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RESEARCH

From hydra to human: in silico investigation of the atavistic model of cancer

Hidradan insana: atavistik kanser modelinin in silico araştırması

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Abstract

Purpose: Cancer manifests as a disruption in the regular functioning of multicellular systems, arising from the malfunctioning of genes responsible for cellular cooperation. Notably, cancer exhibits atavistic characteristics, wherein cancer cells diverge from the conventional Darwinian evolution, highlighting a distinctive trajectory in their evolutionary fate. In this context, cancer cells may display traits such as uncontrolled proliferation, evasion of cell death mechanisms and altered metabolism, which could reflect ancient biological programs related to cell growth and survival. The objective of this study was to trace the evolutionary origin of cancer by analyzing tumor-related proteins in the basal metazoan *Hydra* and their preservation across diverse taxa.

Materials and Methods: Bioinformatic approaches were employed to investigate the conservation status of protein-coding transcripts that are differentially expressed in the tumor-bearing *Hydra* across species, representing both unicellular and multicellular forms of life.

Results: By examining the taxonomic distribution of the *Hydra* polyp-related proteins, we have traced the ancient evolutionary roots of cancer through the tree of life. The majority of protein-coding genes were found to be of unicellular origin and associated with cancer.

Conclusion: We suggest conservation of the atavistic in model of cancer the basal tumor-bearing animals, which can be considered as promising and intriguing candidate model organisms in cancer research.

Keywords: Cancer, atavistic hypothesis, *Hydra*, phylostratigraphy, bioinformatics

Öz

Amaç: Kanser, hücresel iş birliğini sağlayan genlerin görevlerini yerine getirememelerinden kaynaklanarak çok hücreli sistemlerin işleyişini bozar. Dikkat çekici bir şekilde, kanser atavistik özellikler gösterir; bu, kanser hücrelerinin geleneksel Darwinci evrimden saparak evrimsel yollarında kendine özgü bir rota izlediklerini gösterir. Bu bağlamda, kanser hücreleri kontrolsüz çoğalma, hücre ölüm mekanizmalarından kaçış ve değişmiş metabolizma gibi hücre büyümesi ve hayatta kalma ile ilgili eski biyolojik programları yansıtan özellikler sergileyebilir. Bu çalışmada bazal metazoan *Hydra*'da oluşan tümörlerle ilişkili proteinleri ve bunların farklı taksonlar boyunca korunmasını analiz ederek kanserin evrimsel kökenini incelemek amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmada *Hydra* tümörlerinde protein kodlayan transkriptlerin evrimsel korunma durumunu araştırmak için biyoinformatik yaklaşımlar kullanılmıştır. Bu analizler, hem tek hücreli hem de çok hücreli yaşam formlarını temsil eden türler arasında gerçekleştirilmiştir.

Bulgular: *Hydra* tümörleriyle ilişkili proteinlerin taksonomik dağılımını inceleyerek, kanserin evrimsel kökenleri seçilen temsilci türler boyunca takip edilmiştir. *Hydra* tümörlerinde protein kodlayan genlerin çoğunluğunun tek hücreli kökenli olduğu ve insanda kanserle ilişkili olduğu bulunmuştur.

Sonuç: Çalışmada *Hydra* tümörlerinde ifade edilen genlerin evrimsel süreç boyunca korunumu ortaya çıkarılmıştır. *Hydra*'nın kanser araştırmalarında model organizma olarak değerlendirilebileceği önerilmektedir.

Anahtar kelimeler: Kanser, atavism, *Hydra*, filostratigrafi, biyoinformatik

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INTRODUCTION

Multicellularity emerged approximately one billion years ago as a remarkable evolutionary feat, offering advantages to organisms through greater specialization, collaboration among their constituent cells, and enhanced overall adaptability to their environments[1]. Multicellularity arose when formerly independent unicellular entities started to acquire genetic mechanisms that were endowing them with selective advantages through cooperative growth. Moreover, it is believed that multicellularity evolved more than once in different lineages, hence resulting in the vast array of multicellular organisms that populate the contemporary biological landscape[2,3]. Nevertheless, this evolutionary advancement has not been devoid of challenges, with the emergence of cancer representing perhaps the most important evolutionary trait that is associated with multicellularity itself[4].

Defying the species boundaries, cancer disrupts the foundational principles of controlled growth and regulation that underpin multicellularity, affecting nearly all multicellular organisms whether they exhibit colonial or aggregative multicellularity[5]. This observation has led to the intriguing proposition that cancer might have deep-rooted evolutionary origins. Cancer, at its core, arises from the disturbance of intrinsic mechanisms pivotal to multicellularity, governing cell growth, differentiation and cell death. These aberrant cells, often termed "rogue" or "selfish", tend to prioritize their own growth and survival at the expense of the multicellular organism[6]. The connection between multicellularity and cancer has been previously anticipated[7]. Furthermore, cancer cells manifest this self-serving behavior due to the reactivation of genes linked to unicellularity, according to the atavistic model of cancer[8].

In a seminal study, Trigos and colleagues presented comprehensive evidence that there is an expressional shift towards unicellularity genes in tumors[9]. In a study by Louka et al., concerted efforts were made to trace the origins of cancer within the phylogenetic tree of life. In particular, the researchers analyzed twelve pivotal genes associated with metastasis and demonstrated their unicellular ancestry[10]. The atavistic theory postulates that the phenotype of cancer cells arises through an intricate process of reverse evolution, reminiscent of the protistan ancestors during the Cambrian explosion, where multicellular life forms diversified rapidly and many major animal phyla were initially formed[11]. Cancer cells do not merely acquire new traits through random mutations and Darwinian selection; instead, they reactivate the network inherent to unicellularity, an ancient toolkit embedded within our genomes, which enables them to survive[6]. Among the factors triggering healthy cells to reactivate their primitive transcriptional programs are severe environmental pressures, such as nutrient deprivation, hypoxia and DNA damage, which are suggested to be also encountered by our unicellular ancestors[9].

The conservation of the atavistic model in basal cancer-bearing metazoa has not been addressed, although it has been thoroughly studied in human cancers. There are a few cases where abnormal cell growth in cnidaria and sponges has been observed[12,13]. Domazet-Loso and colleagues[14] provided first evidence of naturally occurring tumors in *Hydra*. In particular, they revealed that tumors in *Hydra* are associated with an altered transcriptome, mirroring shifts in gene expression analogous to those observed in cancers in vertebrates. Therefore, our study aims to contribute to the investigation of the conservation status of protein-coding transcripts that are differentially expressed in the tumor-bearing basal metazoan *Hydra* across diverse taxa. This study hypothesizes that by employing a phylostrtigraphic approach, we could trace the ancient evolutionary roots of cancer through the tree of life.

MATERIALS AND METHODS

Differentially regulated genes in *Hydra* polyps

In a microarray analysis, Domazet-Loso et al.[14] identified a set of 193 non-redundant contigs to be differentially expressed between tumorous polyps and controls in *Hydra oligactis*, which were found to correspond to the model organism *Hydra* magnipapillata genes. We used this set in our analysis, by first updating the reported *Hydra* records to a more recent NCBI RefSeq version[15-16], as of September 15, 2023. A few of those records[5] have been removed from NCBI as a result of standard genome annotation processing, and thus were not considered in the subsequent steps of our analysis.

Gene set enrichment analysis

Gene set enrichment analysis (GSEA) was performed to identify over-represented gene ontology (GO) molecular function terms in the polyp-associated differentially expressed genes (DEGs), by using the R package ClusterProfiler[17]; data were retrieved from https://data.broadinstitute.org/gsea-msigdb/msigdb/release/7.5.1/. A dotplot of the enriched terms was generated using the enrichplot R package[18].

Database homology search

The corresponding peptide sequences of the 188 differentially regulated *Hydra* genes were retrieved from the publicly available non-redundant NCBI RefSeq/GenBank[15,16]. These sequences were used as probes in an extensive series of BLASTp[19] reciprocal searches in order to obtain the homologous protein sequences corresponding to species from diverse taxa, ranging from bacteria to human. The official names of the human genes were retrieved from the HGNC database[20]. To ensure that a full representation of protein sequences is achieved, this process was reiterated until no novel sequences could be found.

Alignment and phylogenetic analysis

To investigate the evolutionary relationship between the protein encoded by the differentially expressed *Hydra* gene POLR1C in tumors and their orthologs in the species under study, phylogenetic analysis was conducted. The entire length POLR1C amino acid sequences were aligned with PRALINE[21]. The resulting alignment was used to construct a phylogenetic tree by employing maximum likelihood, a heuristic method for finding the best tree based on the observed data available in the software package MEGA11[22]. The best-fit model of amino acid substitution (LG + G) was selected on the basis of the Akaike and Bayesian information criteria. Bootstrapping (200 pseudo-replicates) was applied to assess the robustness of the inferred phylogeny.

Homology modelling

The tertiary structure of the *Schizosaccharomyces pombe* (fission yeast), *Monosiga brevicollis* (choanoflagellate) and *Hydra* POLR1C orthologous proteins were predicted with homology modeling to investigate the structural conservation of this protein. To this end a spatial restraint-based approach, implemented in the Modeller package[23,24], was employed; the generated 3D models were evaluated using the DOPE (discrete optimized protein energy) method.

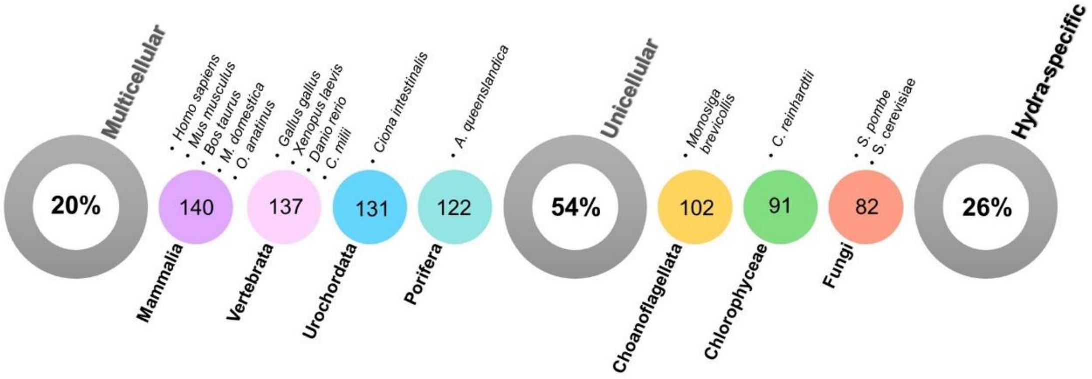

Figure 1. Phylostratigraphic distribution of differentially expressed transcripts in *Hydra* polyps from unicellular eukaryotes to mammals. The numbers inside the solid filled circles indicate the maximum number of cnidarian orthologs per taxonomic division. The percentages inside the circle rings denote the fraction of *Hydra*-specific, unicellular, and multicellular transcripts. The proportion of *Hydra* transcripts of unicellular origin is higher compared to those of multicellular origin.

