGAAG
gpc6b	ACGTCAACCTGGAGGAGATG	ATGGGCTCCATCACAGACTC

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Table 2. Accession numbers of zebrafish glypicans.

						Peptide		
Gene	Chromosome		GenBank Acc No.		GenBank Acc.	length	Human homolog/	
Name	No.	Ensembl Gene ID	(old)	DFCI Identifier	No. (new)	(a.a.)	Peptide length	Comments
gpc1a	22	ENSDARG00000019341*	BC109411	TC366647	KC836776	554	HsGPC1/558	Gpc1 <sup>**</sup>
gpc1b	2	ENSDARG00000090456	BC053161 <sup>*</sup>	TC368439	KC836777	541	HsGPC1/558	
	14	ENSDARG00000037150	BC133103*	TC411825	KC791423	576	HsGPC2/579	Identified by 5'
gpc2								and 3' RACE
дрс3	14	ENSDARG00000032199	XM_682922 <sup>*</sup>	TC371608	-	590	HsGPC3/603	[31]
gpc4	14	ENSDARG00000015472*	NM_131860	TC419247	-	557	HsGPC4/556	[2]
gpc5a	Zv9_NA	ENSDARG0000088858	XM_001920514	TC414869*	KC791424	582	HsGPC5/572	
gpc5b	22	ENSDARG00000024588*		TC376562	KC791425	610	HsGPC5/572	Gpc5
gpc5c	2	ENSDARG00000074082*			KC999393	523	HsGPC5/572	
	10		BC151902*					
gpc6a	12	ENSDARG00000091739	(complete)	TC370142	KC999394	562	HsGPC6/555	
-,	1	ENSDARG00000086960	XM_003197610					
gpc6b	9	ENSDARG00000036468	XM_003199260*	NP13316404	KC999395	543	HsGPC6/555	Gpc6 <sup>**</sup>

\* cloned sequences; HsGPC: Human glypican

\*\* Previously reported names [10]

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new ortholog in the fish genome (*Drgpc2*). Two new orthologs were identified corresponding to *HsGPC1* (*Drgpc1a* and *Drgpc1b*) and *HsGPC6* (*Drgpc6a* and *Drgpc6b*) each, and 3 corresponding to *HsGPC5* (*Drgpc5a*, *Drgpc5b* and *Drgpc5c*). All glypican proteins exhibit more than 56% sequence similarity with their corresponding human orthologs (Table 3).

In order to identify true orthologs of *HsGPC1*, *HsGPC5* and *HsGPC6*, we investigated the chromosomal syntenic relationship between fish and human glypican genes by comparing common markers flanking these genes. The gene

cluster containing *GPC3* and *GPC4* is well conserved in Eumetazoa and is also seen in zebrafish (Figure 2B) [7]. Of the two *gpc1* in fish, *gpc1a* shares one adjacent marker with the *HsGPC1* (Figure 2A), although both *Drgpc1a* and *Drgpc1b* share an almost similar amino acid sequence identity with *HsGPC1* (Table 3). This indicates that *Drgpc1a* is likely to be a functional ortholog of *HsGPC1*. Fish has two orthologs for *HsGPC6*, namely *Drgpc6a* and *Drgpc6b*. Both genes share some synteny with the human form, such that certain markers are common between *HsGPC6* and *Drgpc6a* and others are



**Figure 1. Phylogenetic tree of glypican genes from Danio rerio, Homo sapiens and Drosophila melanogastor.** Phylogenetic comparison was carried out for glypicans genes sequences from zebrafish (Dr in black), humans and Drosophila (Hs and Dm in grey). The evolutionary tree was constructed using Neighbor-Joining method in the MEGA5.1 software using the Poisson model and partially deleted dataset. 500 bootstrap replications were used as a test of phylogeny and the values are indicated next to the branch. Branch length corresponds to evolutionary distances which denote the number of amino acid substitutions per site. Scale bar: 0.1

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common between *HsGPC6* and *Drgpc6b* (Figure 2C and 2D). This suggests that both zebrafish genes are derived from the same ancestral locus but have undergone rearrangements resulting in the final gene arrangements. Currently, *Drgpc6a* is annotated on two chromosomes, Chr1 and Chr12 (Ensembl Zv9), but only the Chr12 version is syntenic with *HsGPC6*.

In the human genome, *GPC5* and *GPC6* are present adjacently, but this contiguity is lost in the fish genome. There are 3 copies of *gpc5* in fish and *Drgpc5a* has the maximum amino acid sequence identity to *HsGPC5* (Table 3) but none are syntenic with humans. On fish Chr22, *Drgpc5b* and *Drgpc1a* are present contiguously, an arrangement not seen in mammals. Absence of synteny implies that along with whole

genome duplication, individual gene duplications for fish *gpc5* might have resulted in the observed multiple paralogs.

#### Glypican conserved domain structure

The glypican family of proteins is characterized by a large and highly conserved N-terminal glypican domain and a Cterminal region containing the residues for heparan sulfate and Gpi-anchor attachment. Multiple sequence alignment confirmed the presence of 14 conserved cysteine residues in all zebrafish glypicans (Figure 3). All these residues are involved in disulfide linkages and are necessary to maintain the folded structure [27]. The HS attachment site is always present within 50 residues of the C-terminal placing them very close to the

	Identity %	Similarty %
DrGpc1a vs HsGPC1	54	70
DrGpc1b vs HsGPC1	52	68
DrGpc2 vs HsGPC2	46	63
DrGpc3 vs HsGPC3	43	58
DrGpc4 vs HsGPC4	58	72
DrGpc5a vs HsGPC5	55	73
DrGpc5b vs HsGPC5	39	56
DrGpc5c vs HsGPC5	39	59
DrGpc6a vs HsGPC6	68	81
DrGpc6b vs HsGPC6	60	77

 Table 3. Protein sequence similarity.

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plasma membrane [28]. It consists of repeating Ser-Gly (SG) cluster ( $n\geq 2$ ) flanked by acidic residues on both sides [29]. There are 4 SG repeats in Gpc1a, Gpc1b, Gpc6a and Gpc6b; 3 repeats in Gpc4; 2 repeats in Gpc2, Gpc3, Gpc5a and 1 repeat in Gpc5b. Gpc5c and also Gpc5b contain a separate SG dipeptide followed by acidic amino acids, a potential chondroitin sulfate priming motif. Since HsGpc5 is known to carry both heparan sulfate and chondroitin sulfate chains [30], this feature may be conserved even in zebrafish Gpc5.

# Spatiotemporal expression of glypicans during early development

The composition of extracellular matrix differs considerably between specific tissues and stages of development. A previous study has focused on the expression of fish glypicans at 5 day post fertilization only in the developing liver [10]. We now analyze the temporal and spatial expression of all glypicans from cleavage to pharyngula stages using Reverse transcriptase PCR (RT-PCR) and in situ hybridization (ISH) (Figures 4-7). As reported before, gpc4 mRNA is present at all stages of embryonic development [2]. A constant expression (both maternal and zygotic) was also seen for gpc2, gpc3, gpc5a, gpc5b, gpc6a and gpc6b. Maternal expression was detected for gpc1b, but zygotic expression started only during segmentation.. Maternal expression was not seen for gpc1a and gpc5c. gpc1a transcripts were first detected at gastrulation stage and gradually increased during segmentation period and *apc5c* was detected from late segmentation stages.

These findings were confirmed and extended by whole mount *in situ* hybridization. As seen by RT-PCR, maternal contribution was observed for *gpc2*, *gpc4*, *gpc5a*, *gpc5b*, *gpc6a* and *gpc6b* (Figure 5A). *gpc1b* was also detected by ISH at cleavage stages but not later during gastrulation. *gpc3* transcripts could not be detected either during blastula or gastrula stages by ISH probably due to low levels of transcripts.

Gastrulation marks the process when cell movements result in the formation of the germ layers and embryonic axis. Gpc3 and Gpc4 influence this process in a mutually exclusive manner [20]. Along with gpc4, we also detected gpc2, gpc5a, gpc5b, gpc6a and gpc6b transcripts at 60% epiboly (Figure 5B). Further functional studies will uncover whether all glypican genes function independently or exhibit redundancy with each other during early stages.

We next examined the expression of glypicans during the segmentation period. Beginning from the 2-somite stage, the expression domains of glypicans became more tissue-restricted (Figure 5C). Whereas *gpc2*, *gpc5b* and *gpc6b* were seen ubiquitously on the dorsal side of the embryo, *gpc1a*, *gpc1b* and *gpc5a* showed restricted expression domains in the developing nervous system. *gpc1a* expression was seen throughout the brain primordium, *gpc1b* was present near the hindbrain and tailbud region and *gpc6a* in the mesencephalic region. *gpc5a* was selectively expressed in the ventral endoderm. *gpc3* or *gpc5c* were not detected.

By the 20 somite stage, all glypicans were detected by ISH. Most genes were expressed in a variety of neural tissues. *gpc1a* was detected in the primordial telencephalon, diencephalon and hindbrain (Figure 6A). By the 24 hpf stage, its expression became more confined to these regions and was also detected in the posterior lateral line primordium (Figure 6A', Figure 7A). *gpc1b* was initially seen in the trigeminal placode and the yolk cells during segmentation (Figure 6B) and at 24 hpf, in somites (Figure 6B') and the branchial arch (Figure 7B).

*gpc3* was expressed very specifically in the midbrain, coinciding with the time of active patterning processes in this tissue (Figure 6D, 6D'). This is in contrast to previous observation where *gpc3* was suggested to be restricted to the prospective hindbrain [31]. *gpc4* was expressed broadly throughout the embryo but excluded from most dorsal regions, including the telencephalon (Figure 6E. E'). *gpc5a* was detected in the midbrain, otic vesicle, primordial fin fold and cloaca (Figure 6F) and this pattern persisted at 24 hpf (Figure 6F'). *gpc5b* was restricted to the floor plate from the 20 somite stage (Figure 6G), but at 24 hpf, its expression was additionally detected throughout the nervous system (Figures 6G', 7C)

*gpc6a* was initially very strongly expressed in the epiphysis and the trigeminal placode (Figure 6I) and at 24 hpf, it was also seen in the telencephalon, tegmentum, cranial ganglia and the hindbrain (Figure 6I'). *gpc6b* was present uniformly in the nervous system (Figure 6J, 6J').

*gpc2* had the most widespread expression domain, seen ubiquitously in the embryo (Figure 6C, 6C'). In contrast, *gpc5c* was expressed outside the nervous tissue, in posterior somites (Figure 6H, 6H').

## Discussion

A previous study of glypican expression pattern in mice revealed that these genes are expressed predominantly in the embryonic brain [32]. In support of this, we also observed widespread expression of zebrafish glypicans in the developing nervous system. Apart from *gpc5c*, which is found in the posterior somites, all zebrafish genes are present either in very specific domains or more generally in the brain. Hence glypicans might have a conserved function during the development and patterning of the nervous system. Several studies in mammals have revealed the importance of glypicans



**Figure 2.** Syntenic conservation between zebrafish and humans glypicans. The figure depicts arrangement of genes surrounding glypicans on corresponding chromosomes in humans and zebrafish. Chromosome numbers from humans (*Hs*) and zebrafish (*Dr*) are indicated on the left. Glypican genes are represented in red and conserved markers around glypicans are in green or yellow. Non-conserved genes are in grey. The diagram is not to scale. doi: 10.1371/journal.pone.0080824.g002

in brain development [4,13]. In *Xenopus* also, Gpc4 is required for proper patterning of the forebrain [16]. Interestingly, the zebrafish *gpc4* mutant, *knypek*, displays craniofacial skeletal defects during the larval to adult stages due to improper chondrocyte and cartilage growth ([33].