RESULTS

Phylostratigraphy of differentially expressed genes in *Hydra* tumors

In this study, species with well-annotated genomes, representing major taxonomic divisions were selected to perform phylostratigraphic tracing of the evolutionary origin of the 188 polyp-associated *Hydra* protein-coding transcripts. Namely, *Homo sapiens* (human), *Mus musculus* (mouse), *Bos taurus* (cattle), *Monodelphis domestica* (possum), *Ornithorhynchus anatinus* (platypus), *Gallus gallus* (chicken), *Xenopus laevis* (frog), *Danio rerio* (zebrafish), *Callorhinchus milii* (shark), *Ciona intestinalis* (sea vase), *Amphimedon queenslandica* (sponge), *Monosiga brevicollis* (choanoflagellate), *Chlamydomonas reinhardtii* (green alga), *Saccharomyces cerevisiae* (baker's yeast), and *Schizosaccharomyces pombe* (fission yeast). The protist *Monosiga* represents the hallmark unicellular organism (Figure 1; Table S1).

A total of 1568 protein sequences corresponding to the deregulated transcripts in *Hydra* polyps were identified in the fifteen representative species under investigation, by performing thorough database sequence similarity searching (Table S1). The phylogenetic distribution of the *Hydra* polyp-related proteins across the major taxa is epitomized in Figure 1, where the numbers inside the filled circles denote the maximum number of predicted *Hydra* homologs found in a single organism from each taxonomic division; for example, *X. laevis* has the highest number of entries (137) among vertebrates (Table S1). Notably, we found that 102 (54%) of these contigs are of unicellular origin (also referred to as "UC"), whilst 38 (20%) of them are of multicellular origin (also "MC"). Due to the cross-hybridization nature of microarray probes, several of those contigs were found to correspond to more than one human gene[25]. As a result, 94, instead of 102, human orthologous genes were retained. Moreover, a significant fraction (26%) of the contigs correspond to *Hydra*-specific genes (Figure 1; circle ring). Notably, a rather small fraction 32 (16.5%) of the contigs were shown to be upregulated in the malignant polyps.

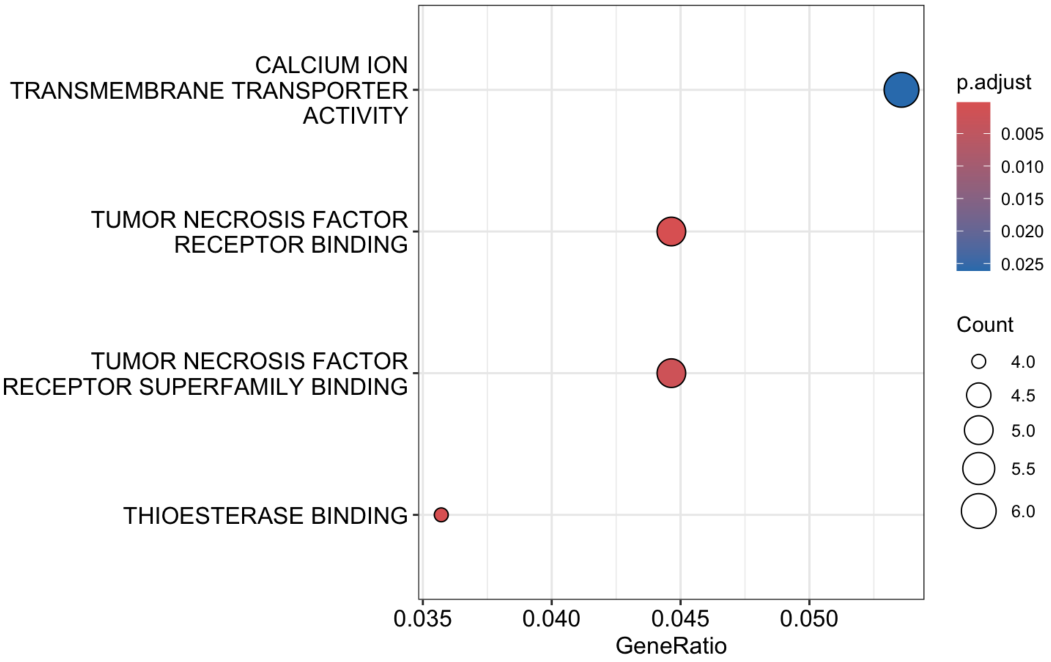

Figure 2. Dotplot of the statistically significant enriched GO molecular functions associated with the DEG in *Hydra* polyps. The dot size is proportional to the number of overlapping genes, and the dots are color-coded according to their corresponding adjusted p-values.

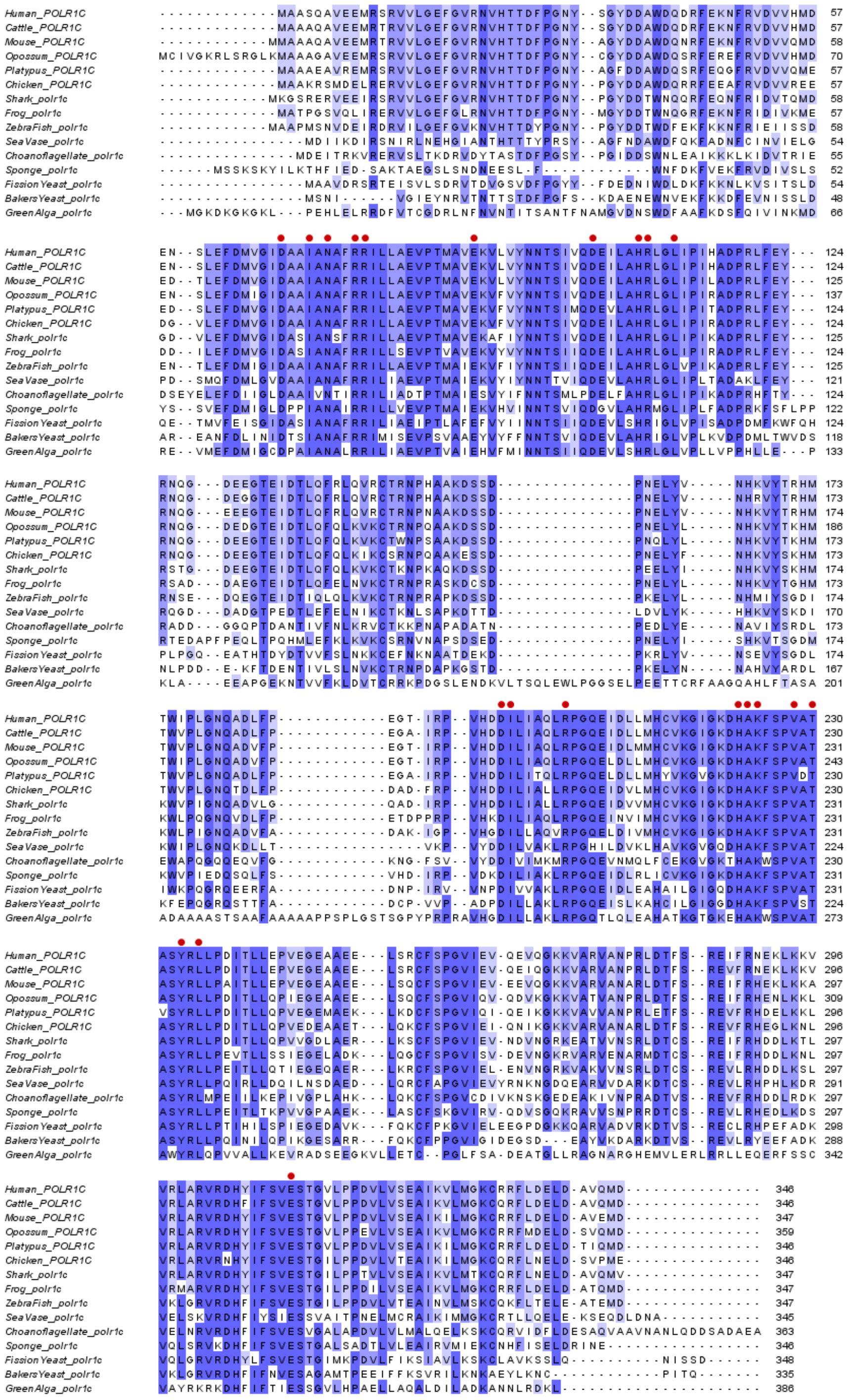

Figure 3. Alignment of the orthologous POLR1C amino acid sequences. Darker shades of blue indicate a higher level of conservation in this site. The functionally important invariant residues are denoted by red dots.

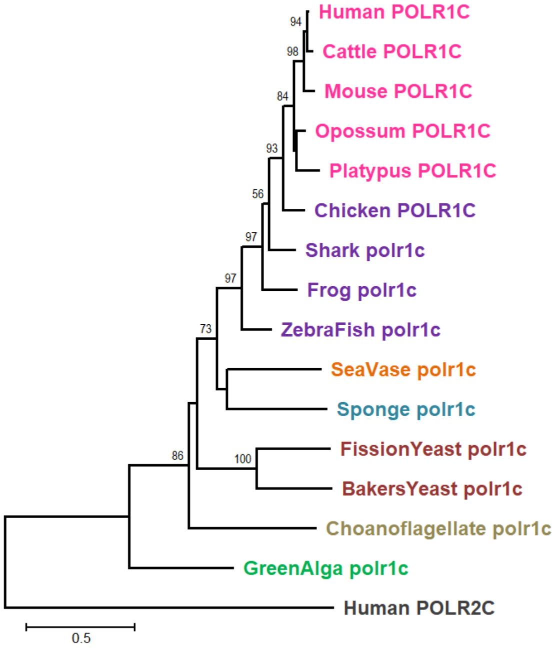

Figure 4. Maximum likelihood-based phylogenetic reconstruction of POLR1C protein sequences. Bootstrap values (≥50) at the nodes of the tree indicate statistical support. The scale bar at the bottom indicates the length of amino acid substitutions per position.

Figure 5. Structural superposition of modeled POLR1C proteins. Human (magenta), *Hydra* (turquoise), Choanoflagellate (yellow) and Yeast (green).

Functional enrichment analysis of dysregulated genes in *Hydra* polyps

Moreover, GSEA revealed over-representation of molecular functions related to the tumor necrosis factors (TNFs). The archetypal TNF-α, a pro-inflammatory cytokine, is potentially implicated in inflammation-driven carcinogenesis[26,27], further supporting that tumor-bearing basal metazoa express genes associated with mammalian cancerogenesis.

Cancer-associated UC genes functional analysis

Furthermore, all of the UC genes, except two (NOTCH2NLC and PIP5K2A), were also found to be associated with cancer, based on MalaCards[28], a publicly accessible database providing information on known human maladies, with a MalaCards information score (MIFTS)>80.

Sequence and structural conservation of POLR1C

POLR1C codes for the component subunit of two enzymes named RNA polymerase I and RNA polymerase III. These enzymes are essential for the production of ribosomal RNA (rRNA) which is crucial for normal protein synthesis in cells[29,30]. Since protein synthesis is an essential function of all living cells, POLR1C is expected to be preserved across diverse species.

The multiple alignment of the orthologous POLR1C protein sequences from the species under study is shown in Figure 3, visualized with Jalview 2.11.1.1[31]. A series of identical or highly conserved amino acids are observed in this alignment. Among the invariant residues, D69, I72, N74, R77, R78, E90, D103, H108, R109, R112, D196, I197, R203, H222, A223, K224, V228, T230, Y233, L235 and E311(human POLR1C numbering) are suggested to be implicated in protein interactions according to the InterPro version 100.0[32], an integrative database which provides functional annotation of protein families and domains.

Moreover, a maximum likelihood inferred phylogenetic tree of the orthologous POLR1C protein sequences is illustrated in Figure 4. The human POLR2C sequence, close homolog of POLR1C, is the outgroup (i.e. occupying a basal position in this phylogenetic tree), whereas the members of the POLR1C protein family cluster together with high bootstrap support, hence representing "true orthologs."

In addition, the predicted POLR1C protein structures of *Hydra*, *Monosiga brevicollis* and *Schizosaccharomyces pombe*, were aligned and superimposed onto the reference *Homo sapiens* protein using PyMol. As shown in Figure 5, the major structural elements (α helices and β sheets) are preserved both in the multicellular organisms (Human and *Hydra*) and the unicellular species (*Monosiga* and fission yeast), indicating structural homology.

DISCUSSION

From an evolutionary perspective, cancer is proposed to occur because in the early stages of life, when unicellular organisms were dominating the biological landscape, rapid replication provided them with evolutionary advantages. Within this framework, cancer exists because of somatic selection; somatic cells with mutations in cancer-related genes often proliferate faster and become more abundant, hence leading to a neoplastic state. These neoplasms disrupt the multicellular mechanisms and acquire self-serving behaviors instead. Nonetheless, cancer is significantly rare because of natural selection. The contemporary genomes originated from individuals with effective cellular control mechanisms, since they were more likely to survive and pass their genes to subsequent generations. Species-level selection favored those phenotypes wherein mutations can be suppressed and cancer cells can be eliminated[1,4]. However, when cancer occurs, it resembles a primitive organization of life, similar to our Cambrian ancestors. This shift is intricately linked to alterations in the human gene network, which consists of two main subnetworks: i) genes with unicellular origin and ii) genes with multicellular origin which were progressively built upon the unicellular network. In healthy organisms, these networks are working together to maintain the homeostasis of the multicellular organism. In cancer cells, multicellular networks are disrupted while the UC genes are expressed at higher rates which ultimately causes de-differentiation or reverse evolution. Consequently, cancer progression unfolds in a sequence of successive regressive changes, mirroring a pattern similar to the gradual shift from a single cell state to a multicellular one but in the opposite direction[11,33]. Therefore, grasping the essence of cancer in the context of evolution is of particular importance for gaining insights into the disease origins as well as developing effective treatment and prevention strategies for cancer.

In the present study, we employed phylostratigraphy[34] (i.e. a method for dating the evolutionary emergence of particular genes through homology conservation) to trace the origin of *Hydra* polyp-relevant genes. In this direction, in order to avoid bias due to incomplete genomic studies, we scanned only the fully annotated genomes of fifteen species from diverse taxonomic groups that form a direct line of descent. Regarding the multicellular organisms under study, human, mouse and cattle represent the placental mammals (eutheria), whereas *M. domestica* and *O. anatinus* are typical non-placental mammals. The non-mammalian vertebrate classes of aves, amphibia, teleost fishes and chondrichthyes are represented by chicken, frog, zebrafish and shark, respectively. *Ciona intestinalis* and *A. queenslandica* are model invertebrate tunicate and sponge organisms, correspondingly.

The choanoflagellate *Monosiga brevicollis* constitutes a hallmark unicellular organism. With more than 125 known species, phylogenetic evidence supports that choanoflagellates are the closest living relatives of metazoa[35]. Efforts towards deciphering the *Monosiga brevicollis* genome revealed that it contains a number of genes that code for cell adhesion and signaling protein domains that were believed to be exclusive to metazoa, hence providing insights into multicellular genes that predate multicellularity[36]. Moreover, the unicellular green alga *Chlamydomonas reinhardtii* (green alga) is a model chlorophyce, that has been widely used to study photosynthesis, chloroplast biogenesis and metabolism, cell–cell recognition, cell cycle control, and adhesion[37]. In this study, the genomes of the single-cell yeasts *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe* were also investigated, which have long been utilized as model systems for eukaryotic cell biology[38,39]. Of note, fungal multicellularity evolved via unique evolutionary and molecular mechanisms compared to other lineages[40]. Fungi can be either unicellular or multicellular, depending on the species. Similarities in the lifestyles of fungi and metazoan point to convergent evolution[41]. With these characteristics, these rudimentary life forms have emerged as representative organisms on the evolution of multicellularity.

In our study, by performing thorough database sequence similarity searches, based on reciprocal BLAST (Table S1), 131 orthologous protein-coding genes were detected in the fifteen species under investigation that correspond to the transcripts deregulated in *Hydra* polyps. Of those, 94 genes are of unicellular origin, constituting a considerable fraction (71%) of the evolutionarily conserved genes. Furthermore, 48 genes were found to be restricted to *Hydra*, without any detected orthologs in the species under study, suggesting a species-specific role.

Orthologs tend to share a high degree of sequence similarity and adopt similar three-dimensional fold. Given that the function of a protein is dictated by its tertiary structure, conservation of a given structure across distant relatives in the tree of life suggests an ancient evolutionary origin of this protein. More specifically, it underscores its essential role in the common ancestor of all organisms possessing this protein, highlighting its crucial function throughout evolutionary history. Herein, the primary amino acid sequences and the three-dimensional structures of the orthologous POLR1C were compared. POLR1C protein exhibits a high degree of sequence and structural conservation across species (Figure 3 and 5), which is indicative of its importance in the structural and functional integrity of the host cell as well as its ancient origins.

The UC genes are implicated in cancer, according to MalaCards; a high MIFTS score was applied, which reflects the richness of information for this entry, so as to ensure that the given gene-disease relationship is of high confidence. Of note, only a small fraction (17%) of the UC genes were found to be up-regulated in *Hydra* polyps, contrary to our expectations. These genes, or their corresponding encoded proteins, could be probably involved in the "cross-talk" between older (UC) and younger (MC) cancer genes; this merits further research. Nonetheless, our findings reveal a general trend of genes of unicellular origin present in cancer.

Nowadays, there is an increasing need for non-mammalial and non-vertebrate model organisms for experimental studies that simulate human pathophysiology. These organisms represent unique advantages stemming from their distinct biological characteristics[42]. *Hydra* is an aquatic organism, belonging to the phylum Cnidaria, which also includes jellyfish, corals and sea anemones. It can be cultivated easily and also possesses regenerative abilities. In this study, we provide further evidence to support the utilization of cnidaria in cancer research as emerging model organisms for the study of fundamental mechanisms of vertebrate cancers[43]. Of note, a considerable number of polyp-related cnidarian orthologs was also detected in the sponge *Amphimedon* (Table S1). Porifera are presumed to be the simplest group of multicellular animals. However, despite their low structural complexity, they possess numerous genes/proteins related to human cancer [44], thereby highlighting their potential as model systems for studying carcinogenesis.

The limitations of this study are that the function of the identified putative proteins has not been validated experimentally.

In conclusion, herein, by applying an in silico approach, we provide evidence for the conservation of the atavistic model of cancer in the basal tumor-bearing animal *Hydra*, given the preservation of cnidarian tumor-related genes/proteins throughout the tree of life. We also propose *Hydra* as a promising model organism in cancer research, shedding light on the evolutionary underpinnings of cancer and highlighting its relevance in broader biological contexts.

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REFERENCES

1. Aktipis CA, Nesse RM. Evolutionary foundations for cancer biology. Evol Appl. 2013;6:144-59.
2. Rokas A. The origins of multicellularity and the early history of the genetic toolkit for animal development. Annu Rev Genet. 2008;42:235-51.
3. Grosberg RK, Strathmann RR. The evolution of multicellularity: a minor major transition? Annual Review of Ecology, Evolution and Systematics. 2007;38:621-54.
4. Nedelcu AM. The evolution of multicellularity and cancer: views and paradigms. Biochem Soc Trans. 2020;48:1505-18.
5. Aktipis CA, Boddy AM, Jansen G, Hibner U, Hochberg ME, Maley CC et al. Cancer across the tree of life: cooperation and cheating in multicellularity. Philos Trans R Soc Lond B Biol Sci. 2015;370.
6. Davies PC, Lineweaver CH. Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors. Phys Biol. 2011;8:015001.
7. Domazet-Loso T, Tautz D. Phylostratigraphic tracking of cancer genes suggests a link to the emergence of multicellularity in metazoa. BMC Biol. 2010;8:66.
8. Lineweaver CH, Bussey KJ, Blackburn AC, Davies PCW. Cancer progression as a sequence of atavistic reversions. Bioessays. 2021;43:e2000305.
9. Trigos AS, Pearson RB, Papenfuss AT, Goode DL. Altered interactions between unicellular and multicellular genes drive hallmarks of transformation in a diverse range of solid tumors. Proc Natl Acad Sci U S A. 2017;114:6406-11.
10. Louka A, Takan I, Pavlopoulou A, Georgakilas AG. Bioinformatic approaches to the investigation of the atavistic genes implicated in cancer. Front Biosci (Landmark Ed). 2021;26:279-311.
11. Chen H, Lin F, Xing K, He X. The reverse evolution from multicellularity to unicellularity during carcinogenesis. Nat Commun. 2015;6:6367.
12. Robert J. Comparative study of tumorigenesis and tumor immunity in invertebrates and nonmammalian vertebrates. Dev Comp Immunol. 2010;34:915-25.
13. Squires DF. Neoplasia in a Coral? Science. 1965;148:503-5.
14. Domazet-Loso T, Klimovich A, Anokhin B, Anton-Erxleben F, Hamm MJ, Lange C et al. Naturally occurring tumours in the basal metazoan Hydra. Nat Commun. 2014;5:4222.
15. Sayers EW, Bolton EE, Brister JR, Canese K, Chan J, Comeau DC et al. Database resources of the National Center for Biotechnology Information in 2023. Nucleic Acids Res. 2023;51:D29-D38.
16. Sayers EW, Cavanaugh M, Clark K, Pruitt KD, Sherry ST, Yankie L et al. GenBank 2023 update. Nucleic Acids Res. 2023;51:D141-D44.
17. Xu S, Hu E, Cai Y, Xie Z, Luo X, Zhan L et al. Using clusterProfiler to characterize multiomics data. Nat Protoc. 2024.
18. Yu G: enrichplot: Visualization of Functional Enrichment Result. R package version 1.24.2, 2024.
19. Altschul SF, Gish W, Miller W, Myers EW, Lipman DJ. Basic local alignment search tool. J Mol Biol. 1990;215:403-10.
20. Seal RL, Braschi B, Gray K, Jones TEM, Tweedie S, Haim-Vilmovsky L et al. Genenames.org: the HGNC resources in 2023. Nucleic Acids Res. 2023;51:D1003-09.
21. Simossis VA, Heringa J. PRALINE: a multiple sequence alignment toolbox that integrates homology-extended and secondary structure information. Nucleic Acids Res. 2005;33:W289-94.
22. Tamura K, Stecher G, Kumar S. MEGA11: Molecular Evolutionary Genetics Analysis Version 11. Mol Biol Evol. 2021;38:3022-27.