A direct comparison of expression domains between mouse versus zebrafish glypicans reveals interesting analogous features. During rat and mouse embryogenesis, *Gpc1* is

predominantly expressed in the developing nervous system and skeletal system. It is specifically present in the proliferating neural progenitors of forebrain, midbrain and hindbrain at E14/ E18 pharyngula stages [34]. The expression of zebrafish *gpc1a* seen at 24 hpf corresponds well with that of rat/mouse *Gpc1*. Moreover we observed partial synteny between human *GPC1* and zebrafish *gpc1a* (Figure 2A). Hence based on comparable expression pattern and partial synteny, we conclude that

	10	20	30	40	50	60	70	80
DrGpc1a	MDLTAVALLVS	S L V S V S L S A E N .	A G G K A R S <mark>C</mark> T D V	R - Q F Y S G K G F T L	NGVPQSEIS	GEHLRICP-(	2 <mark>G Y T <mark>C C</mark>T S A</mark>	MEETLSNL
DrGpc1b	MGFVSLVLLCA	ALTGLVFGDN -	KPKTCSDI	R - L F Y SN K G F N L	NGVPQTEIS	GEHLRVCA-(	2 <b>G Y T C C T</b> S V	MEENLLNL
DrGpc2			DESOVIDEREV	R - RVYAEN - HGS			CITCCSSH	MEERVIIT
DrGpc3		CMSVVVI ASAO	ADOKSKNONEV	R S S F Q F L Y P G - N		GAHLKVCP-	GESCOTIE	MEEKISOL
DrGpc5a	MEMAIRGILF	FYTEFAVETDV		K V F OL KOI GP A	KSIPDTPRT	GSDLOVCLSI	RNLTCCTKK	MEERYOVA
DrGpc5b	ML R G T A P R V C WMWI L	LFSVLIWRVQ	SAG-AQSCHEV	K T A F Q L R Q V G S L	RWVPETAATI	DAELLICKH	Q G P T C C T R K	MEESYYSA
DrGpc5c	WSRVNVSWII	ITVLAVELATL	S A T R AH S <mark>C</mark> H E V	K T A F Q V R Q I G Q L	. KWVPETPATI	D V E L S V <mark>C</mark> KH	A <mark>G P S <mark>C C T</mark> R R</mark>	ME D S Y R A A
DrGpc6a	MVKTPV <mark>V</mark> VFTS	S L S L L L S L S C A	GD V K S R S <mark>C</mark> S D V	R - L A F T T K G F S L	. HN V P H Q E I S	GEHLRV <mark>C</mark> A-(	2 G Y T C C T S D	MEDQLGQQ
DrGpc6b	MW/	AVCAL VLLCVP.	A N V R A L N C S L V	K - D A Y S A L G F S S	DD VP AEQTS	GEDLRV <mark>C</mark> A-I	PLEA <mark>CC</mark> NTQ	MEESFSHR
	90	100	110 :	130	) 14	0 1	.50	160
DrGpc1a	SRREFEGLVREAGRS	SIOALLNAOYR'	TEDTYELELLD	G S E R W L E E A F V A	ALGELYRLN	AGVERDLYA	E L H R Y Y S G A	SLNLEE
DrGpc1b	SRREFEMQVKESGRS	LQAKLNGQFK	SFDEYFLELLN	RSEASLQSSFQS	GFGSLFSQM	SKVFQDLFSI	LRRYFRGS	N VNLEE
DrGpc2	S Q Q H F L S A V R D S <mark>S</mark> H F	F L F S S F S H T H R	R F D E L F R K L I D '	V S E E S M S E M F T H	ITYGRRYTQN.	AHIITQLF TI	D L R R Y <mark>Y</mark> T G <mark>G</mark>	6 R V S L A E
DrGpc3	A K Q N M E S S L Q A T S A Q	QLKGLIIQNAA	LFQEAFDMVLR	L G R N S T L M V L R E	EFPGLG-AG	ASGAVTQLFI	. D M S L Y I L G	- SDAN VND
DrGpc4	SRVDLKVPVHQLSSN	NLQSTFTQRH RI	HEDQFERELLD	NAEKSLNHMEVE	RTYGLMYVKN	KELFEGFFSI	OLRRYYSH G	SSEVNLDD
DrGpc5a DrGpc5b	ARROIQNELQISSS	ELKYLTI GHAS	SEOD TEHSLIS		TYFTIS	ASAPVGEFF		
DrGpc5c	VLRDTTONIGSYSYE	ELKFLISAHAA	AFODTFOSLIS	FSONHLTSLFET	TYSSLM-SS	ISPHIVCLF	DLSRFLOG	TGNVSVEA
DrGpc6a	S K L D F E R L V D D S S R N	NIRTTFTSRHK	K F D E F F L E L L D I	N S E K S L N D M F V F	RTYGKLYTHN	SEMFEDLFS	LKRYYTGG	N VNLEE
DrGpc6b	S S H D F Q K L MD D A <mark>S</mark> E E	E L RD T F MS GH K	R F D D F F L E L L E :	5 A <mark>E</mark> R S L N E M <mark>F</mark> V F	R T Y G K P Y L Q N .	AEVFQSLFSI	E L R R F <mark>Y</mark> T G G	N VNLEE
	170 180	0 190	200	210	220	230	240	1
DrGpc1a		KASDPETASLL	SDDEL		PEGDAPREL	KAKLVRAFT	ARAEVOGI	NAAGELVR
DrGpc1b	ALNEFWARLLDRLF	KALNPOYS I	GEEYL	- ECVAKOSEKL	PFGETPREL	KTKITRTVI	ARTEVOGL	VISGEAVR
DrGpc2	V L D D F WAGL L E C V F S	S L LN PQ Y E L	S D D Y L	- E C V R K H S E Q L L	. <mark>P F G</mark> D R P L K L I	HTQVSRAFT	AARALVQAL	AAGREIVS
DrGpc3	M V S T F F S R L F P L T Y F	R R L L GN G A V A G	I S	E E C L R GAWK G S S	SAYGSFPKMMI	VIT R L S R S L L	ATRVFLQAL	NLGIEVVN
DrGpc4	MLAEFWSELLERMFF	RLVNVQYE F	S D S Y M	- ECVSRHTDQL	(PFGDVPRKL	RLQLTRSFI	AVRAFTRGL	TLMPDVVR
DrGpc5a DrGpc5b	SSQSFFNALFPLIYE		Р Y V S T W S A E G		APFGAAPIRL.	ASQIAHASLI	CPALSPAL	AVGADVIN
DrGpc5c	AVHCEEDSLEPLVHT	TOTVNPGMEGS	IGTDASEGNOL	GDCI RMT ROD VN	PEGPHPKAM	AKDLADALR	AGRVISLAL	AFGSEVMN
DrGpc6a	V L N D F WS R L L E R M F C	QLLNSQFT F	SDDYL	ECISKYTDQL	P F G D V P R K L	KAQVTKAFI	AARSEVQGL	MVGREVAN
DrGpc6b	ML KD <b>F</b> WT R L L E R M F Q	QLLNSQFQ I	T D E Y L	- ECIGKYTEQLF	R P F G D V P K K L	KSQVTRAFI	A A R T F VQ G L	A V G R D V A N
	250 260	270	280	290	300	310	320	330
DrGpc1a	KUSOVELS PECNEAT		GL GS VKPCINY				SEGAEDSN	
DrGpc1b	KVSOVSLSTECVRAV	VMKOTYCPHCS	GVALAKPCSNY	CRNVLKGCLANC	ADLDTEWRN		OKLSRPYSV	DSVVLSLP
DrGpc2	KATQLRAGPECVRAL	LMRQWFCPLCR	G L P S L K P C H S L	CLNIMK GCLANC	ADLNSEWNS	FIDALTVVV	KLGGPFNF	ELAADAIA
DrGpc3	T T Q H L R A G R D C G R S L	L L K L WY <mark>C P H C</mark> Q :	S <mark>L</mark> L E A R <mark>P C</mark> R P L	CVSTMGA <mark>CL</mark> GGT	TEVQPHWRA	Y V D E L G S L A	AAMK <mark>G</mark> EQD I	EAVVLRLH
DrGpc4	K V S T V S A S P S C V R A S	SMKMLYCPYCS	GQVALKPCKNY	CLNVMRGCLANC	ADLDTEWNN	FLDSMLGLA	RLEGPFNF	ESVVDPID
DrGpc5a	TTDHIQLSRECREGL		ALTSSKPCLGY		AEVDAHWRE	FVRSLETLA	RMH GELDL	EQVELGAN
DrGpc5b	I TESVGMGRVCGRAL		GLTLIHACSNY		SELHOPWRD	Y V S L L E K L S I	JALSERYEV MVAGAHNI	FLALLGIR
DrGpc6a	RVAKVNISPGCSKAL	LTKMWYCPYCG	GMS GL K P C AN Y	ON VMR GCL AND	ADLDPEWNL	FIDAMLLVAL	RLEGPFNI	EAVMEPID
DrGpc6b	R	F T KML Y C S Y CQ	GL F T L K P <mark>C</mark> R N Y	CLNVMK G <mark>C</mark> LANC	ADLNNEWSK	FIDALLLT	ERLE <mark>G</mark> PFNI	E S VME P I D
	340	350	360	370 3	80 3	290	400	410
DrGnc1a				370 3 SSISEEPKK	80 KERTVTA	390		
DrGpc1a DrGpc1b	340 VRISEAVLAMQENME KRIAEAILYMODNOD	350 E I Y T S K <mark>V</mark> F DMF I N K V F	360 K A C G D R G E E G T L E C G T P A P	370 3 P S S I S E E P K K S S N I O E O I K R	80 : KERTVTA GRNTAEE	390 	400 L E Y K P S P V S S T P G -	410 KSAARLEV
DrGpc1a DrGpc1b DrGpc2	340 V R I S E A V L AMQ E N ME K R I A E A I L Y MQ D N Q C V T V S E G I MN MQ E N S I	350 E I Y T S K <mark>V F</mark> DMF I N K V F I S I S A K <mark>V</mark> F (	360 K A <mark>C G</mark> D R G E E G T L E C G T P A P Q G <mark>C G</mark> I P R P V P G	370 3 P S S I S E E P K K S S N I Q E Q I K R - R N K R <mark>S</mark> A A E R D A	80 K E R T V T A G R N T A E E A K P K F R S F R -	390 	400 L E Y K P S P V S S T P G - T E E K P S S	410 • K S A A R L E V • A Q L E R • G S G T D L D Q
DrGpc1a DrGpc1b DrGpc2 DrGpc3	340 V R I S E A V L AMQ E NME K R I A E A I L Y MQ D N Q D V T V S E G I MN MQ E N S I V I I RQ A L K Q A V A S K S	350 E I Y T S K V F DMF I N K V F I S I S A K V F 0 S K V S A Q V S	360 K A C G D R G E E G T L E C G T P A P Q G C G I P R P V P G G M C V H A P P R V S	370 P S S I S E E P K K - S S N I Q E Q I K R - - R N K R S A A E R D A R A V P V S A E H T S A	80 K E R T V T A G R N T A E E A K P K F R S F R - A S	390 	400 L E Y K P S P V S S T P G - T E E K P S S T V N H N R P	410
DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc4	340 VRISEAVLAMOENME KRIAEATLYMODNQU VTVSEGIMNMOENSI VIIRQALKQAVASKS VKISDATMNMOENSI	350 E I Y T S K V F D M F I N K V F I S I S A K V F ( S K V S AQ V S MQ V S Q K V F (	360 K A C G D R G E E G T L E C G T P A P Q G C I P R P V P G G M C V H A P P R V S Q G C Q P K L S M G	370 P S S I S E E P K K S S N I Q E Q I K R - - RN K R S A A E RD A R A V P V S A E H T S A F R S R R S A K D S G F	80 K E R T V T A G R N T A E E A K P K F R S F R - A S	390 	400 L E Y K P S P V S S T P G - - T E E K P S S - T V N H N R P P E A R P T T	410 PKSAARLEV AQLER GSGTDLDQ PMNFDPDE AAGTTLDR
DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5a DrGpc5b	340 VRISEAVLAMQENME KRIAEATLYMQDNQU VTVSEGIMNMQENSI VIIRQALKQAVASKS VKISDAIMNMQENSN ELVNDAVAHAQRSTA	350 E I Y T S K V F D M F I N K V F I S I S A K V F S K V S AQ V S MQ V S Q K V F A R I H AQ V Q	360 K A C G D R G E E G T L E C G T P A P Q G C G I P R P V P G G M C V H A P P R V S Q G C G Q P K L S M G R V C G Q S S R W T E K V C G S L T E S V S	370 P S S I S E E P K K S S N I Q E Q I K R - R N K R S A A E R D A R A V P V S A E H T S A F R S R R S A K D S G F P V N S V Q H S T G R A S T P A N S T G S I T	80		400 L E Y K P S P V S S T P G - T E E K P S S T V N H N R P P E A R P T T - D S I P L R G	410 PKSAARLEV GSGTDLDQ PMNFDPDE AAGTTLDR GANRNTED
DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5a DrGpc5b DrGpc5c	340 VRISEAVLAVQENME KRIAEALLYMQDNQQ VTVSEGIMNMQENSI VIIRQALKQAVASKS VKISDATMNMQENSI ELVRDAVAHAQRSTA ERINDATLAQLHGG GOVEEALLYADLHGG	350 EIYTSK VF DMFINKVF ISISAKVF KVVSQKVF MQVSQKVF ARIHAQVQ PHLSAVVSHVG PRLTATVD	360 K A C G D R G E E G T L E C G T P A P G C G I P R P V P G G M C V H A P P R V S Q G C G Q P K L S M G R V C G Q S S R W T E K V C G S L T E S V S K V C G H S S N T S T	370 5 S N I Q E Q I K K 5 S N I Q E Q I K R R N K R S A A E R D A R A V P V S A E H T S A F R S R R S A K D S G F P V N S V Q H S T G R A S T P A N S T L G S L I S T V R T F P P A S V H	80 K E R T V T A G R N T A E E A K P K F R S F R - A S P G R F R P Y S - A S P - S V N P S L E S P P P V N I S OD	190 	400 L E Y K P S P V S S T P G - T E E K P S S T V N H N R P P E A R P T T - D S I P L R G [ S S S H T L P - A H L H S S L P	410 PKSAARLEV GSGTDLDQ PPMNFDPDE AAGTTLDR GARTLDR GTGNQHEH PLKNSKSDR
DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5a DrGpc5b DrGpc5c DrGpc6a	340 VRISENVLANGENME KRIAEAILYMODNOZ VTVSEGIMNMENSI VIIRQALKQAVASKS VKISDAIMNMENSA ELVROAVAHAQRSTA ERINDAILTACHGF GQVEEAILYAQHGF VKISEAIMTMODNSA	350 E I Y TS K V F DMF I N K V F I S I S AK V F K V S Q K V F VQ V S Q K V F PH L S A V V S H V G P R L T A T V D	360 K A C G D R G E E G T L E C G T P A P Q G C G I P R P V P G G M C V H A P P R V S Q G C G Q P K L S M G R V C G Q S S R W T E K V C G S L T S N T S T Q G C G H P K A A S V	370 S S I S E E P K K S S N I Q E Q I K R R N K R S A A E R D A R A V P V S A E H T S A F R S R R S A K D S G F P V N S V H S T G R A S T P A N S T L G S L T S T V R T F P P A S V H G R S A R G I S D V - F	80 :	190 LQTSN	400 L E Y K P S P V S S T P G - T E E K P S S T V NH N R P P E A R P T T - S S S H T T L P - A H L H S S L P P E E R P T T	410 PKSAARLEV GSGTDLDQ PPMNFDPDE AAGTTLDR - ANRNTED DTGNQHEH LKNSKSDR
DrGpc1a DrGpc2 DrGpc3 DrGpc4 DrGpc5a DrGpc5b DrGpc5c DrGpc6a DrGpc6b	340 KRI A E A VL A MO E NME KRI A E A LI YMO DNQC VT VS E GI MNMC EN SI VI I RQ A KQ A VA SK VK I S D A TMNMC EN SI E L VRD A VAHAQ RS T Z E T NDA TL TA Q LH G GQ VE E A I LYA LH G VK I S E A I MNMC EN SI VK S E A I MNMC EN SI	350 DMF I N K V F I S I S A K V F I S I S A K V F VQ V S Q K V F ( A R I H AQ VQ PH L S A V V S H V G P R L T AT V D VQ V S K V F ( VQ I S N P V F (	360 K A C G D R G E E G T L E C G - T P A P Q G C G I P R P V P G G M C V H A P P R V S Q G C G Q P K L S M G R V C G S S R W T E K V C G S L T E S V S K V C G H S S N T S T K V C G C H S S N T S T Q G C G H P K A S S V Q G C G Q P E P A G M	370 5 S I S E E P K K 5 S N I Q E Q I K R F N K R S A A E R D / F R S R S A K B G F 9 V N S V Q H S T G R / 5 T P A N S T L G S L T 5 T V R T F P P A S V H G R S A R G I S V - F T R S A R S V H D S - F	80	990 L Q T S N	400 L E Y K P S P V S S T P G - - T E E K P S S - T V N N R P - P E A R P T T - D S I P L R G I S S S H T L P A H L H S S L P - P E E R P T T - P E E R P T V	410 PKSAARLEV GSGTDLDQ PMNFDPDE AAGTTLDR CANRNTED DTGNQHEH LKNSKSDR AAGTSLDR AAGTSLDR
DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc5a DrGpc5b DrGpc5b DrGpc5c DrGpc6a DrGpc6b	340 KR I SE AV LAMO ENME KR I AEA LAMO DNOC VT VSE GI MNME EN SI VI I RQA LKQAVASKS VKI SOA TIMNMO EN SI ELVRO AVAHAR SI I ER INDA I LA CHAG QVE EA I LYAC LHGF VKI SE AI IMTMO DN SI VKI SE AI IMTMO DN SI VKI SE AI MTMO DN SI 420 420 420 420	350 E I Y T S K V F JNF I N K V F I S I S A K V F K V S AQ V S MQ V S Q K V F MQ V S Q K V F P H L S AV V S H V G P R L T A T V D MQ V S K V F MQ V S K V F (0 1 S N P V F 130 44	360 K A C D R G E E G T LE C G - T P A P: Q G C I P R P V P G G M C V A P P R V S Q G C Q P K L S M G R V C Q S C S W T E K V C Q S L T E S V S K V C G S L T E S V S K V C G H S S N T S T Q G C Q P E P A G M 0 450	370 5 S N I QE QI KR	80 K E T V T A 	990 LQTSN	400 L E Y K P S P V S T P G - - T E E K P S S - T V NH N R P - P E A R P T T - D S I P L R G S S S H T L P A H L H S L P - P E E R P T T - P E E R P T T E E L P T V	410 PKSAARLEV GSGTDLDQ PMNFDPDE AAGTTLDR CANRTDD DTGNQHEH LKNSKSDR AAGTSLDR AAGTSLDR ASGAPLHR
DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5b DrGpc5b DrGpc5c DrGpc6a DrGpc6b	340 VR TISE A VLAMO ENME KRI A EA LI VMO DNOC VT VSE GI MNMO EN SI VI TROAL KOAVASKS VKI SO A TIMMO EN SI EL VRD A VAHA RST Z ER TND AT LI TA OLH GF GVEE ALL VA OLH GF VKI SE A TIMTMO EN SI VKI SE A TIMTMO EN SI 420 0	350 E I Y T S K V F J M F I N K V F I S I S A K V F G X K V S AQ V S WQ V S Q V F WQ V S K V F 130 44 V S K K K K MOL V I	360 K A C GD R G E E G T LE C G T P A P Q G C G I P R P V P G G M V H A P P R V S Q G C G P K L S M G R V C G S S R W T E K V C G S S L T E S V S K V C G H S S N T S T Q G C G P P C A G M 0 0 0 0 0 0 0 0 0 0 0 0 0	370         3           > S S I S E E P K K         -           - RN KR S A E RD / KR         -           - RN KR S A A E RD / KR         -           - RN KR S A A E RD / S / F S R S A S A H S / S / S / S / S / S / S / S / S / S	80 GRNTAEE GRNTAEE XKPKFRSFR NS	190 L Q T S N A P G A D K I G MI 480 - S W I P F W M GI	400 L E Y K P S P V S S T P G- T E E K P S S T V N H N R P P E A R P T T D S I P L R G S S S H T L P A H L H S S L P P E E R P T T 	410 YKSAARLEV GSGTDLDQ PMNFDPDE AAGTLDR CANRTED DTGNQHEH VKNSKSDR AAGTSLDR AAGTSLDR 90 90 90
DrGpc1a DrGpc1b DrGpc2 DrGpc4 DrGpc4 DrGpc5b DrGpc5b DrGpc5c DrGpc6a DrGpc6b	340 KR I A E A V L AMO E NME KR I A E A L L YMO DNQC VT VS E CI MNMG EN SI VI I RQ ALKQ AVASKS VK I SD A I MNMG EN SA E L VRD AVAHAO RST A E R INDA KI L TAO LHG G Q VEE AI L YAC LHG G VK I SE AI MNMO EN SA VK I SE AI MNMO EN SA 420 4 Q	350 E I Y T S K V F J S I S A K V F NF I N K V F Q V S Q K V F A R I H AQ VQ H L S A V V S H V G P R L T AT V D H L S A V V F ( MQ I S N P V F ( 130 40 V S K L K EMQL Y V S K L K EMQL Y	360 K A CGD R GE E GT L E CG T P AP Q G CG I P R P V P G Q G CG P K L S MG R V CGQ S R WT E K V CG L T E S V S K V CG L T E S V S K V CG L T E S V S Q G CG P K A A S V Q G CG P C A A S V Q G CG P C A S V Q G C G P C C C C C C C C C C C C C C C C	370         37           PS S I S E S E S E S E S E S E S E S E S	80 KE RT VT A GRN TA E E KP KF RS F R - S P - S VN PS LE E - P P S VN PS LE E - S GR F K P F N S S GR F K P Y 470 DK CWN G I T K A R CWN G I T K A	990 LQTSN	400 L E Y K P S P V S S T P G - - T E E K P S S T V N H N R P P E A R P T T D S I P L R G S S H T L P - A H L H S S L P P E E R P T T E E L P T V E L D T V G L A N Q I N N G L A S Q I N N	410 PKSAARLEV GSGTDLDQ PMNFDPDE AAGTTLDR GAAGTTLDR CANRNTED DTGNQHEH ZKNSKSDR AAGTSLDR AAGTSLDR AGTSLDR 90 IPE VEIDIT
DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5a DrGpc5b DrGpc5b DrGpc5b DrGpc6a DrGpc1a DrGpc1b DrGpc1b DrGpc1	340 VR IS E A VLAMO ENME KRI A EA LLYMO DNQC VT VS E GIMNING EN SI VK IS D A TIMNING EN SI VK IS D A TIMNING EN SI E L VRD A VAHAQ RS I Z E TINDA IL TA Q LHG Q V E E A ILYAQ LHG VK IS E A IMMING EN SI VK IS E A IMMING EN SI 420 4 Q	350 E I Y T S K V F J S I S A K V F VQ V S Q K V F VQ V S Q K V F VQ V S Q K V F VQ V S X V F VQ V S K V F VQ V S K V F VQ V S K K K E M Q V 30 44 V Y S K K K E M Q M Y V S RML R D M Q F	360 K A CGD R G E E G T L E C G T P A P Q G C G P R P V P G Q G C Q P K L S MG R V C G S L T E S V S. K V C G S L T E S V S. K V C G L T E S V S. K V C G L Q P E P A GM 0 0 0 0 0 0 0 0 0 0 0 0 0	370         3           2 S S I S E E P K         -           5 S I S E E P K         -           - RN KR S A A E RO J         -           - RN KR S A A E RO J         -           - RN K S A A E RO J         -           - RN K S A A E RO J         -           - ST R S R S A KD S GF         -           - ST P AN ST L GS L I         -           ST S A R S VHD S - F         -           - RS A R S VHD S - F         -           - 460         -           KT A SS T S E         -           H T A AD - V TN E E         -	80 KERTVTA GRNTAEE KPKFRSFR PGRFRPYS - SS P - SVNPSLE P - SVNPSLE P - SVNPSLE SGRFKPY 470 K CWN G I TKA RCWN GMS VG Q CWN GQ TRG	990 LQTSN	400 - L E YK P S P - V S S T P G - T E E K P S S - T V N N R P - P E A R P T T - D S I P L R G S S S H T L P - P E E R P T T - E E L P T V - E E L P T V - G L A N Q I N N G L L N Q L N N	410 YK SAARLE V 
DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5a DrGpc5b DrGpc5b DrGpc6b DrGpc1b DrGpc1b DrGpc1a DrGpc12 DrGpc2 DrGpc2 DrGpc2	340 VR T S E A V L AMO E NME KR I A EA IL VM DO NOC VT VS E GI MNME EN SI VI T RQA L KQ AV AS KS VK I SO A TIMNKO E N SI E L VRD A VAHA R ST I E R IND A IL TA C L HG GQ V E E A IL VA Q L HG F VK I S E A I MT MO N SI VK I S E A I MT MO N SI 420 Q	350 E I Y T S K V F J M F I N K V F I S I S A K V F WQ V S Q K V F MQ V S Q K V F MQ V S K V F MQ V S K V F I S S K V F I S S K V F Q I S N P V F Q I S N P V F Q I S N P V F I S S K V F Q I S R V F I S S K K K K K K K K K K K K K K K K K	360 K A CGD R G E E GT L E C G T P A P Q G C G I P R P V P G G G Q P K L S M G R V C G S S R WT E K V C G L T S V S K V C G H S K N T S T Q G C G P P A G M 0 WIQ P S A L C S G W V H P R K L C V D W IQ L P S A L C S G W A L P H T C S D Y S G G G A L C S K	370         3           > S S I S E E P K         -           > S S I S E E P K         -           - RAKR S AAE RD / AVP VS AE HT S / A         -           R R R S AKD SG F         -           > VN S VQ H S T GR / A         -           > T P AN ST L GS L I         -           S T P AN ST L GS L I         -           S T AN ST M S - F         -           G R S ARG I S D V - F         -           460         -           K T AS S T T GE         -           R S G G E S G         -           P T S L N S S T GE         -	80	900 L Q T S N	400 - L E Y K P S P G - V S S T P G - T E K P S S - T V N H N R P - P E A R P T T - D S I P L R G S S S H T L P A H L H S S L P - P E E R P T T E E L P T V G L A N G I N N G L A S C I N N R V H P H G	410 VKSAARLEV VKSAARLEV OKSTDLDQ PANFDPDE AAGTTLDR AAGTTLDR CKNSKSDR AAGTSLDR 90 IPE VEIDIT IPE VEIDIT IPE VEIDIT IPE VEIDIT IPE LELDVS SSESKQKTP
DrGpc1a DrGpc2 DrGpc3 DrGpc4 DrGpc5s DrGpc5s DrGpc5s DrGpc5s DrGpc6s DrGpc6b DrGpc1a DrGpc1b DrGpc1b DrGpc1b DrGpc2 DrGpc4 DrGpc4	340 WR IS E & V LAMO E NME KR I A E AT L Y MO DNOC VT VS E G IMNMG EN SI VI I RQ ALKQ AV AS KS VK I S D A IMNMG EN SI E V VR DV AH A R ST J E V VR DV AH A R ST J VK I S E A I MMMO EN SI VK I S E A I MMMO EN SI VK I S E A I MMMO EN SI 420 4 Q	350 E I Y T S K V F J S I S A K V F NF I N K V F S K V S A Q V S PH L S A V V S H V G A R I H A Q V PH L S A V V S H V G WQ V S K V G (WQ V S K V F WQ V S K L K E MQ Y V S K L K E MQ Y V S K L K E MM Q Y L Q A R L K P M R GF I S C L R G S Q F V K K K K K H A K K F V S K K L K H A K K F	360 K A G D R G E E G T L E G G T P A P Q G C I P R P V P G Q G C G P K L S MG V G G S R WT E K V C G S L T S V S K V C G S L T S V S Q G C G P K A A S V Q G C G Q P E A A G M 0 MI Q P S A L C S K W H L P K L C V D WL A L P H T I C S D W S G G E A L C S K W S T P D T V C V G	370         370           PS S I S E S E S E S E S E S E S E S E S	80	90 LQTSN APGADKIGM - SYLPEVMG RYLPEVMG RYLPAVTG KPGPGK - RYESVMS - RYESVMS 	400 - L E Y K P S P - V S S T P G - T E K P S S - T E K P S S - T V N N R P - P E A R P T T - D S I P L R G S S S H T L P A H L H S L P - P E E R P T T E E L P T V G L A N G I N N G L L N G L N G L L N G L N G L L N G L N G L A N O Y S V P H G G L A N O Y S V P H G G L A N O Y S V P H G G L A N O Y S V P H G G L A N O Y S V P H G V P H G 	410 VKSAARLEV VKSAARLEV GSGTDLDQ GSGTDLDQ PMNFDDPDE AAGTTLDR DTGNQHEH VKSKSDR 4AGTSLDR 4AGTSLDR 90 IPE VEIDIT IPE VEIDIT IPE VEIDIT IPE VEIDIT IPE VEIVEA
DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5a DrGpc5b DrGpc5c DrGpc5c DrGpc6b DrGpc1a DrGpc1b DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc3 DrGpc5a DrGpc5a DrGpc5a	340 KR I A E A V L AMO E NME KR I A E A I L YMO DNQC VT VS E GI MNMG EN SI VI I RQ A LKQ AV ASK S VK I S D A I MNM E N SA E L VRD A VAHAQ RS I / E L VRD A VAHAQ RS I / E ND A I L T A Q LH G VK I S E A I MMM E N SA VK I S E A I MMM E N SA 420 Q	350 E I Y T S K V F J S I S A K V F VQ V S Q K V F VQ V S Q K V F VQ V S Q K V F VQ V S K V S H V G P R L T A T V D V S S K L S H V G V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E MQ L V V S S K L K E M X K F I S K K L K E M X K F I S K K L K L X V K S E K K F I S K K L K L X V K S E K K F I S K K L X V K S E K K F I S K K L X V K S E K K F I S K K S K K K K F I S K K S K K K K K F I S K K S K K K K K K K F I S K K S K K K K K K K F I S K K S K K K K K K K K K K K K K K K K	360 K A GG D R G E E G T L E G T P A P Q G C I P R P V P G Q G C Q P K L S MG R V G Q S S RWT E K V C G L T E S V S K V C G L T E S V S K V C G L F S V S Q G C G Q P E P A GM 0 0 0 0 0 0 0 0 0 0 0 0 0	370         3           PS S I SEQ LK         -           S S I Q Q I K         -           RNKRSAAERD         -           RNKSSAERD         -           RNKSSAERD         -           RNKSSAERD         -           RNKSSAERD         -           STVRTPPAST         -           GRSARGISU         -           IRSARGISU         -           CASST         -           CRSSP         -           BSSSAES         -           CRSARGISU         -           IRSARGISU         -           IRSARGISU         -           IRSARGISU         -           ISSARGISU	80 KERTVTA GRNTAEE KEPKFRSFR P GRFRPYS - S P SVNPSLE P - SVNPSLE P - SVNPSLE P - SVNPSLE K CWN GITKA K CWN GITKA CWN GQTRG L CWN GQTRG L CWN GQTRG L CWN GDVA	490 400 - S Y L P E VMG - S Y L P E VMG - R V L P E VMG - R V L P A W T AI K F P G P G L K K F P G P G V MS - R Y E S V VMS	400 - L E Y K P S P - V S S T P G - T E K P S S - T E K P S S - T S S S H T L P - P E A R P T T - D S I P L R G S S S H T L P A H L H S L P - P E E R P T - P E E R P T - P E E R P T - P E E R V S G L A N G L N G L N G L N G L N G V S G G A A C S N G G A A C K H	410 VK S A A R L E V VK S A A R L E V VK S A A R L E V VK S C VK S C
DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5a DrGpc5b DrGpc5c DrGpc6a DrGpc1b DrGpc1b DrGpc1b DrGpc2 DrGpc4 DrGpc3 DrGpc4 DrGpc3 DrGpc5a DrGpc5b DrGpc5b DrGpc5c	340 VR IS E A VL AMO ENME KRI A EA IL VM DONCY VT VS E GI MNME EN SI VK IS D A TMNME EN SI VK IS D A TMNME EN SI E L VRD A VAHAQ RS I Z E T ND A IL TA Q LH G GQ VE E AI L YA Q LH G VK IS E A IMMME EN SI 420 Q	350 E I Y T S K V F J S I S A K V F I S I S A K V F VQ V S Q K V F VQ V S Q K V F VQ V S Q K V F VQ V S K V F VQ V S K K K F V Y S K L K E MQ L Y V S K L K E M X F F I S L C Y K S F F M S I Q R Y K S F F T I Y I S R Y K S F	360 K A CGD R G E E GT LE C G T P AP Q G C G P R P V P G Q G C Q P K L S MG R V C Q S S R WT E Q G C Q P K L S V S K V C G S L T E S V S K V C G L T E S V S K V C G L A P K A S V Q G C Q P E P A GM 0 0 WI Q P S A L C S G WVH L P R K L C V D W A L P H T I C S D Y S G G E A L C S C W S T P D T V C V G Y G A L AD Q L C I S F S N L P E M L C B G	370         3           2 S S I S E E P K K         -           2 S S I S E E P K K         -           5 S I S E E P K K         -           - RN KR S A A E RO J         -           - RN KR S A A E RO J         -           - RN K S A K B S G F         >           - S R R S A K D S G F         -           - S T P AN S T L G S L I         -           S T V A S T F P A S W H         -           - R S A R S V H D S - F         -           - R S A R S V H D S - F         -           - R S A R S V H D S - F         -           - R S A R S V H D S - F         -           - R S A R S V H D S - F         -           - R S A R S V H D S - F         -           - R S A R S V H D S - F         -           - R S A R S V H D S - F         -           - V N M E R         -           - V W M D R         -           - K V V D E F         -	80 KE RT VT A GRNT A E E K P KF R S F R P G R F R P Y S - S P - S VN P S L E I P - S VN P S L E I P P - V N I S Q D S G R K P Y 470 K CWN G I T K A R CWN G Q T R G Q CWN G Q T R G L CWN G Q T R G A CWN G D V X I C S G B D V V I S CWS G D V V I	480 	400 - L E YK P S P - V S S T P G - T E E K P S S - T E E K P S S - T V N H N R P - P E A R P T T - D S I P L R O S S S H T L P A H L S S L P C L AN Q I N G L AN Q I N G L AN Q I N G L AN Q V N G L AN Q V S G L AN Q V S N G I K AQ A E N N G I C AQ K H N N G V A Q R Q N	410 VK S A AR L E V VK S A R L E V PMN FD PD E A A GT L D R A A GT L D R A A GT S L D R VK S K S D R PE VE I D I T I PE VE VE I D I T I PE VE V VK E A I PE VK VK E A
DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5c DrGpc5c DrGpc5c DrGpc6b DrGpc1a DrGpc1b DrGpc1b DrGpc1 DrGpc1b DrGpc3 DrGpc4 DrGpc5c DrGpc5c DrGpc5c DrGpc5c	340 WR IS E K V LAMO ENME K RI A E M L YMO DNOC VT VS E G IMNME EN SI VI I R Q A LKQ AV AS K VK I S D A IMNME EN SI E V V D V AH A C RST I VK I S E A IMNME EN SI VK I S E A IMNME EN SI VK I S E A IMNME EN SI 420 4 Q	350 EIYTSKVF DMFINKVF ISISAKVF KVSAQVF PHLSAVVSHVG ARIHAQVG PHLSAVVSHVG ARIHAQVG PHLSAVVSHVG ARIHAQVG PHLSAVSHVG AVSKLKF AUST 130 VSKLKEN VSKLKEN FISGLRGSQF VSKKLKHAKKF FISGLRGSQF FISGLRGSQF FISGLRGSQF FISGLRGSQF FISGLRGSQF FISGLRGSQF FISGLRGSQF FISGLRGSQF FISGLRGSQF FISGLRGSQF FISGLRGSQF FISGLRGSQF FISGLRGSQF FISGLRGSQF FISGLRGSQF FISGLRGSQF FISGLRGSQF	360 K A C GD R G E E G T L E G G T P A P Q G C I P R P V P G Q G C Q P K L S MG W C G S S WT E K V C G S L T E S V S K V C G S L T E S V S K V C G S L T E S V S Q G C H P K A S V Q G C G Q P E P A GM W Q P S A L C S W Q H P R K L C V D W A L P H T I C S D W S G G E A L C S K W S T P D T V C V G F S N P E M L C E G Y A M P D M L C A E Y S S L P D C A EI S S L P D C A EI	370         3           PS S I S E SE S         S E S I S E SE S I S E SE S I SE S	80	90 LQTSN APGADKIGM 480 - SVLPEVMG RVLPEVMG RVLPAVTA KPEPGLK - RVESVWG KSVTLRVVG ESVTGHVVG KSVTARVVG KSVTARVVG	400 - L E YK P S P - V S S T P G - T E E K P S S - T E L K P S S - P E L R P T T - P E L R N Q I N G L A N Q I N G L A N Q V S G L A N Q V S V P H G G L A N Q V S G L N V	410 2K S A AR LE V 2K S A R N LE V 2D T GNQH EH 2D T GNQH EH
DrGpc1a DrGpc1b DrGpc2 DrGpc4 DrGpc5c DrGpc5c DrGpc5c DrGpc6b DrGpc1a DrGpc1b DrGpc1b DrGpc1b DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5a DrGpc5a DrGpc5c DrGpc5c DrGpc5c DrGpc5c DrGpc5c DrGpc5c DrGpc5c	340 KR I A E A V L AMO E NME KR I A E AT L Y MO D NOC VT VS E GI MINME EN SI VI I R Q A KA Q V A SK S KK I S D A I MNME EN SI E L V R D V A H A Q R ST A E L V R D V A H A Q R ST A E T N D A I L T A Q L H G VK I SE A I MNMO EN SI VK I SE A I MNMO EN SI 420 4 Q V D V L	350 E I Y T S K V F J S I S A K V F I S I S A K V F S K V S A Q K V F V Q V S Q K V F P H L S A V V S H V G A R I H A Q V S H V G W Q V S K V G W Q V S K V F W Q V S K L K E MQ V Y S K L K E MQ Y L Q A R L K P M R G F I S G L R G S Q F V K K L K H A K K F F L H S L R L Y R K F F T I J I S R Y K S F F T I J I S R Y K S F F T I J I S R Y K S F F T I J I S R Y K S F F T I J I S R Y K S F	360 K A C GD R G E E G T L E C G T P A P Q G C I P R P V P G Q G C I P R P V P S Q G C G P K L S MG R V G Q S R WT E K V C Q S C T E S V S K V C Q S C T E S V S K V C Q C G Q P E P A GM 0 0 WI Q P S A L C S W H L P R K L C V D W L A P H T I C S D W H L P R K L C V D W L A P H T I C S D Y G G C A L C S K W S T P D T V C V G Y G A A D Q L C E S NL P E ML C E G Y AML P D ML C D G Y S S L P S I C A EI W S S L P D L V F C K D	370         3           PS S I S E S E S E S E S E S E S E S E S	80	900 	400 - L E YK P S P - V S S T P G - T E E K P S S - T E E K P S S - T V N N R P - P E A R P T T - D S I P L R G S S H T L P A H L H S L P C G L A N Q I N N G L A N Q I N N G L A Q Q A S G L A Q Q A S - V P H G G L A Q Q A S	410 VK S A AR L E V VK S A AR L E V VK S A AR L E V VK S A AR L E V S S C D L DQ G S CT D L DQ P MN F D P DE A A GT T L DR O T GNQH EH VK S K S D R VA S G A P L H P E VE I D I T P E VE VD I T P E VE VD I T P E I K VK TA A P E V KV KTA A
DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5a DrGpc5b DrGpc5c DrGpc6b DrGpc1a DrGpc1b DrGpc1b DrGpc1b DrGpc2 DrGpc4 DrGpc5 DrGpc5b DrGpc5b DrGpc5b DrGpc5b DrGpc5b DrGpc5b DrGpc5b DrGpc5b DrGpc5b DrGpc5b	340 VR IS E A VLAMO ENME KR IA E A LLYMO DNOC VT VS E GI MNMG EN SI VK IS D A IMNMO EN SI VK IS D A IMNMO EN SI E L VRD A VAHAO RS I / E L VRD A VAHAO RS I / E RIND A ILTA Q LLG G VK IS E A IMMMO EN SI VK IS E A IMMMO EN SI 420 420 Q	350 E I Y T S K V F J S I S A K V F NF I N K V F WQ Y S Q K V F MQ Y S Q K V F MQ Y S Q K V F MQ Y S K V S H V G MQ Y S K V S H V G WY S K K K EMQ L Y Y Y S K K K EMQ L Y Y Y S K K K EMQ Y Y Y S K K K EMQ K Y Y S K K K K H X K F Y F I J S R Y K S F F I J Y I S R Y K S F F T I Y I S R Y K S F F T I Y I S R Y K S F F I I Y I S R Y K S F F I I Y I S R Y K S F F I I Y I S R Y K S F F I I Y I S R Y K S F F I I Y I S R Y K S F F I K K K K K F K F S F F X F S F F X F S F S F S F S F F X F S F S F S F S F F X F S F S F S F S F S F S F F X F S F S F S F S F S F S F S F S F S	360 K A GD R GE E GT LE C T P AP Q G C I P R P V P G Q G C I P R P V P S Q G C Q P K L S MG R V C Q S S R W T E K V C G L T E S V S K V C G L T E S V S K V C G L P R A A S V Q G C Q P E P A GM 0 0 W I Q P S AL C S Q G C Q P E P A GM 0 W I Q P S AL C S W H P R K L S V W H P R K L S V W H P R K L S V W H P R K L C V D W A A D Q L C I S Y G A A D Q L C I S Y G A A D Q L C I S Y S A D A D A D A D A D A	370         3           PS S I SE E PK K         -           PS S I SE E PK K         -           S NI QE QI K R         -           RNK RS AAE RD X         -           RNK S AAE RD X         -           RNK S AAE RD X         -           RS RS RS AKD S GF         -           ST VRT F P PAS WH S         -           GRS AR GI SD Y - F         -           I RS AR S WH S         -           400         -           KT ASST         -           I RS AR GI SD Y - F         -           I RS AR GI SD Y - F         -           I RS AR GI SD Y - F         -           I RS AR GI SD Y - F         -           I SA D GR         -           I NS AN GI SD Y - F         -           - VVWD E N         -           - VVWD E N         -           QI S AD GQT E DO         -           GI S AD GQT E DO         540	80	490 L Q T S N	400 - L E YK P S P - V S S T P G - T E E K P S S - T E E K P S S - T V N N R P - P E A R P T T - D S I P L R G S S S H T L P A H L H S L P C G L A N G I N N G G L N G L N G G G L N G L N G L N G G G L N G L N G L N G G G L N G L N G L N G L N G G G L N G L N G L N G L N G L N G L N G L N G L N G	410 VK S AA R L E V VK S AA R L E V VK S AA R L E V VK S C VK
DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5a DrGpc5b DrGpc5b DrGpc5b DrGpc1a DrGpc1b DrGpc1b DrGpc2 DrGpc4 DrGpc5a DrGpc5b	340           VR IS E A VLAMO ENMER           KRIAELUMD DUCK           VY VS E GIMNMO ENSI           VI IRQLKQAVASKS           VK IS D A TMMMO ENSI           VK IS A TMMMO ENSI           VK IS E A IMMMO ENSI           420           420           420	350 E I Y T S K V F I S I S A K V F I S I S A K V F K V S A V F VQ V S Q K V F VQ V S Q K V F VQ V S K V S H V G P R L T A T V D VY S K K K K M Q L V V S K K K K M Q L V V S K K K K M Q L V V S K K K K M Q K V V S K K K K M Q K V V S K K K K M Q K V V S K K K K M Q K V V S K K K K M X K K K K F L S L R L Y R T F F I S L R L Y R T F F I S L R L K K S R F I K K K K K K S R F I K K K K K K S R F I K K K K K K S R F I K K K K K K S R F I K K K K K K S R F I K K K K K K S R F I K K K K K K K S R F I K K K K K K K S R F I K K K K K K K K K K K K K K K K K K K	360 K A GD R G E E GT LE C G - T P AP Q G C G P R P V P G Q G C G P R V S MG R V C G S L T E S V S. K V C G S L T E S V S. K V C G S L T E S V S. K V C G S L T E S V S. K V C G S L T S V S. K V C G S L C S M W I Q P S A L C S G W H L P R K L C V D W I Q P S A L C S G W H L P R K L C V D W S T L P D T V C V G Y G A A D Q L C I S. F S N A D Q L C I S. F S N A D Q L C I S. S S L P D S I C A E S 30 A A A A A A A A A A A A A A A A A A A	370         3           2 S S I S E E P K K         -           2 S S I S E E P K K         -           5 S I S E E P K K         -           - RN KR S A A E RO J         -           - RN KR S A A E RO J         -           - RN K S A K D S G F         -           - S N I Q E G I K R         -           - S N I Q E S T F A N S T L G S L I S         -           S T F A N S T H S S T V D S - F         -           - R S A R S V H D S - F         -           - K S A R S V H D S - F         -           - T S A R S V H D S - F         -           - R S A R S V H D S - F         -           - R S A R S V H D S - F         -           - T S A R S V H D S - F         -           - T S A R S V H D S - F         -           - T S A R S V H D S - F         -           - T S A S D G E S D         -           - K V D E F         -           - K V D E F         -           - Q I S A D G Q T E D E         -           - S 40         -           - K V D E F         -           - S 40         -           - K V D E F         -           - G N D Q T D D         - <td< td=""><td>80</td><td>490 490 490 - SYLPPE VMGI - SYLPPE VMGI - RYLPPE VMGI - RYLPEVMGI - RYLPEVMGI - RYLPEVMGI - RYLPEVVG - RYFPEVVKI - RYFPEVVKI - RYFPEVVKI - RYFPEVVKI - RYFPEVKI - RYFPEVKI</td><td>400 - L E YK P S P - VS ST P G - T E E K P SS - T E E K P SS - T V NH NR P - P E AR PT T - D S I P L RG S S S H T L P A H L S S L P C G L A N G I NN G L NG I NN G L NG L NN G L ANG I NN G L A G A K N NG L A G A K N S T O S T O A D H L C V R G R</td><td>410 VK S AARLE V VK S AARLE V VK S AARLE V VK S S S S S S S S S S S S S S S S S S S</td></td<>	80	490 490 490 - SYLPPE VMGI - SYLPPE VMGI - RYLPPE VMGI - RYLPEVMGI - RYLPEVMGI - RYLPEVMGI - RYLPEVVG - RYFPEVVKI - RYFPEVVKI - RYFPEVVKI - RYFPEVVKI - RYFPEVKI - RYFPEVKI	400 - L E YK P S P - VS ST P G - T E E K P SS - T E E K P SS - T V NH NR P - P E AR PT T - D S I P L RG S S S H T L P A H L S S L P C G L A N G I NN G L NG I NN G L NG L NN G L ANG I NN G L A G A K N NG L A G A K N S T O S T O A D H L C V R G R	410 VK S AARLE V VK S AARLE V VK S AARLE V VK S S S S S S S S S S S S S S S S S S S