23. Webb B, Sali A. Protein structure modeling with MODELLER. Methods Mol Biol. 2017;1654:39-54.
24. Janson G, Grottesi A, Pietrosanto M, Ausiello G, Guarguaglini G, Paiardini A. Revisiting the "satisfaction of spatial restraints" approach of MODELLER for protein homology modeling. PLoS Comput Biol. 2019;15:e1007219.
25. Kontou PI, Pavlopoulou A, Bagos PG. Methods of analysis and meta-analysis for identifying differentially expressed genes. Methods Mol Biol. 2018;1793:183-210.
26. Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y et al. Inflammation and tumor progression: signaling pathways and targeted intervention. Signal Transduct Target Ther. 2021;6:263.
27. Ben-Baruch A. Tumor Necrosis Factor alpha: Taking a Personalized Road in Cancer Therapy. Front Immunol. 2022;13:903679.
28. Rappaport N, Twik M, Plaschkes I, Nudel R, Iny Stein T, Levitt J et al. MalaCards: an amalgamated human disease compendium with diverse clinical and genetic annotation and structured search. Nucleic Acids Res. 2017;45:D877-D87.
29. De Angelis R, Iezzi S, Bruno T, Corbi N, Di Padova M, Floridi A et al. Functional interaction of the subunit 3 of RNA polymerase II (RPB3) with transcription factor-4 (ATF4). FEBS Lett. 2003;547:15-9.
30. Thiffault I, Wolf NI, Forget D, Guerrero K, Tran LT, Choquet K et al. Recessive mutations in POLR1C cause a leukodystrophy by impairing biogenesis of RNA polymerase III. Nat Commun. 2015;6:7623.
31. Waterhouse AM, Procter JB, Martin DM, Clamp M, Barton GJ. Jalview Version 2--a multiple sequence alignment editor and analysis workbench. Bioinformatics. 2009;25:1189-91.
32. National Cancer Institute. https://www.cancer.gov/news-events/press-releases/2020 (accessed on 7 June 2021) (accessed June 7, 2021.
33. Trigos AS, Pearson RB, Papenfuss AT, Goode DL. How the evolution of multicellularity set the stage for cancer. Br J Cancer. 2018;118:145-52.
34. Domazet-Loso T, Brajkovic J, Tautz D. A phylostratigraphy approach to uncover the genomic history of major adaptations in metazoan lineages. Trends Genet. 2007;23:533-9.
35. Lang BF, O'Kelly C, Nerad T, Gray MW, Burger G. The closest unicellular relatives of animals. Curr Biol. 2002;12:1773-8.
36. King N, Westbrook MJ, Young SL, Kuo A, Abedin M, Chapman J et al. The genome of the choanoflagellate Monosiga brevicollis and the origin of metazoans. Nature. 2008;451:783-8.
37. Harris EH. Chlamydomonas as a model organism. Annu Rev Plant Physiol Plant Mol Biol. 2001;52:363-406.
38. Vanderwaeren L, Dok R, Voordeckers K, Nuyts S, Verstrepen KJ. Saccharomyces cerevisiae as a model system for eukaryotic cell biology, from cell cycle control to dna damage response. Int J Mol Sci. 2022;23.
39. Vyas A, Freitas AV, Ralston ZA, Tang Z. Fission yeast schizosaccharomyces pombe: a unicellular "micromammal" model organism. Curr Protoc. 2021;1:e151.
40. Nagy LG, Varga T, Csernetics Á, Virágh M. Fungi took a unique evolutionary route to multicellularity: Seven key challenges for fungal multicellular life. Fungal Biology Reviews. 2020;34:151-69.
41. Torruella G, de Mendoza A, Grau-Bove X, Anto M, Chaplin MA, del Campo J et al. Phylogenomics reveals convergent evolution of lifestyles in close relatives of animals and fungi. Curr Biol. 2015;25:2404-10.
42. Bertile F, Matallana-Surget S, Tholey A, Cristobal S, Armengaud J. Diversifying the concept of model organisms in the age of -omics. Commun Biol. 2023;6:1062.
43. Yum S, Woo S, Lee A, Won H, Kim J. Hydra, a candidate for an alternative model in environmental genomics. Mol Cell Toxicol. 2014;10:339–46.
44. Cetkovic H, Halasz M, Herak Bosnar M. Sponges: A reservoir of genes implicated in human cancer. Mar Drugs. 2018;16:20.

Table S1. Phylogenetic distribution of the Hydra polyp-related genes in the species under investigation. The genes up-regulated in Hydra polyps are indicated by red.

Hydra	**Updated ACC**	**Human Gene symbols**	***Homo sapiens***	***Mus musculus***	***Bos taurus***	***Monodelphis domestica***	***Ornithorhynchus anatinus***	***Gallus gallus***	***Xenopus laevis***	***Danio rerio***	***Callorhinchus milii***	***Ciona intestinalis***	***Amphimedon queenslandica***	***Monosiga brevicollis***	***Chlamydomonas reinhardtii***	***Schizosaccharomyces pombe***	***Saccharomyces cerevisiae***
XP_003387239.1		HSDL2	NP_115679.2	XP_036020353.1	NP_001098433.1	XP_056662591.1	XP_028909690.2	XP_003643140.1	NP_001083285.1	NP_955893.1	NP_001279740.1	XP_002120177.1	XP_003387239.1	XP_001746982.1	XP_001693094.1	NP_588241.1	GFP73661.1
XP_002170777.1	XP_047145276.1	MINPP1	NP_004888.2	NP_034929.1	NP_001033664.2	XP_001374318.2	XP_028916135.1	NP_989975.2	XP_018082801.1	NP_957394.1	XP_007895111.1	XP_002131712.1	XP_019853182.1				
XP_002170759.1	XP_047143718.1	Hydra-specific															
XP_002170725.1	XP_047123669.1	Hydra-specific															
XP_002170624.1		WDR48	NP_001333156.1	NP_080512.1	NP_001069992.1	XP_007500721.1	XP_028933750.1	NP_001026135.1	XP_041421711.1	NP_999874.1	XP_042188054.1	XP_002127032.1	XP_019855207.1	XP_001750275.1		NP_592926.1	
XP_002170522.1	XP_047144022.1	PKD1L2	NP_443124.4	NP_083962.4	XP_059733360.1	XP_007502675.1	XP_028934523.1	XP_015146243.4	XP_041443686.1	XP_021333711.1	XP_007892914.2	XP_026696450.1	XP_019853400.1	XP_001742874.1	XP_042920117.1	NP_001342849.1	CAI4587529.1
XP_002170357.1	XP_047133850.1	NLRP7	NP_631915.2	XP_006522213.1	XP_002683779.2	XP_007492316.1	XP_028917427.1	XP_040556738.1	XP_041429599.1	XP_017209832.1	XP_042201642.1	XP_018668540.1	XP_019852853.1	XP_001746606.1	XP_001695420.1	NP_595792.1	AJV75478.1
XP_002170231.1	XP_047126577.1	ZBED1	NP_001164606.1	NP_852077.1	XP_024844566.1	XP_001376061.1	XP_028935360.1	XP_046763088.1	XP_018108103.1	NP_001076410.1	XP_007888700.1	XP_018671780.1	XP_019858606.1				
XP_002170216.1	XP_047134919.1	GVINP1	Q7Z2Y8.2	NP_001229968.1	XP_059731100.1	XP_001380380.2	XP_007665737.1	XP_040524270.1	XP_041419563.1	XP_021327097.1	XP_042192908.1	XP_002121682.1	XP_019850149.1	XP_001742566.1			
XP_002170140.1	XP_002170140.2	MDH1B	NP_001269869.1	XP_036010132.1	NP_001076921.1	XP_056664145.1	XP_028924248.1	XP_040532153.1	XP_018091685.1	XP_009303919.1	XP_007888793.1	XP_002122460.3	XP_011405019.2	XP_001744311.1	XP_042927723.1	NP_592908.1	CAI4348083.1
XP_002169972.1	XP_012566885.1	PRSS16	NP_005856.1	NP_062302.1	XP_010816800.1	XP_001372314.3	XP_028925206.1	XP_040514679.1	XP_018088823.1	XP_021322229.1	XP_007887994.1	XP_018667737.1	XP_003386675.1	XP_001743761.1	XP_042919890.1	NP_594983.1	AJT21925.1
XP_002169912.1	XP_047124938.1	Hydra-specific															
XP_002169865.1		record removed															
XP_002169546.1		Hydra-specific															
XP_002169472.1	XP_012558740.1	KCNQ2	NP_742107.1	NP_001006675.1	XP_024856871.1	XP_007475626.1	XP_028926226.1	XP_004947155.4	XP_018092537.1	XP_009301043.1	XP_042187602.1	NP_001139030.1	XP_019848892.1	XP_001746676.1	XP_042914472.1	NP_594274.1	EDZ71481.1
XP_002169288.1		AK3	NP_057366.2	NP_067274.1	NP_776662.1	XP_001365155.1	XP_028911424.1	XP_015135676.2	NP_001084561.1	NP_998295.2	XP_007910523.1	XP_026690497.1	XP_003383231.1	XP_001744461.1	XP_042918880.1	NP_593685.1	AJU61509.1
XP_002169207.1	XP_047130875.1	SLC2A8	NP_001138571.1	NP_001171098.1	XP_005213301.1	XP_007475295.1	XP_028917976.1	XP_423637.5	XP_041428009.1	XP_689092.6	XP_007909673.1	XP_002128611.2	XP_003385376.1	XP_001748408.1	XP_001693177.1	NP_593320.1	CAI7235084.1
XP_002169178.1	XP_047146519.1	PGS1	XP_047293058.1	NP_598518.1	NP_001039860.2	XP_056673379.1	XP_028912665.1	NP_001008463.1	XP_018093006.1	XP_003199680.3	XP_042198232.1	XP_026693645.1	XP_019853737.1	XP_001750016.1	XP_001702812.1	NP_595992.2	CAI4912429.1
XP_002169177.1	XP_047146614.1	FADD	NP_003815.1	NP_034305.1	NP_001007817.1	XP_001381076.1	XP_001507113.1	XP_040529199.1	XP_018112847.1	NP_001373289.1	XP_007885916.1	XP_009861145.2	XP_003387950.1				
XP_002169062.1	XP_047132250.1	STK40	NP_001269475.1	NP_001289733.1	XP_015315541.1	XP_001371175.1	XP_028924428.1	XP_004934981.3	NP_001082434.1	NP_997897.2	NP_001279495.1						
XP_002169050.1	XP_012564446.2	Hydra-specific															
XP_002168718.1	XP_047130218.1	Hydra-specific															
XP_002168699.1		PKD2L1	NP_001240766.1	NP_852087.2	XP_015316200.1	XP_056653688.1	XP_039770201.1	XP_040531230.1	XP_018082982.1	XP_695404.3	XP_007897917.2	XP_002119742.1					
XP_002168652.1		KHK	NP_000212.1	NP_001335995.1	XP_024854918.1	XP_001371076.1	XP_028928283.1	XP_015140518.1	NP_001087493.1	XP_005158696.1	XP_007900097.1	XP_002123654.1	XP_003388714.1	XP_001742353.1	XP_001702739.2	NP_596751.1	CAI4869609.1

Hydra	**Updated ACC**	**Human Gene symbols**	***Homo sapiens***	***Mus musculus***	***Bos taurus***	***Monodelphis domestica***	***Ornithorhynchus anatinus***	***Gallus gallus***	***Xenopus laevis***	***Danio rerio***	***Callorhinchus milii***	***Ciona intestinalis***	***Amphimedon queenslandica***	***Monosiga brevicollis***	***Chlamydomonas reinhardtii***	***Schizosaccharomyces pombe***	***Saccharomyces cerevisiae***
XP_002168448.1		TUBGCP6	NP_065194.3	XP_036015362.1	NP_001002887.3	XP_056677250.1	XP_028912293.1	XP_040509775.1	XP_041422762.1	XP_021331201.1	XP_007908714.1	XP_018670999.1	XP_019853365.1	XP_001745797.1			
XP_002168291.1	XP_047132839.1	Hydra-specific															
XP_002168023.1	XP_004211264.1	B3GNT4	NP_110392.1	NP_001369783.1	XP_024833467.1	XP_001374027.2	XP_028913695.1	XP_046757219.1	XP_018118633.1	NP_991315.2	XP_007902875.1	XP_002124350.1	XP_011405158.1	XP_001744321.1	XP_001702968.2	NP_595999.1	
XP_002167948.1		ITPA	NP_258412.1	NP_080198.2	NP_001069750.1	XP_001377329.3	XP_003430905.2	NP_001258859.1	NP_001089939.1	NP_001093456.1	XP_007893813.1	XP_002131447.1	XP_003382506.1	XP_001750992.1	XP_001701193.1	NP_588480.1	AJR69241.1
XP_002167861.1		Hydra-specific															
XP_002167842.1		CALM2	NP_001292553.1	NP_031615.1	XP_059746977.1	XP_056675563.1	XP_001506524.2	NP_001103834.2	NP_001080864.1	NP_852475.3	XP_007901645.1	NP_001027633.1	XP_019849868.1	XP_001749021.1	XP_001703420.1	NP_593340.1	NP_009667.1
XP_002167611.1		TPI1	NP_000356.1	NP_033441.3	NP_001013607.1	XP_001370168.2	XP_028910144.1	NP_990782.1	XP_018080520.1	NP_705954.2	XP_042191374.1	XP_002127794.1	XP_019849782.1	XP_001747261.1	XP_042915514.1	NP_593426.1	AJR54378.1
XP_002167426.1		Hydra-specific															
XP_002167219.1		Hydra-specific															
XP_002167217.1	XP_002167217.3	Hydra-specific															
XP_002167033.1	XP_002167033.3	PDX1	NP_000200.1	NP_032840.1	NP_001179065.1	XP_001376171.1	XP_028904360.1	XP_001234636.3	NP_001165682.1	NP_571518.2	XP_007898801.1	NP_001027673.1					
XP_002166865.1		record removed															
XP_002166844.1	XP_047123476.1	ADGRE1	NP_001243181.1	NP_032019.2	XP_010805238.2	XP_056678553.1	XP_039766244.1	XP_046779197.1	NP_001083660.1	NP_998532.2	XP_007885430.1	XP_018668293.1	XP_019854598.1	ACR39371.1	XP_042918065.1	NP_595866.1	
XP_002166553.1	XP_047127206.1	Hydra-specific															
XP_002166467.1		RIPK3	NP_006862.2	NP_064339.2	XP_024839191.1	XP_007488097.2	XP_001510675.2	NP_989733.3	XP_041421503.1	NP_001036815.1	XP_007887810.2	XP_009858304.1	XP_011403964.1				
XP_002166425.1	XP_012555841.2	Hydra-specific															
XP_002166379.1	XP_002166379.2	LIG4	NP_001091738.1	NP_001178055.1	NP_001363971.1	XP_007501369.2	XP_007666847.2	XP_015129663.2	NP_001081114.1	XP_005160015.1	XP_007891664.1	XP_026689651.1	XP_019856983.1	XP_001742128.1	XP_042920079.1	NP_587888.2	CAI4741592.1
XP_002166285.1		CALM1	NP_001350598.1	NP_001300863.1	XP_059746644.1	XP_056681853.1	XP_001506524.2	NP_001103834.2	NP_001080864.1	NP_852475.3	XP_007901645.1	NP_001027633.1	XP_019849868.1	XP_001749021.1	XP_001703420.1	NP_593340.1	NP_009667.1
XP_002166209.1	XP_047141914.1	ADGRD1	NP_942122.2	XP_036011624.1	XP_002690336.3	XP_016284410.2	XP_028911643.1	XP_015139567.1	XP_018120665.1	NP_001356058.1	XP_042188664.1	XP_004226800.2	XP_019853407.1	XP_001748001.1	XP_042915998.1	NP_595141.1	
XP_002166189.1		LMNA	NP_001269554.1	NP_001104572.1	NP_001029225.1	XP_001367284.1	XP_028911651.1	NP_990618.1	NP_001095210.1	XP_005158224.1	XP_007906490.1	NP_001093902.2	XP_011405655.2	XP_001744550.1	XP_042918251.1	NP_594886.1	AJW02937.1
XP_002166075.1	XP_002166075.2	GALNT2	NP_001278795.1	NP_644678.2	NP_001180032.1	XP_001369295.1	XP_028903372.1	XP_015139872.1	XP_018120759.1	NP_001121823.1	XP_042189011.1	XP_009861068.1	XP_003387611.2	XP_001749871.1			
XP_002166070.1	XP_002166070.3	POLR1C	NP_976035.1	AAI30019.1	NP_001033213.1	XP_001362696.2	XP_028903314.1	NP_001264559.1	NP_001085237.1	NP_956860.1	XP_007896445.1	XP_002120101.1	XP_003386510.1	XP_001749387.1	XP_042922405.1	NP_596831.1	CAI4857723.1
XP_002165983.1		KMO	NP_003670.2	NP_598570.1	NP_001230227.1	XP_007481618.1	XP_001514157.1	XP_040531686.1	XP_041418727.1	NP_001314753.2	XP_042189382.1	XP_002131315.1	XP_003388773.1	XP_001747492.1	XP_001690012.2	NP_594133.1	CAD6607714.1
XP_002165955.1	XP_002165955.2	PON1	NP_000437.3	NP_035264.2	NP_001039734.1	XP_056656919.1	XP_028927166.1	NP_001188397.2	XP_018122811.1	NP_001098592.2	XP_007888990.1	XP_002129191.1	XP_011409611.2				
XP_002165886.1		CRNKL1	NP_057736.4	NP_080096.1	NP_001193451.2	XP_007507884.2	XP_039768404.1	XP_040522975.1	XP_018120592.1	NP_957240.1	XP_007896530.1	XP_002125953.1	XP_003383105.1	XP_001749122.1	XP_042916853.1	NP_596573.1	CAI4628978.1
XP_002165877.1	XP_002165877.3	TRAF4	NP_004286.2	NP_033449.2	NP_001094750.1	XP_001368795.1	XP_028937555.1	XP_015151572.3	NP_001087501.1	NP_991325.1	XP_042194667.1	NP_001123338.1	XP_011403162.2	XP_001746838.1	XP_001703257.1	NP_593310.1	CAD6619561.1

Hydra	**Updated ACC**	**Human Gene symbols**	***Homo sapiens***	***Mus musculus***	***Bos taurus***	***Monodelphis domestica***	***Ornithorhynchus anatinus***	***Gallus gallus***	***Xenopus laevis***	***Danio rerio***	***Callorhinchus milii***	***Ciona intestinalis***	***Amphimedon queenslandica***	***Monosiga brevicollis***	***Chlamydomonas reinhardtii***	***Schizosaccharomyces pombe***	***Saccharomyces cerevisiae***
XP_002165847.1		ANK2	NP_001373087	XP_036018729.1	XP_024849262.1	XP_056659025.1	XP_039769735.1	XP_040526423.1	XP_041435565.1	XP_021333183.1	XP_042195766.1	XP_026693225.1	XP_019851861.1	XP_001742781.1	XP_042924645.1		
XP_002165691.1	XP_047143231.1	TRAF6	NP_665802.1	NP_033450.2	NP_001029833.1	XP_001362131.1	XP_001509071.1	XP_040529244.1	NP_001089863.1	NP_001038217.1	XP_042197525.1	NP_001071979.1	XP_003383545.3	XP_001750277.1	XP_001703257.1	NP_593310.1	CAD6619561.1
XP_002165649.1		VPS35L	NP_064710.5	XP_006508275.1	XP_005224812.1	XP_007498241.2	XP_028910754.1	XP_015150273.3	XP_018094615.1	NP_001091651.1	XP_007891938.1	XP_002131713.1	XP_019849231.1	XP_001749136.1			
XP_002165614.1		record removed															
XP_002165582.1	XP_002165582.2	Hydra-specific															
XP_002165562.1	XP_047143403.1	MARF1	NP_055462.2	NP_001074623.1	NP_001258923.1	XP_056662171.1	XP_028903451.1	NP_001383444.1	XP_018091814.1	XP_021332636.1	XP_042197155.1	XP_009861611.2					
XP_002165457.1		ZNF112	NP_001398000.1	NP_001135883.1	XP_024835240.1	XP_056669380.1	XP_028904944.1	XP_040509775.1	XP_041422762.1	XP_021331333.1	XP_007908714.1	XP_026694697.1					
XP_002165426.1	XP_047130481.1	Hydra-specific															
XP_002165382.1	XP_047132954.1	MRPS9	NP_872578.1	NP_076003.3	XP_005212500.1	XP_007501239.1	XP_028913609.1	NP_001264686.1	NP_001090517.1	NP_001038861.1	XP_007883334.1	XP_002126231.1	XP_019854305.1	XP_001748670.1	XP_001699966.2	NP_594879.2	KZV13227.1
XP_002165352.1	XP_047132955.1	MEA1	NP_001305871.1	NP_001264239.1	NP_777073.1	XP_007484000.1	XP_001508617.3	XP_040523001.1	XP_018118272.1	XP_005156553.1	XP_042188848.1	XP_009859704.1	XP_003384585.1				
XP_002165184.1		ARSJ	NP_001341139.1	NP_033842.3	NP_001094645.1	XP_001381590.2	XP_028926611.1	XP_003642960.2	XP_018120981.1	XP_021324609.1	XP_042187672.1	XP_002127641.1	XP_019850110.1	XP_001742119.1	XP_042924917.1	NP_593087.1	CAI4412231.1
XP_002165016.1		TBC1D1	NP_055988.2	XP_036021280.1	XP_024855684.1	XP_056663192.1	XP_028913836.1	XP_015132521.2	XP_018100562.1	XP_002663441.2	XP_042190308.1	XP_018673312.1					
XP_002164996.1	XP_002164996.3	B3GNT4	NP_110392.1	NP_001369783.1	XP_024833467.1	XP_001374027.2	XP_028913695.1	XP_046757219.1	XP_018118633.1	XP_005159205.1	XP_007902875.1	XP_002124350.1	XP_003386686.2	XP_001744321.1	XP_001702968.2	NP_595999.1	
XP_002164957.1	XP_047139900.1	Hydra-specific															
XP_002164787.1		SLC17A5	NP_001369565.1	XP_011241039.1	NP_001192903.1	XP_007484263.1	XP_028920912.1	NP_001026257.1	XP_018096067.1	NP_001070195.1	XP_007910508.2	XP_026696646.1	XP_011404686.1	XP_001746784.1	XP_042922239.1	NP_594995.1	CAI4374037.1
XP_002164758.1	XP_047145735.1	Hydra-specific															
XP_002164717.1	XP_002164717.2	UNC13D	NP_954712.1	XP_006534251.1	NP_001179012.2	XP_056673103.1	XP_028912672.1	XP_040542191.1	XP_041432586.1	XP_009305114.1	XP_042198522.1	XP_018669899.1	XP_019853517.1	XP_001743696.1	XP_042914711.1	NP_593894.1	AJS02959.1
XP_002164671.1	XP_002164671.3	Hydra-specific															
XP_002164488.1		TOR1A	NP_000104.1	NP_659133.1	NP_001092528.1	XP_001369302.1	XP_001508626.2	NP_001025858.2	XP_018088182.1	NP_001186944.1	XP_042193250.1	XP_002125069.3					
XP_002164425.1	XP_012554162.2	ATP7B	NP_001393444.1	NP_031537.2	XP_005213777.1	XP_056650787.1	XP_028903748.1	XP_040561463.1	XP_041438548.1	NP_001036185.1	XP_007889395.1	XP_009860869.1	XP_019862991.1	XP_001748178.1	XP_042915749.1	NP_595829.1	AJU97948.1
XP_002164394.1		CHURC1	NP_001373857.1	NP_996257.1	NP_001040046.1	XP_007473101.1	XP_001505710.4	NP_990040.1	NP_001079208.1	NP_001007381.1	XP_007886304.1	XP_026695101.1	XP_003386737.2				
XP_002164348.1	XP_047138567.1	C1orf50	NP_077002.2	NP_001012400.1	NP_001029451.2	XP_001381649.1	XP_028920287.1	XP_040507356.1	NP_001088694.1	NP_001018505.1	XP_042199599.1	XP_002126260.1	XP_003385304.1	XP_001745050.1	XP_001693031.2	NP_593772.2	AJW02504.1
XP_002164232.1	XP_047131245.1	Hydra-specific															
XP_002164073.1	XP_047145458.1	ATP5IF1	NP_057395.1	NP_001407692.1	NP_787010.1	XP_016277614.2	XP_028936183.1	XP_015153068.3	NP_001086362.1	NP_001082990.1	NP_001280083.1	XP_026690369.1	XP_003387512.1				
XP_002163925.1		Hydra-specific															