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DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5a DrGpc5b DrGpc5c DrGpc5b DrGpc1a DrGpc1b DrGpc1b DrGpc2 DrGpc7 DrGpc4 DrGpc5b DrGpc5b DrGpc5b DrGpc5b DrGpc5a DrGpc4 DrGpc1b DrGpc2 DrGpc5a DrGpc5b DrGpc5a DrGpc4 DrGpc1b DrGpc2 DrGpc5a DrGpc5a DrGpc5a DrGpc5a DrGpc4 DrGpc3 DrGpc4 DrGpc3 DrGpc4 DrGpc3 DrGpc4 DrGpc3 DrGpc4 DrGpc5a DrGpc5b DrGpc5a DrGpc5b DrGpc5a DrGpc5b DrGpc5a DrGpc5b DrGpc5a D	340           YR I SE E V LAMO ENMENT           KR I AE KI LYMO DNOC           YTYSE CIMMING ENSI           YI T RQ LKQ AVASKS           YK I SE MILLYAD LHGF           GQ VE FAILYAD LHGF           YK I SE ALIMINMO ENSI           GO	350 EIYT SK VF DMF INK VF ISI SAK VF K VS AQ VF MQ VS QK VF PHL SAV VSH VG PRLTAT VD PHL SAV VSH VG VS KK VF WA TIS NP VF WISK V	360 K A C GD R G E E G T L A C GD R G E E G T L A C GD R G E E G T L A C GD R G E E G T L G G T P A P Q G C I P R P V P G Q G C Q P K A S N T E K V C G A T S N T E K V C G A S N T E K V C G A C C Q P E A GM 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	370         3           PSS IS ES IS ES IS         SERIT S           PSS IS IS EQ IK         -           RNKR SAAE RD         -           RNKR SAAE RD         -           RNK SAAE RD SI         -           FRS RS AKD SG IS         -           ST VRT FPPAS WHOS S         -           GRS ARGISTOV - F         -           FRS RG SHOV - F         -           GRS ARGISTOV - F         -           FR SR SG SHOV - S         -           GRS ARGISTOV - F         -           FR SR SAGE SHOV - S         -           GRS ARGISTOV - F         -           F SARS VHOS         -           F TANS         -           C LAS AD GR         -           C LAS AD GR TH T D GR         -           C G GG GA R R N P         -           C G S LO Q IT GR TH T D GR         -	80	490 	400 - L E YK P S P - V S S T P G - T E E K P S S - T E L K P S S - T V N N R P - P E A R T T - P E A R T T T - P E A R T T T - P E A R T T - P E A R T T - P E A	410 2K S A AR L E V 2K S A AR L E V 2D T GN QH EH 2D T GN QH CH 2D T GN QH 2D T GN QH
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DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5c DrGpc5c DrGpc6a DrGpc1a DrGpc1b DrGpc1b DrGpc1b DrGpc2 DrGpc5c DrGpc5c DrGpc5c DrGpc5c DrGpc5c DrGpc5c DrGpc5c DrGpc5c DrGpc5c DrGpc5c DrGpc5c DrGpc5c DrGpc5b DrGpc1b DrGpc1b DrGpc1b DrGpc2 DrGpc5b DrG	340 VR IS E A V L AMO EN ME KR I A E IL V MO DNOC VT VS E GI MINME EN SI VI I RQ LKQ AVASKS VK IS DA I MINME EN SI E L V RD AVA HA OR ST A E L V RD AVA HA OR ST A E L V RD AVA HA OR ST A E L V RD AVA HA OR ST A 420 4 Q	350 E I Y T S K V F I S I S A K V F I S I S A K V F S K V S A V F V S K V S A V F V S K V S A V S H V G P R L T A T V D P H L S A V V S H V G WQ V S K V G V S F WQ V S K L K E MQ V Y S K L K E MQ V V S K L K E M K V V S K L K E M K V V S K L K F Q S V V K K L K H K K F V F T I V S V S K V S Z V S M L K V A A I H T L R L I N Q L R M I N Q L Q K I N Q L K K I N Q L Q K I N Q L Q K I N S N K L K N GOO	360 K A G G D R G E E G T L A C G D R G E E G T L A C G D R G E E G T L C G T P A P G G G I P R P V P G G G I P R P V P G G G P K L S MG V G G C G Q K L S M T E K V G G C I T S V S K V G G C G Q K A A S V G G G Q P E P A GM 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	370         3           PS S I SE E PK K         -           PS S I SE E PK K         -           S NI QE QI K R         -           RNKR S AAE RD X         -           RNK S AAE RD X         -           RNK S AAE RD X         -           RS RS S RS AKD SG I         -           ST VAT F P PAS W         -           GS SAR GI SD V         -           I RS AR GI SD V         -           R SAR GI SD V         -           GE SG PG -         -           R S AR GI SD V         -           R SAR GI SD V         -           C S L D GI SA D GR -         -           C WD EN -         -           C S L D Q I T GO D         -           C S D GG GAR RN PG 1         -           C S L D Q I T GO D         -           C G G GAR RN PG 1         -           C G T D YKES SS /         -           C G T D YKES SS /         -           C G D Q W F Q D -         - </td <td>80 - KERT VTA - GRNTAEE KKPKFRSFR- PGRFRPYS- S PSVNPSLE P-SVNPSLE P-SVNPSLE P-SVNPSLE P-SVNPSLE P-SVNPSLE CVNGTRASS GRFKPY</td> <td>490 LQTSN APGADKIGH AP</td> <td>400 - L E Y K P S P - V S S T P G - T E E K P S S - T E E K P S S - T E L K P S P - P E A R P T T - D S I P L R G S S H T L P A H L H S L P C G L A N G I N N C G L A Q Q A S N G I K A Q A E N N G I C A Q Q A S N G I K A Q A E N C G L A Q Q A S C G I N N C I N N C G L A Q Q A S C G I N N C I N N C G L A Q Q A S C G I N N C I N N C G I C Q C K N C G I N C I N N C G I C Q C K N C G I N C V S R G - S D W P E Y G D C G C W S - C D C G C W S - C D C G C G S G R T E P E V V H T E M S C V T A S D 650</td> <td>410 PK S A AR L E V PK S A AR L E V PK S A AR L E V PK S A AR L E V G S GT D L DQ G S GT D L DQ D M F D PD E A A GT T L DR A A GT S L DR PE VE I D I T PE VE V V V V V V V V V V V V V V V V V</td>	80 - KERT VTA - GRNTAEE KKPKFRSFR- PGRFRPYS- S PSVNPSLE P-SVNPSLE P-SVNPSLE P-SVNPSLE P-SVNPSLE P-SVNPSLE CVNGTRASS GRFKPY	490 LQTSN APGADKIGH AP	400 - L E Y K P S P - V S S T P G - T E E K P S S - T E E K P S S - T E L K P S P - P E A R P T T - D S I P L R G S S H T L P A H L H S L P C G L A N G I N N C G L A Q Q A S N G I K A Q A E N N G I C A Q Q A S N G I K A Q A E N C G L A Q Q A S C G I N N C I N N C G L A Q Q A S C G I N N C I N N C G L A Q Q A S C G I N N C I N N C G I C Q C K N C G I N C I N N C G I C Q C K N C G I N C V S R G - S D W P E Y G D C G C W S - C D C G C W S - C D C G C G S G R T E P E V V H T E M S C V T A S D 650	410 PK S A AR L E V PK S A AR L E V PK S A AR L E V PK S A AR L E V G S GT D L DQ G S GT D L DQ D M F D PD E A A GT T L DR A A GT S L DR PE VE I D I T PE VE V V V V V V V V V V V V V V V V V
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DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5a DrGpc5c DrGpc5c DrGpc5c DrGpc1a DrGpc1b DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5b DrGpc5b DrGpc5b DrGpc5c DrGpc5b DrGpc5c DrGpc1a DrGpc1b DrGpc2 DrGpc5c DrGpc5b DrGpc5b DrGpc5a DrGpc5b DrGpc	340 V R I S E R V L AMO ENNO K R I A E R L L Y MO DNOC V T V S E G I MINME EN SI V T V S E G I MINME EN SI V I I R Q L K Q A V A S K V K I S D A I MINME EN SI E V V D V A H A R S T I V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI V K I S E A I MINMO EN SI S I S S R T E F A I V V K V K V K V K V K K I V K D K I T R Q I ML K K K K D MA V K K Q MA V K K V M V I R Q I A V K K K MI E I N M V I R Q I A V K K K I D V L N V K N K I E I R D T F I R Q MI T A K R D S L I R Q U L A R I S 90	350 EIYT SK VF DMF INK VF ISI SAK VF SK VS AQ VF WQ VS QK VF PHL SA V VS H VG PR L T AT VD PHL SA V VS H VG WQ VS KV F WQ VS KK VF WQ VS KK VF WG VS KK VF SC VS VS KK VF - WG VS KK VF WG VS KK VF - WG VS KK VF WG VS KK VF - WG VS KK VF - WG VS KK VF - WG VS KK VF - WG VS KK VF WG VS KK VF - WG VS KK VF WG VS KK VF - WG VS KK VF WG VS KK VF - WG VS KK VS - WG VS KK VS - - VS VS KK VS - - VS VS KK VS - - - VS VS VS KK VS - - - - - - - - - - - - - - - - -	360 K A C GD R G E E G T L E G G T P A P Q G C I P R P V P G Q G C Q P K L S MG W C Q S S WT E K V C Q S L T E S V S K V G S L T E S V S K V G S L T E S V S Q G C Q P K A S V Q G C Q P E A GM 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	370         3           PSS IS ES IS         SERVEX           PSS IS IS EQUINARIAN         S           RNKRSAAERD         S           RNKRSAAERD         S           RNKSSAERSAKDSGE         S           PNS XONSTGAR         S           ST VRTFPPASUM         S           ST VRTFPPASUM         S           ST VRTFPPASUM         S           ST VRTFPASS         S           ST VRTPANSTLGSL         S           ST VND SQC         S           ST VND SQC         S           ST VND SQC         S           SAD GQTED         S      <	80 - KERT A SER - GRNTAEE KEPK FRSFR- P GRTFRPSSE - FSVNPSLE (PPPVNISQD - FSVNPSLE (PPVNISQD - FSVNPSLE - FSVNPSLE - FSVNPSLE - FSVNPSLE - FSS - FSSS - FSS - FSS	490 	400 - L E YK P S P - V S S TP G - T E E K P S S - T E L K P S S - T V N N R P - P E A R T T - P E A R T T - P E E R P T - P E E R P T - P E E R P T - E E L P T V G L AN G I N G L AN G I N G L AN G I N G L AN G V A G L A G R Q N G L A G R R C N N G L A	410 2K S A AR L E V 2K S A AR L E V 2D T G N Q H E H 2D T G N Q H 2D T G N Q H E H 2D T G N Q H E H 2D T G N Q H 2D T G N
DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5c DrGpc5c DrGpc6b DrGpc1a DrGpc1b DrGpc1b DrGpc1b DrGpc1 DrGpc4 DrGpc4 DrGpc5c DrGpc5c DrGpc5c DrGpc6b DrGpc1b DrGpc1b DrGpc1b DrGpc1b DrGpc7 DrGpc5c DrGpc5c DrGpc5a DrGpc5a DrGpc4 DrGpc5a DrGpc4 DrGpc1b DrGpc1b DrGpc4 DrGpc4 DrGpc5a DrGpc5a DrGpc5a DrGpc4 DrGpc5a DrGpc5a DrGpc4 DrGpc5a DrGpc5a DrGpc5b DrGpc5a DrGpc5b DrGpc5a DrGpc5b DrGpc7b DrG	340 VR IS E N VLAMO EN ME KR I A E AL LYMO DNQU VT VS E GIMMMG EN SI VI I RQ ALKQ AV ASK S VK IS D A IMMMG EN SI E L VRD VAH A (RST A VK IS E A IMMMG EN SI VK IS E A IMMMO EN SI VK IS E A IMMO EN SI SI VK IS E A IMMO EN SI SI VK IS E A IMMO EN SI SI VK IS E A IMMO EN SI SI SI SI SI SI SI SI SI SI	350 EIYT S K V F DMF I N K V F IS I S A K V F S K V S A V F PH L S A V V S H V G A R I H A Q V C PH L S A V V S H V G WQ V S K V G WQ V S K L K E MQ L Y V Y K L K E MQ L Y V K K L K E K K K K S F TI Y I S R V K S F TI Y S R V K S F TI Y S K K K S F TI Y S R V K S F TI Y S R K K K S F TI Y S K K K S F TI Y S R K K K S F TI Y S K K S F TI Y S K K S S F TI Y S K K S S F TI Y S K K S S F TI Y S S S S S S S S S S S S S S S S S S	360 K K G GD R G E E G T L E G G T P A P G G G I P R P V P G G G I P R P V P G G G G P K L S MG V G G S S RWT E K V G G S L T E S V S K V G G S L T E S V S K V G G G H P K A A S V G G G H P K A A S V G G G H P K L G V G WI Q P S A L G S G G H P K L C V G WI A P R K L C V D WI A P R K L C V D WI A P R K L C V C Y G G G A L A C S K WS T P D T V C V G Y G G G A L A C S K WS T P D T V C V G Y G G G A L C S K WS T P D T V C V G Y G G G A L C S K WS T P D T V C V G Y G G G A L C S K WS T P D T V C V G S 30	370         3           PS S I SE E PK K         -           S S I SE E PK K         -           S S I SE E PK K         -           R K K S A A E RD X         -           R K K S A A E RD X         -           R S R S A KD S G K         -           S T P AN ST L G S L 1         -           S T P AN ST L G S L 1         -           S T P AN ST L G S L 1         -           S T S A S Y H D S -         -           G S S A G S T T G L C 1         -           R T A A - VT NE E         -           R T A P S T G L A S D G R D E E         -           R T A P S D E E         -           S M D VD F Q D T S         -           S M D VD F Q D T S         -           C G G G A T P T C 0         -           C G G G A T P T T D G G G G C A R N P G T S         -           C G G D Q I T F T D G G G C A R N P G T S         -           C G G D Q I T F T G G G G C A R N P G T S         -           C G G T D V K E S S S S S         -           C G D Q I T F T G G G C A R N P G T T S         -           C G G D Q I T F T G G G C A R N P G T T F T D G G G G C A R N P G T T G T D V K E S S S S S S S S S S S S S S S S S S	80 - KERTVTA - GRNTAEE KPKFRSFR- S GRTRPYS- S S- P S VNPSLE: P S VNPSLE: P P VNISQD V KWNGITKA R CWNGITKA R CWNGITKA R CWNGOTKG CWNGTRG CWNGOTKG CWNGTR CWNGOTKG CWNGTR CWNGOTKG CWNGTR CW	490 LQ T S N	400 - L E YK P S P - V S S TP G - - T E E K P S S - T E L K P S S - T V N N R P - P E A R T T - P E A R	410 2K S A AR L E V 2K S A AR L E V 2D T GN QH EH 2D T
DrGpc1a DrGpc1b DrGpc3 DrGpc4 DrGpc5c DrGpc5c DrGpc5c DrGpc6a DrGpc1a DrGpc1b DrGpc1 DrGpc2 DrGpc5c Dr	340           VR IS E A VLAMO EN ME           KRI A E E ILVMO DNOC           VTVS E GIMNMG EN SI           VIT IR QLKQ AVASKS           KI SA E ILVMO NOC           E LVRD VAHAORSTA           E LVRD VAHAORSTA           E LVRD VAHAORSTA           E LVRD VAHAORSTA           GQVEE AILVACLHG           VK IS E AIMMODENSA           YK IS E AIMMODENSA           420           420           420           420           L           L           L           SISS RTEF           L           L           L           L           SISS RTEF           L           L ILKRKREF           L ILVROKARD           SO0           SIO           SO0           SIO           K PDARTI RQO           K PDART RQI AVLKK           R DT RT RQ MME L RI           P - VI SQI IDK KK           K PONT RQ AVLKE           R DT FI RQQ ML KI           R DSLI RQU LAL RI           S90           S90           S90           S90 <t< td=""><td>350 E I Y T S K V F I S I S A K V F I S I S A K V F I S I S A K V F S K V S A V S F WQ V S K V Q K V F WQ V S K V Q F WQ V S K V F WQ V S K K F WQ V S K K K F WZ S K K K F S S WZ S K K K F S S WZ S K K K F S S S S S</td><td>360 K A C G D R G E E G T L E C G - T P A P Q G C I P R P V P G Q G C G P K L S MG R V G Q S R WT E K V C Q S L T S V S K V S L P S A L C S K V S L P L V F C K D S 30 A C S P S N S P S N S A K V L P E K R W R A R S I P K A C I O K L V A T G P E N K K K V Y A S P S E N K K K V Y A S Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y</td><td>370         3           PS S I SE E PK K         -           PS S I SE E PK K         -           S NI QE QI K R         -           RNK RS AAE RD X         -           RNK S AAE RD X         -           RNK S AAE RD X         -           RS RS RS AKD SG I         -           ST VNS VQH ST GR A         -           ST S RS RS GN X- F         -           GR SA RG ISD V - F         -           ST S RS AR GIS DV - F         -           CT AS ST T GC         -           RS SA RG ISD V - F         -           CT AS ST T GC         -           RS AR GIS DV - F         -           CT AS ST T GC         -           RS AR GIS DV - F         -           CT AS ST T GC         -           R S AP GIS AND GR</td><td>80 - KERTVTA - GRNTAEE KKPKFRSFR- PGRTRPYS- S</td><td>490 LQTSN</td><td>400 - L E Y K P S P - V S S T P G - T E E K P S S - T E E K P S S - T E K P S P - P E A P T T - D S I P L R G S S H T L P A H L H S L P V D G L AN Q I N C L N Q L N C L N</td><td>410 PK S A AR L E V PK S A AR L E V G S GT D L DQ G S GT D L DQ F P W S T D P D E A A GT S L D R A A GT S L D R PB VE I D I T PF VE V I D I T PF VE V I D I T PF VE V V I D PF V V V V I T PF V V V V V V PF V V V V V V V PF V V V V V V V PF V V V V V V V V PF V V V V V V V V PF V V V V V V V V V V V V V V V V V V V</td></t<>	350 E I Y T S K V F I S I S A K V F I S I S A K V F I S I S A K V F S K V S A V S F WQ V S K V Q K V F WQ V S K V Q F WQ V S K V F WQ V S K K F WQ V S K K K F WZ S K K K F S S WZ S K K K F S S WZ S K K K F S S S S S	360 K A C G D R G E E G T L E C G - T P A P Q G C I P R P V P G Q G C G P K L S MG R V G Q S R WT E K V C Q S L T S V S K V S L P S A L C S K V S L P L V F C K D S 30 A C S P S N S P S N S A K V L P E K R W R A R S I P K A C I O K L V A T G P E N K K K V Y A S P S E N K K K V Y A S Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y	370         3           PS S I SE E PK K         -           PS S I SE E PK K         -           S NI QE QI K R         -           RNK RS AAE RD X         -           RNK S AAE RD X         -           RNK S AAE RD X         -           RS RS RS AKD SG I         -           ST VNS VQH ST GR A         -           ST S RS RS GN X- F         -           GR SA RG ISD V - F         -           ST S RS AR GIS DV - F         -           CT AS ST T GC         -           RS SA RG ISD V - F         -           CT AS ST T GC         -           RS AR GIS DV - F         -           CT AS ST T GC         -           RS AR GIS DV - F         -           CT AS ST T GC         -           R S AP GIS AND GR	80 - KERTVTA - GRNTAEE KKPKFRSFR- PGRTRPYS- S	490 LQTSN	400 - L E Y K P S P - V S S T P G - T E E K P S S - T E E K P S S - T E K P S P - P E A P T T - D S I P L R G S S H T L P A H L H S L P V D G L AN Q I N C L N Q L N C L N	410 PK S A AR L E V PK S A AR L E V G S GT D L DQ G S GT D L DQ F P W S T D P D E A A GT S L D R A A GT S L D R PB VE I D I T PF VE V I D I T PF VE V I D I T PF VE V V I D PF V V V V I T PF V V V V V V PF V V V V V V V PF V V V V V V V PF V V V V V V V V PF V V V V V V V V PF V V V V V V V V V V V V V V V V V V V
DrGpc1a DrGpc1b DrGpc2 DrGpc3 DrGpc4 DrGpc5b DrGpc5c DrGpc5b DrGpc5c DrGpc1a DrGpc1b DrGpc2 DrGpc1b DrGpc2 DrGpc4 DrGpc5b DrGpc5b DrGpc5b DrGpc5b DrGpc5b DrGpc2 DrGpc1a DrGpc1b DrGpc1b DrGpc2 DrGpc5b DrGpc1b DrGpc2b DrGpc5b DrGpc5b DrGpc5b DrGpc5b DrGpc5b DrGpc5b DrGpc5b DrGpc5b DrGpc7b DrGpc4 DrGpc1b DrGpc1b DrGpc1b DrGpc1b DrGpc1b DrGpc1b DrGpc1b DrGpc1b DrGpc1b DrGpc2b DrGpc4 DrGpc2b DrGpc4 DrGpc2b DrGpc5b D	340 VR IS E A VLAMO ENME KR IA E A LLYMO DNOC VT VS E GI MINME EN SI VK IS D I IMNME EN SI VK IS D I IMNME EN SI E L VRD A VAHAO RS I A E L VRD A VAHAO RS I A E L VRD A VAHAO RS I A E L VRD A VAHAO RS I A VK IS E A IMMME EN SI 420 420 420 420 420 420 420 420	350 EI YT SK VF DMF I NK VF SK VS AQ VF MQ VS QK VF MQ VS QK VF PHL SA VS H VG PR L T AT VD PHL SA VS H VG VS KK VF ( WQ VS KK VF ( WQ VS KK VF ( WG I SN P VF ( WG I SN P VF ( WG VS KK VF ( SO VS KK VF NI SN KK VF NI SN KK VF - NI SN KK VF - NI SN KK VF - NI SN KK KN - I MS NR L KN - F NG C - - - - - - - - - - - - - - - - - - -	360 K A C GD R G E E G T L E C G T P A P Q G C I P R P V P G Q G C Q P K L S MG W C Q S S WT E K V C G S L T E S V S K V C G H F K A S V Q G C Q P E P A GM W Q P E A C S G W V L P K K C C S D W I Q P S A C C S C W V L P R K L C V D W I Q P S A C C S C W V L P R K L C V C W I Q P S A C C S C W V L P C K C S C C S C W S T P D T V C V G S 30 C S C C S C C S C S C S C K V C G G C S C S C S C S S C P D S I C A E W S L P D S I C A E W S L P D S I C A E W S L P D S I C A E W S L P C S C S C S S C S C S C S C S C S S C S C S C S C S C S S C S C S C S C S C S S C S C S C S C S C S S C S C S C S C S C S S C S C S C S C S C S S C S C S C S C S C S S C S C S C S C S C S S C S C S C S C S C S C S S C S C S C S C S C S C S S C S C S C S C S C S C S C S S C S C S C S C S C S C S C S S C S C S C S C S C S C S C S C S S C S C S C S C S C S C S C S C S C S S C S C S C S C S C S C S C S C S C S	370         3           25 S I S E E P K K         -           25 S I S E E P K K         -           25 S I S E E P K K         -           27 S S I S E E P K K         -           27 R K K S A A E RD V         -           27 R K K S A K D S G F         -           27 R N K S A K D S G F         -           27 R N K S A K D S G F         -           28 S G F G T G G G         -           28 S G F G E S G F         -           28 S G F G E S G F         -           28 S G F G - E S G F         -           28 S G F G E S G F         -           21 S A D G R	80 - KERNTAE - KRNTAE - KRNTAE - KRNTAE - KRNTAE - KRNTAE - KRNTAE - KRNTAE - KRNTAE - S	490 L Q T S N	400 - L E YK P S P - V S S TP G - T V S S T S - T V N N R P - P E A R T T - P E A R T T - P E A R T T - P E A R T S - P E A R T S - S S S H T L P A H L H S L P C G L A N G V S G L A Q A S N - V P H G G L A Q A S N G L A Q A S N - V P H G G L A Q C S R G - C V C R G R D G C C S G - S C G D G C V S G - S C G G G G - S C G C S - S C C V T S C - S C C S C C C S C - S C C S C C S C - S C C C S	410 2K S A AR L E V 2K S A AR L E V 2D T GN V H E A 2D T C C C L F T L GL Q 2T R
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**Figure 3. Multiple sequence alignment of glypican protein sequences from zebrafish.** All protein sequences were aligned to compare conserved features between glypicans. Residues highlighted in blue are well conserved. Black highlights indicate the 14 conserved cysteine residues; yellow highlights are the multiple Ser-Gly repeats flanked by acidic residues for sugar attachment; in red is the potential chondroitin sulfate attachment site. doi: 10.1371/journal.pone.0080824.g003