Hydra	**Updated ACC**	**Human Gene symbols**	***Homo sapiens***	***Mus musculus***	***Bos taurus***	***Monodelphis domestica***	***Ornithorhynchus anatinus***	***Gallus gallus***	***Xenopus laevis***	***Danio rerio***	***Callorhinchus milii***	***Ciona intestinalis***	***Amphimedon queenslandica***	***Monosiga brevicollis***	***Chlamydomonas reinhardtii***	***Schizosaccharomyces pombe***	***Saccharomyces cerevisiae***
XP_002163761.1	XP_047142653.1	NCAN	NP_004377.2	NP_033069.1	NP_001180011.1												
XP_002163744.1	XP_002163744.2	CSDC2	NP_055275.1	NP_663448.2	NP_001070345.1	XP_001363729.1	XP_028935218.1	XP_046763575.1	XP_018114214.1	NP_001002690.1	XP_007907755.1	XP_004226327.1	XP_003384057.1	XP_001748284.1	XP_042914243.1	NP_588430.1	NP_013684.1
XP_002163606.1		UNC5CL	NP_775832.2	NP_080288.1	XP_005223573.1	XP_056674164.1	XP_028925649.1	NP_989782.2	XP_041446685.1	NP_001093454.1	XP_007900714.1	XP_026691758.1					
XP_002163590.1	XP_047146470.1	Hydra-specific															
XP_002163381.1		CEACAM21	NP_291021.4	XP_006540452.1	XP_015313685.1	XP_007491613.1	XP_039768112.1										
XP_002163349.1	XP_047122486.1	Hydra-specific															
XP_002163318.1		CHDH	NP_060867.2	NP_001129712.1	NP_001192493.1	XP_016280112.2	XP_028907315.1	XP_025010308.1	XP_018095879.1	XP_002663301.2	XP_007901594.1	XP_002129749.1	XP_019857956.1	XP_001749753.1	XP_001703004.1	NP_593749.1	NP_011062.1
XP_002163235.1		ALOX15B	NP_000689.1	NP_033792.1	NP_001179721.1	XP_001364255.2	XP_028917546.1	XP_003641560.1	XP_041427019.1	NP_001290191.1	XP_007902723.1	XP_002123813.5	XP_003383419.1	XP_001742874.1	XP_042926129.1		
XP_002163208.1		MFSD14B	NP_115947.2	NP_001077370.1	NP_001095508.1	XP_001372129.1	XP_028918500.1	NP_001026733.2	NP_001080241.1	NP_998692.2	XP_007901108.1	XP_009858603.1	XP_011404646.1	XP_001749764.1	XP_042915542.1	NP_595028.1	AJV29791.1
XP_002163192.1		ARHGAP21	NP_065875.3	NP_001121556.2	XP_005214354.1	XP_001376289.2	XP_039769856.1	NP_001385180.1	XP_041421274.1	NP_001340279.1	XP_042202713.1	XP_026690539.1	XP_019854224.1	XP_001750836.1	XP_042924383.1	NP_593448.1	GMC30046.1
XP_002163157.1	XP_047131443.1	Hydra-specific															
XP_002163000.1		Hydra-specific															
XP_002162455.1		B3GALT6	NP_542172.2	NP_536693.1	XP_002694179.1	XP_001376070.3	XP_007660958.2	XP_015152615.1	XP_018083363.1	NP_001038690.1	XP_042199664.1	NP_001072016.1	XP_003386686.2	XP_001744321.1	XP_001702968.2	NP_595999.1	
XP_002162432.1		SFXN2	NP_001337918.1	NP_444426.3	XP_005225575.1	XP_056660628.1	XP_007665833.1	XP_040531144.1	XP_041424619.1	NP_997895.1	XP_042192918.1	XP_018669676.1	XP_003383928.1	XP_001746826.1	XP_001697036.2	NP_594262.2	NP_014914.1
XP_002162218.1		Hydra-specific															
XP_002162152.1		MFSD8	NP_001358521.1	NP_082416.2	NP_001192752.1	XP_007495548.2	XP_028923140.1	XP_004941064.2	NP_001085636.1	NP_001038513.1	XP_007908880.1	XP_018668152.1	XP_019854633.1				
XP_002162110.1	XP_012565675.1	Hydra-specific															
XP_002162106.1		SDK2	XP_024302452.1	XP_006504775.1	XP_024836860.1	XP_056673186.1	XP_028935754.1	XP_015135354.1	XP_018093809.1	XP_009305145.1	XP_007886763.1						
XP_002161986.1		Hydra-specific															
XP_002161934.1		FLT1	NP_002010.2	XP_036020680.1	NP_001178061.2	XP_007495324.2	XP_007662302.2	NP_989583.2	XP_018110424.1	NP_001014829.3	XP_007898795.2	XP_009860892.2	XP_011406831.2				
XP_002161887.1		GALNT6	NP_009141.2	NP_001155239.1	NP_001179787.3	XP_056653194.1	XP_028927920.1	XP_025008423.1	XP_018094328.1	XP_021334717.1	XP_007888017.1	XP_002121130.1	XP_019851218.1	XP_001747831.1	XP_042924008.1	NP_594608.1	AJV62970.1
XP_002161434.1		MCOLN3	NP_001317576.1	XP_006501149.1	NP_001179663.1	XP_056671383.1	XP_039767817.1	XP_004936703.1	NP_001085127.1	NP_957442.1	XP_007885392.2	XP_002129787.1	XP_011405686.2	XP_001742271.1			
XP_002161382.1	XP_047131353.1	NLRP12	NP_653288.1	NP_001028603.1	XP_024835162.1	XP_007492316.1	XP_039769327.1	XP_046774066.1	XP_041429606.1	XP_017211004.1	XP_042201407.1						
XP_002161268.1		PIP5K2A	NP_005019.2	NP_032871.3	NP_001179698.1	XP_001367748.3	XP_028933571.1	NP_001026142.2	XP_018124586.1	NP_001122174.1	XP_007909100.1	XP_002119441.3	XP_003383716.3	XP_001745617.1			
XP_002161255.1		SLC37A3	NP_996996.1	NP_001348546.1	NP_001068752.1	XP_001367985.1	XP_028931119.1	NP_001012556.2	NP_001082192.1	XP_005174644.1	XP_042191833.1	XP_002119376.3	XP_019852978.1				
XP_002161203.1		MAP3K2	NP_006600.3	NP_036076.2	XP_002685278.2	XP_007482614.1	XP_028931406.1	XP_040509185.1	XP_041432122.1	XP_688694.2	XP_007905525.1	XP_009859795.2	XP_019861315.1	XP_001742951.1	XP_001698436.2	NP_595714.2	CAI5313658.1

Hydra	**Updated ACC**	**Human Gene symbols**	***Homo sapiens***	***Mus musculus***	***Bos taurus***	***Monodelphis domestica***	***Ornithorhynchus anatinus***	***Gallus gallus***	***Xenopus laevis***	***Danio rerio***	***Callorhinchus milii***	***Ciona intestinalis***	***Amphimedon queenslandica***	***Monosiga brevicollis***	***Chlamydomonas reinhardtii***	***Schizosaccharomyces pombe***	***Saccharomyces cerevisiae***
XP_002161107.1		SLC22A15	NP_060890.2	NP_001034460.2	XP_002690418.1	XP_001381481.2	XP_028903584.1	XP_040523877.1	XP_041418173.1	NP_998315.1	XP_007887876.2	XP_004225963.2	XP_019850717.1	XP_001747900.1	XP_042922862.1	NP_593320.1	CAI7235084.1
XP_002161070.1		TTN	NP_596869.4	XP_036016420.1	DAA32835.1	XP_056650054.1	XP_039768977.1	XP_046799681.1	XP_041432154.1	XP_021334746.1	XP_042192251.1	XP_026691544.1	XP_019849858.1	XP_001750784.1	XP_001698569.2	NP_593464.1	CAI7207653.1
XP_002160959.1	XP_047122855.1	ZNF7	NP_001269724.1	NP_001403096.1	XP_010813714.3	XP_056682286.1	XP_028904944.1	XP_040509774.1	XP_041422762.1	XP_021331333.1	XP_007908714.1	XP_026694697.1	XP_019853365.1	XP_001745797.1	XP_042914403.1	NP_595717.1	GMC40873.1
XP_002160935.1		EVA1C	NP_478067.2	NP_001186139.1	XP_024844027.1	XP_001377554.1	XP_007662761.1	XP_040514210.2	XP_018104364.1	XP_009303778.2	XP_007904898.1	XP_018672065.1	XP_019862089.1	XP_001746549.1	XP_042927069.1	NP_592974.1	CAI6579439.1
XP_002160864.1		CUBN	NP_001072.2	NP_001035161.1	NP_001193829.1	XP_001377380.2	XP_028933098.1	XP_001235156.4	XP_041421805.1	XP_021326049.1	XP_042187752.1	XP_026695897.1					
XP_002160840.1		CYP4F12	NP_076433.3	XP_006523799.1	NP_001068790.1	XP_007489776.1	XP_028907030.1	NP_001316566.2	NP_001091388.1	NP_001083010.1	XP_042200639.1	XP_002124012.1	XP_019849740.1	XP_001747608.1	XP_001700492.1	NP_592966.1	MBE7182706.1
XP_002160774.1	XP_002160774.2	SLC23A2	NP_005107.4	XP_006506197.1	XP_024846929.1	XP_016281664.2	XP_028921224.1	XP_040518104.1	XP_018110651.1	XP_002663244.1	XP_007904441.1	XP_002126663.1	XP_019848770.1	XP_001743938.1			
XP_002160524.1		record removed															
XP_002160509.1	XP_012562501.2	Hydra-specific															
XP_002160403.1	XP_047137203.1	SLC35F6	NP_060347.2	NP_783606.2	NP_001077173.1	XP_001380284.1	XP_001520514.1	XP_040554023.1	XP_018121546.1	NP_001002559.1	XP_007891103.1	XP_026689904.1	XP_003387308.1	XP_001743312.1	XP_042916313.1	NP_592886.1	
XP_002160277.1		ASTL	NP_001002036.3	NP_001277932.1	XP_024855482.1	XP_056673745.1	XP_028928813.1	NP_001292019.2	NP_001088112.1	NP_998800.2	XP_042197358.1	XP_002120042.3	XP_019858826.1	XP_001743689.1	XP_001700076.2		
XP_002160024.1	XP_047134040.1	SPOUT1	NP_057474.2	NP_766248.3	XP_005213493.1	XP_007475167.1	XP_028919799.1	NP_001384023.1	NP_001084926.1	NP_001004627.1	XP_042193384.1	XP_002131245.1	XP_019853232.1	XP_001742973.1	XP_001699220.1	NP_595578.1	
XP_002159970.1	XP_002159970.2	MS4A12	NP_060186.2	NP_780357.1	XP_005212935.1	XP_001374596.1	XP_028927514.1	XP_015133525.1	XP_018118301.1	NP_571968.1	XP_042189624.1	XP_018669122.1	XP_011409566.1	XP_001748446.1	XP_001690848.2	NP_001342874.1	
XP_002159947.1		SF3B2	XP_016872633.1	NP_084385.2	XP_005227170.1	XP_056657286.1	XP_028915993.1		XP_018115445.1	NP_001098747.1		XP_002131663.1	XP_011402894.1	XP_001747256.1	XP_042918375.1	NP_594733.1	CAI4682685.1
XP_002159861.1		TRPA1	NP_015628.2	NP_808449.1	XP_015329969.1	XP_007487041.2	XP_028924250.1	NP_001305389.1	XP_018097008.1	XP_017213756.1	XP_007885526.1	XP_026693679.1	XP_011402710.1				
XP_002159853.1		NFIC	NP_005588.2	XP_030100800.1	XP_024850341.1	XP_056678366.1	XP_028908580.1	NP_001384236.1	XP_041435805.1	XP_009302191.1	XP_042198706.1	XP_018667578.1	XP_003382958.1				
XP_002159761.1	XP_047142710.1	TRPM3	NP_057738.1	NP_001030316.1	XP_024853324.1	XP_056666164.1	XP_028920811.1	XP_046755000.1	NP_001094397.1	NP_001070918.1	XP_007903760.1	XP_009858860.1	XP_019854631.1	XP_001742486.1	XP_042914991.1	NP_592981.1	CAI4356331.1
XP_002159671.1		RET	NP_001393672.1	NP_033076.2	NP_001178412.1	XP_007478546.3	XP_028917087.1	NP_990521.3	XP_018081021.2	NP_858048.2	XP_042192766.1	NP_001037820.1	XP_019857826.1	XP_001742753.1	XP_042915599.1		CAI4534287.1
XP_002159481.1	XP_047125070.1	Hydra-specific															
XP_002159421.1		Hydra-specific															
XP_002159385.1		Hydra-specific															
XP_002159265.1		SHQ1	NP_060600.2	NP_853621.2	XP_024838279.1	XP_007500156.1	XP_028907704.1	XP_040538116.1	NP_001124419.1	NP_001074069.2	XP_007893429.1	XP_002127366.1	XP_019853814.1	XP_001748444.1	XP_042916993.1	NP_596572.1	EDZ70112.1
XP_002159235.1		SHQ1	NP_060600.2	NP_853621.2	XP_024838279.1	XP_007500156.1	XP_028907704.1	XP_040538116.1	NP_001124419.1	NP_001074069.2	XP_007893429.1	XP_002127366.1	XP_019853814.1	XP_001748444.1	XP_042916993.1	NP_596572.1	EDZ70112.1
XP_002159205.1	XP_047144643.1	Hydra-specific															
XP_002159147.1		MRPL43	NP_115488.2	NP_444394.1	NP_776988.2	XP_007479225.2	XP_001512046.3	XP_015144248.4	NP_001079525.1	NP_001002428.1	XP_007910428.1	XP_009857917.1	XP_003389470.2	XP_003389470.2	XP_003389470.2	NP_595697.1	XP_003389470.2
XP_002159127.1		SLD5	NP_115712.1	NP_077202.1	NP_001075929.1	XP_007476453.1	XP_001510297.2	NP_001341793.1	XP_007907409.2	NP_001003546.2	NP_001084702.1	XP_002129349.1	XP_011409593.1	XP_001742971.1	XP_042920945.1	NP_596195.1	AJU70882.1

Hydra	**Updated ACC**	**Human Gene symbols**	***Homo sapiens***	***Mus musculus***	***Bos taurus***	***Monodelphis domestica***	***Ornithorhynchus anatinus***	***Gallus gallus***	***Xenopus laevis***	***Danio rerio***	***Callorhinchus milii***	***Ciona intestinalis***	***Amphimedon queenslandica***	***Monosiga brevicollis***	***Chlamydomonas reinhardtii***	***Schizosaccharomyces pombe***	***Saccharomyces cerevisiae***
XP_002158988.1	XP_047124347.1	Hydra-specific															
XP_002158969.1	XP_047131095.1	Hydra-specific															
XP_002158944.1		Hydra-specific															
XP_002158792.1	XP_002158792.3	CHCHD3	NP_060282.1	NP_079612.1	NP_001030552.1	XP_001367301.4	XP_007669227.1	XP_040515921.1	NP_001085505.1	XP_009298538.1	NP_001279945.1	XP_002124656.1	XP_019864488.1				
XP_002158704.1		Hydra-specific															
XP_002158701.1		MRC2	NP_006030.2	XP_006532469.1	NP_001179599.1	XP_007482601.2	XP_028931648.1	XP_015154875.1	XP_018093597.1	XP_021327061.1	XP_042199392.1	XP_002120905.3	XP_019854230.1				
XP_002158624.1	XP_047142730.1	RET	NP_001393672.1	NP_033076.2	NP_001178412.1	XP_007478546.3	XP_028917087.1	NP_990521.3	XP_018081021.2	NP_858048.2	XP_042192766.1	NP_001037820.1	XP_019857826.1	XP_001742753.1	XP_042915599.1		CAI4534287.1
XP_002158561.1		LRRC31	NP_079003.2	NP_001296162.1	XP_015328122.1	XP_007502304.2	XP_028915753.1	XP_040535539.1	XP_018119203.1	XP_009295766.1	XP_007910058.1	XP_009859277.1					
XP_002158546.1	XP_047123110.1	TTC28	NP_001138890.1	XP_006534909.1	XP_059732181.1	XP_056676904.1	XP_028904913.1	XP_046757110.1	XP_018116837.1	XP_017213483.1	XP_042193600.1	XP_026690437.1	XP_003387135.1	XP_001750733.1	XP_042918776.1	NP_596790.1	KAJ1534576
XP_002158450.1	XP_047130484.1	Hydra-specific															
XP_002158369.1	XP_047132235.1	RNF114	NP_061153.1	NP_001347859.1	NP_001019702.1	XP_001378899.1	XP_028926728.1	NP_001001767.3	NP_001088839.1	NP_001001828.2	XP_007909998.1						
XP_002158309.1		CENPV	NP_001138508.1	NP_084022.2	XP_005226618.1	XP_001369328.1	XP_028903192.1	XP_040523802.1	XP_018120753.1	NP_998519.1	XP_007903668.2	XP_002132051.1	XP_019853699.1	XP_001746771.1	XP_042920765.1	NP_001342717.1	CAI5210321.1
XP_002158290.1	XP_047142669.1	Hydra-specific															
XP_002158274.1		PCK2	NP_004554.3	NP_083270.2	NP_001192523.1	XP_056666076.1	XP_028933881.1	NP_990802.2	NP_001080152.1	NP_999916.1	XP_007882639.1	XP_002128953.1	XP_019855078.1				
XP_002158249.1	XP_047141658.1	TTC28	NP_001138890.1	XP_006534909.1	XP_059732181.1	XP_056676904.1	XP_028904913.1	XP_046757110.1	XP_018116837.1	XP_017213483.1	XP_042193600.1	XP_026690437.1	XP_003387135.1				
XP_002158239.1		TRAF1	NP_001177876.1	NP_001313530.1	XP_005210655.1	XP_007474623.2	XP_028918927.1	XP_046757781.1	XP_018084995.1	NP_001121853.1	XP_007900919.1	XP_002121961.1	XP_003383545.3				
XP_002158222.1	XP_047137337.1	LIM2	NP_001155220.1	NP_808361.1	NP_776527.1	XP_007491773.1	XP_028921455.1	XP_040508397.1	NP_001089381.1	NP_001013540.1	XP_007894235.1	XP_002125056.1	XP_011406357.1	XP_001750617.1	XP_001692095.1	NP_594531.1	
XP_002157995.1		UNC13D	NP_954712.1	XP_006534251.1	NP_001179012.2	XP_056673103.1	XP_028912672.1	XP_040542191.1	XP_041432586.1	XP_009305114.1	XP_042198522.1	XP_018669899.1	XP_019853517.1	XP_001743696.1	XP_042914711.1	NP_593894.1	AJS02959.1
XP_002157942.1		RET	NP_001393672.1	NP_033076.2	NP_001178412.1	XP_007478546.3	XP_028917087.1	NP_990521.3	XP_018081021.2	NP_858048.2	XP_042192766.1	NP_001037820.1	XP_019857826.1	XP_001742753.1	XP_042915599.1		CAI4534287.1
XP_002157743.1		THBS3	NP_001394488.1	XP_006501358.1	NP_001095309.1	XP_056672277.1	XP_028911920.1	XP_040511385.1	NP_001081597.1	NP_775333.1	XP_007890281.1	XP_026690556.1	XP_019856517.1	XP_001748060.1	XP_042921473.1	NP_588370.1	CAI4636995.1
XP_002157729.1		ANK3	NP_001140.2	XP_006513202.1	XP_024842398.1	XP_056651836.1	XP_028915482.1	XP_040558234.1	XP_041426139.1	XP_021335920.1	XP_007895304.2	XP_026693225.1	XP_019851861.1	XP_001742781.1	XP_042924645.1	NP_593787.1	AJT31173.1
XP_002157611.1	XP_002157611.4	CA5A	NP_940986.1	NP_444300.1	NP_001179451.1	XP_001364411.1	XP_028913222.1	XP_040537246.1	XP_018095960.1	NP_957107.1	XP_007906064.1	XP_002121562.1	XP_003383417.1				
XP_002157583.1		ZMYM1	NP_001276020.1	XP_030109595.1	XP_010801949.2												
XP_002157458.1	XP_047129144.1	Hydra-specific															
XP_002157377.1		MED4	NP_054885.1	NP_080395.1	NP_001029658.1	XP_007495490.1	XP_007666798.1	XP_004938759.1	XP_018102832.1	NP_001017883.1	XP_042190213.1	XP_002127402.1	XP_019850452.1				
XP_002157350.1		Hydra-specific															