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zebrafish gpc1a is more likely to be the true ortholog of mammalian Gpc1.

In a previous study on *gpc3*, it was reported that it is ubiquitously present during early zebrafish development [31]. We detected transcripts of *gpc3* by RT-PCR at all stages, but these could not be detected by ISH, possibly due to very low levels. Interestingly, *gpc3* expression in zebrafish does not correlate with mammalian expression. *GPC3* is the causative gene for Simpson-Golabi Behmel Syndrome and is strongly up-regulated in hepatocellular carcinoma. In humans and mice, it is expressed in hepatocytes, several kidney structures, mesenchyme of limb buds, vertebrae and the liver [35]. In contrast, we observed a very specific expression of zebrafish *gpc3* only in the midbrain. It is likely that this function of *Gpc3* is

preserved only in mammals, although later developmental stages in zebrafish remain to be analyzed.

Another parallel can be drawn between the *Gpc5* expression patterns. In *Xenopus*, *gpc5* is expressed strongly during neurulation and becomes restricted to the floor plate, somites and optic vesicle in the late neural stages [13]. It has been implicated in neural tube closure defects [13]. Zebrafish *gpc5b* is also specific to the floor plate and is diffusely present in the nervous system. This indicates that *gpc5b* might be the cognate zebrafish gene and also suggests for a potential conserved role of *gpc5b* in neural tube defects. In mice and humans, *Gpc5* is prominent in kidney, limb and brain both in developing and adult tissues [30]. But so far, we did not examine later stages of zebrafish development for *gpc5* expression.



**Figure 5.** Spatial expression of zebrafish glypicans during cleavage to early segmentation stages. *In situ* hybridization was performed to detect glypican mRNA during early developmental stages. Lateral views with anterior to the top (A, B, C) and dorsal to the right (B, C). Developmental stages and gene names are indicated. tb, tailbud; hb, hindbrain; en, endoderm; me, mesencephalon; n.d: not detected.

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Taken together, zebrafish glypicans exhibit quite dynamic expression pattern during early embryonic development. The 10 genes identified in this study are selectively turned on in different tissues and hence have the potential to mediate important morphogenetic functions either independently or in conjunction with each other. Multiple signaling pathways are known to be modulated by glypicans in a context dependent manner [2-5], and our data will therefore contribute to elucidating the mechanisms by which glypicans mediate these functions.



**Figure 6.** Spatial expression pattern of zebrafish glypicans during segmentation and pharyngula stages. *In situ* hybridization was carried out to detect glypican mRNA at 20 somite stage: 19 hpf and pharyngula stages: 24-26 hpf. Lateral view of whole mount embryos, anterior to the left. Expression pattern of *gpc1a* (A, A'), *gpc1b* (B, B'); subfigure in B is an optical section indicating expression in yolk cells (arrowheads) and branchial arch primordium, *gpc2* (C, C'), *gpc3* (D, D'), *gpc4* (E, E'), *gpc5a* (F, F'), *gpc5b* (G, G'), *gpc5c* (H, H'), *gpc6a* (I, I'), *gpc6b* (J, J'). di, diencephalon; te, telencephalon; hb, hindbrain; tg, tegmentum; nc, neural crest; pm, paraxial mesoderm; som, somites; ba, branchial arch; y, yolk; mb, midbrain; ff, fin fold; ov, otic vesicle; fp, floor plate; psom, posterior somites; ep, epiphysis; tri, trigeminal placode; cl, cloaca; pllp, posterior lateral line primordium; cg, cranial ganglion.

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**Figure 7.** Specific expression domains for *gpc1a*, *gpc1b* and *gpc5b*. Transverse cross sections revealed the expression details of *gpc1a*, *gpc1b* and *gpc5b*. Dotted line indicates the plane of section. pllp: posterior lateral line primordium; pba: posterior branchial arch; my: myotome; fp: floor plate; nc: notochord. doi: 10.1371/journal.pone.0080824.g007

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## **Author Contributions**

Conceived and designed the experiments: MG MB. Performed the experiments: MG. Analyzed the data: MG MB. Contributed reagents/materials/analysis tools: MG. Wrote the manuscript: MG.

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