Hydra	**Updated ACC**	**Human Gene symbols**	***Homo sapiens***	***Mus musculus***	***Bos taurus***	***Monodelphis domestica***	***Ornithorhynchus anatinus***	***Gallus gallus***	***Xenopus laevis***	***Danio rerio***	***Callorhinchus milii***	***Ciona intestinalis***	***Amphimedon queenslandica***	***Monosiga brevicollis***	***Chlamydomonas reinhardtii***	***Schizosaccharomyces pombe***	***Saccharomyces cerevisiae***
XP_002156996.1		TRAF3	NP_004286.2	NP_033449.2	NP_001094750.1	XP_001368795.1	XP_028937555.1	XP_015151572.3	NP_001087501.1	NP_991325.1	XP_042194667.1	NP_001123338.1	XP_011407462.1	XP_001746838.1			
XP_002156982.1		MPHOSPH10	NP_005782.1	NP_080759.2	NP_001039782.1	XP_001373719.1	XP_028922285.1	XP_015134483.1	XP_018108490.1	NP_001292472.1	XP_007907069.2	XP_002129730.1	XP_011408404.1	XP_001749930.1	XP_042922026.1	NP_593634.1	CAI4559208.1
XP_002156802.1		ABHD5	NP_001352579.1	NP_080455.1	NP_001029540.1	XP_007479852.1	XP_007662257.1	NP_001265074.1	XP_041421963.1	XP_003200181.1	XP_007899088.2	XP_009858632.1	XP_019850698.1	XP_001750136.1	XP_042927988.1	NP_594100.1	
XP_002156769.1	XP_047142841.1	Hydra-specific															
XP_002156748.1		CHN1	NP_001020372.2	NP_001157112.1	XP_005205546.1	XP_007505324.1	XP_001511818.3	XP_040518795.1	XP_041421365.1	XP_699642.6	XP_042187792.1	XP_018671064.1	XP_003385452.1	XP_001745469.1	XP_042916082.1	NP_001342904.1	CAD6639786.1
XP_002156708.1		RAB2	NP_001020471.3	NP_077768.3	NP_001095762.1	XP_001364776.2	XP_028922049.2	XP_003640848.2	XP_018123391.1	NP_001018466.1	XP_007895447.1	XP_002129883.1	XP_003388590.1	XP_001750494.1	XP_001703135.1	NP_594580.1	AJV24896.1
XP_002156669.1	XP_012559207.1	GGH	NP_003869.1	NP_034411.2	NP_001098864.1	XP_007487124.1	XP_028925103.1	XP_419226.5	NP_001086160.1	NP_998487.1	XP_007894923.1		XP_019857008.1	XP_001749715.1	XP_042923704.1	NP_593055.1	AJR71689.1
XP_002156630.1		FBN3	NP_115823.3	NP_032019.2	XP_024850699.1	XP_056678553.1	XP_039766246.1	XP_046778654.1	XP_018113654.1	XP_021335394.1	XP_007885423.1	XP_018668293.1	XP_011410208.2	XP_001748001.1	XP_042928002.1	NP_001343037.1	
XP_002156619.1		DDX4	NP_001160006.1	NP_034159.1	XP_024836997.1	XP_007486389.1	XP_028915696.1	NP_990039.2	NP_001081728.1	XP_005156510.1	XP_042191191.1	NP_001027593.1	XP_019854879.1	XP_001747837.1	XP_042919977.1	NP_588033.1	CAI4914070.1
XP_002156475.1		ADAM33	NP_079496.1	NP_001009547.1	XP_024851813.1	XP_007496940.1	XP_028919837.1	NP_001075887.2	NP_001080914.1	XP_005172418.1	XP_042195894.1	XP_002129509.1	XP_019849967.1	XP_001750336.1	XP_042915598.1	NP_593472.1	CAI7368654.1
XP_002156427.1		record removed															
XP_002156299.1	XP_002156326.3	Hydra-specific															
XP_002156189.1		Hydra-specific															
XP_002156064.1		MAP3K3	NP_002392.2	NP_036077.1	XP_002685278.2	XP_007482614.1	XP_028931406.1	XP_040509185.1	XP_041432122.1	XP_688694.2	XP_007905525.1	XP_009859795.2	XP_019861315.1	XP_001742951.1	XP_001698436.2	NP_595714.2	AJV60758.1
XP_002155516.1	XP_047122517.1	BMP1	NP_001190.1	NP_033416.2	XP_024852019.1	XP_056669663.1	XP_028921619.1	NP_990034.2	XP_018097190.1	NP_571085.1	XP_007889657.1	NP_001071840.1	XP_019855870.1	XP_001748060.1	XP_042921473.1		
XP_002155387.1	XP_002155387.3	DNPEP	NP_036232.2	NP_001407066.1	XP_005202875.1	XP_056663515.1	XP_028920162.1	NP_001012937.2	NP_001085525.1	XP_005165919.1	NP_001279935.1	XP_002129082.1	XP_019853573.1	XP_001745410.1	XP_042920107.1	NP_594745.1	CAD6627882.1
XP_002155109.1		PLAC8	NP_001124187.1	NP_001357683.1	NP_001070455.1	XP_007495824.1	XP_028930139.2	NP_001376326.1	XP_018081798.1	NP_001077342.2	NP_001279359.1	XP_002127381.1	XP_011402808.1	XP_001744550.1	XP_042918251.1	NP_594886.1	AJW02937.1
XP_002154953.1		JRKL	NP_001248762.1	NP_001028353.1	XP_005215350.1	XP_001367318.2	XP_028933413.1	XP_046768399.1	XP_018123813.1		XP_007892178.2		XP_003391456.1	XP_001745610.1			
XP_002154875.1	XP_047127038.1	Hydra-specific															
XP_002154840.1		INTU	NP_056508.2	XP_017175117.1	NP_001192784.1	XP_056659492.1	XP_028923065.1	XP_015132122.2	NP_001089157.1	NP_001340861.1	XP_007908873.1	XP_009862305.1	XP_019860192.1				
XP_002154819.1	XP_012558459.2	TRPM6	NP_060132.3	XP_006527014.1	XP_024851944.2	XP_007498606.2	XP_028911358.1	XP_046761456.1	XP_018114314.1	NP_001238760.1	XP_007897564.2	XP_018667443.1	XP_011409120.1	XP_001749743.1			
XP_002154489.1	XP_002154489.2	SLC36A2	NP_861441.2	NP_694779.3	NP_001179427.1	XP_007473970.1	XP_028906593.1	XP_004944995.1	XP_018110349.1	XP_021336836.1	XP_042195859.1	XP_009857644.1	XP_019852314.1	XP_001744195.1	XP_001703505.1	NP_593551.1	CAI4575602.1
XP_002154479.1	XP_047123091.1	CACNA1B	NP_001123304.1	XP_006505499.1	XP_024848524.1	XP_056656727.1	XP_028910254.1	XP_015142055.1	XP_041441869.1	XP_021330582.1	XP_042191356.1	XP_026689962.1	XP_019855146.1	XP_001743090.1	XP_042915693.1	NP_593894.1	PTN21583.1
XP_002154361.1		FGFR3	NP_075254.1	NP_001345966.1	NP_776743.1	XP_056658276.1	XP_028918923.1	XP_015141368.1	XP_041439240.1	NP_571681.2	XP_042199148.1	NP_001037820.1	XP_019863322.1	XP_001749064.1	XP_042915598.1	NP_001018849.1	CAI4794309.1
XP_002153998.1	XP_002153998.2	PUS3	NP_112597.4	NP_075781.3	NP_001029684.1	XP_007495143.2	XP_007661144.2	XP_004948004.1	XP_018089389.1	NP_956361.1	XP_042202439.1	XP_002130657.1	XP_019854104.1	XP_001750305.1	XP_042926965.1	NP_594465.1	CAD6622921.1
XP_002153922.1	XP_047124620.1	Hydra-specific															

Hydra	**Updated ACC**	**Human Gene symbols**	***Homo sapiens***	***Mus musculus***	***Bos taurus***	***Monodelphis domestica***	***Ornithorhynchus anatinus***	***Gallus gallus***	***Xenopus laevis***	***Danio rerio***	***Callorhinchus milii***	***Ciona intestinalis***	***Amphimedon queenslandica***	***Monosiga brevicollis***	***Chlamydomonas reinhardtii***	***Schizosaccharomyces pombe***	***Saccharomyces cerevisiae***
XP_001641891.1	XP_047125269.1	TBC1D9	NP_942568.2	NP_001104774.1	XP_024833342.1	XP_016278689.2	XP_028932327.1	XP_004941005.1	XP_018087129.1	XP_692034.2	XP_042195119.1	XP_009857558.1	XP_019848868.1	XP_001748214.1	XP_001698588.1	NP_596678.2	AJR93020.1
XP_001641393.1	XP_004209651.2	NOTCH2NLC	NP_001350941.1	NP_035058.2	XP_024845771.1	XP_007485364.1	XP_028937380.1	NP_001238962.2	XP_018114267.1	NP_001108566.2	XP_042190840.1	NP_001037825.1	XP_019853114.1	XP_001748060.1	XP_042921473.1	NP_594069.2	EDZ69831.1
XP_001640653.1		Hydra-specific															
XP_001635064.1	XP_002167006.2	RTRAF	NP_057123.1	NP_080804.1	NP_001030357.1	XP_001362101.1	XP_001514963.1	NP_001384250.1	NP_001088113.1	NP_956564.2	XP_007886364.1	XP_004226325.1					
XP_001632616.1	XP_047129784.1	AFG3L2	NP_006787.2	NP_081406.1	NP_001039676.1	XP_001371403.2	XP_028921437.1	XP_040520764.1	XP_018123360.1	NP_001104667.1	XP_042187994.1	XP_002132138.1	XP_003383809.1	XP_001744500.1	XP_042928366.1	NP_596797.1	EGA77558.1
XP_001625620.1	XP_047145960.1	Hydra-specific															
XP_001623866.1		POLR3K	NP_057394.3	NP_080177.1	DAA15753.1	XP_001364724.1	XP_028904515.1	NP_001377779.1	NP_001083658.1	NP_001002553.1	XP_042197131.1	NP_001037832.1	XP_003384810.1	XP_001744784.1	XP_001699794.1	NP_593235.1	MDC6270666.1
BAD67147.1		OPN5	NP_859528.1	NP_034228.1	NP_001193009.1	XP_007484118.2	XP_028928374.1	XP_040553243.1	XP_018120306.1	NP_001186975.1	XP_007901513.1	NP_001027727.1	XP_011402721.1	NP_696986.1	XP_001699266.1	NP_587829.1	CAI5318966.1
BAD67145.1		RRH	NP_006574.1	AAI05647.1	NP_001179153.1	XP_056659063.1	XP_001506416.1	XP_046772533.1	XP_041435529.1	NP_001004654.1	XP_007895211.1	NP_001027727.1	XP_019850789.1	XP_001745932.1	XP_042924512.1	NP_587901.1	CAI7034013.1
ADU79234.1		NLRP7	NP_631915.2	XP_006522213.1	XP_002683779.2	XP_007492316.1	XP_028917427.1	XP_040556738.1	XP_041429599.1	XP_017209832.1	XP_042201642.1	XP_018668540.1	XP_019852853.1	XP_001746606.1	XP_001695420.1	NP_595792.1	AJV75478.1
ACF20993.1		Hydra-specific															
AAC28629.1		ZAP70	NP_001070.2	NP_001276694.1	NP_001179946.1	XP_007489513.1	NP_001308485.1	XP_028912388.1	XP_018099124.1	NP_001018425.1	XP_007899176.1	XP_002123000.1	XP_003385896.1	XP_033820571.1	XP_042928285.1		
AAA29221.1		RET	NP_001393672.1	NP_033076.2	NP_001178412.1	XP_007478546.3	XP_028917087.1	NP_990521.3	XP_018081021.2	NP_858048.2	XP_042192766.1	NP_001037820.1	XP_019857826.1	XP_001742753.1	XP_042915599.1		CAI4534287.1
AAA29218.2		RET	NP_001393672.1	NP_033076.2	NP_001178412.1	XP_007478546.3	XP_028917087.1	NP_990521.3	XP_018081021.2	NP_858048.2	XP_042192766.1	NP_001037820.1	XP_019857826.1	XP_001742753.1	XP_042915599.1		CAI4534287.1