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Comparative genomic and phylogenetic analysis of vitellogenin and other large lipid transfer proteins in metazoans

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ABSTRACT

Vitellogenins and other large lipid transfer proteins (LLTP) are well known to play significant roles in the development, metabolism and reproduction of animals. Comparative genomics and phylogenetic analyses of LLTPs using the most comprehensive dataset in metazoans to date are carried out. Our analyses demonstrate that LLTP genes arose significantly earlier, and are more widespread than previously proposed – being present in numerous additional bilaterian and non-bilaterian lineages. A hypothesis is advanced that the most ancestral animal LLTP gene is Vtg, while loss of domains occurred at the bilaterians stem giving rise to apolipoprotein and microsomal triglyceride transfer proteins genes.

1. Introduction

Lipoproteins are crucial components of a wide range of biological processes in animals, from basic cellular structural support to enzymatic and transportation reactions. Some lipoproteins are processed by large lipid transfer proteins (LLTP), which include vitellogenin (Vtg), the cytosolic large subunit of microsomal triglyceride transfer protein (MTP) and apolipoproteins (Apo). Apolipoproteins can be further subdivided into vertebrate apolipoprotein B (ApoB), crustacean apolipocrustacein (ApoCr), and insect apolipophorin II/I precursor (ApoLp-II/I) [1,2].

Over recent decades, extensive effort has gone into identifying the underlying mechanism of LLTP processing in animals (mainly from the phyla Arthropoda and Vertebrata). Today, the primary functions of these LLTPs are relatively well known. For example, ApoB is the primary apolipoprotein responsible for transporting cholesterol to tissues in humans, and high levels of ApoB are related to cardiovascular diseases. MTP is known to be crucial in the processing of lipoprotein, and mutations in MTP cause abetalipoproteinemia in humans. Vtg (Gr: *vitello* = yolk and *gener* = creation) is the most extensively characterized lipoprotein, and plays a central role in vitellogenesis for bilaterians, including arthropods, nematodes and vertebrates [3–5].

Given the relatively high amino acid sequence similarity found among LLTP proteins, surprisingly few studies have investigated their relationships across animal phyla. In addition, most previous studies have assigned cloned gene fragments to particular LLTP gene families on the basis of sequence similarity rather than via phylogenetic analysis. Subsequently, a "chain-reaction" problem in nomenclature arose when a misclassification occurred in a given study. This was recently demonstrated during a study in which phylogenetic trees were constructed using LLTP genes mainly from arthropods and vertebrates, resulting in the long studied "Vtg" gene in crustaceans being re-classified as an apolipoprotein (ApoCr), and the orthologue of insect ApoLp-II/I and vertebrate ApoB [1].

To date, only one LLTP gene has so far been reported in non-bilaterians [10], which hinders the understanding of the LLTP

Abbreviations: Vtg, vitellogenins; LLTP, large lipid transfer proteins; ApoB, apolipoprotein B; ApoLp-II/I, apolipophorin II/I precursor; ApoCr, apolipocrustacein; MTP, microsomal triglyceride transfer protein

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family relationships in animals. With the increasing numbers of animal genomes other than vertebrates and insects are becoming available (e.g. [6–9]), it is pertinent to compare the LLTP genes across diverse animal phyla, with the aim of reconstructing an accurate evolutionary history. Here, we have performed the most comprehensive comparative genomic analyses of the LLTP genes in metazoans to date, which lay the framework for further research into the evolution of functions of LLTP genes. Moreover, we propose the first evolutionary model to explain how LLTP genes potentially arose in animals.

2. Materials and methods

2.1. Sequence retrieval

LLTP sequences were obtained in public databases (NCBI and JGI). A dataset consisting of 94 LLTP sequences was assembled for analysis. To avoid confusion arising from different gene nomenclature, we have chosen to follow the terms classified in [1]. Methods, gene names and accession numbers obtained from NCBI and JGI databases are summarized in Supplementary data 7.

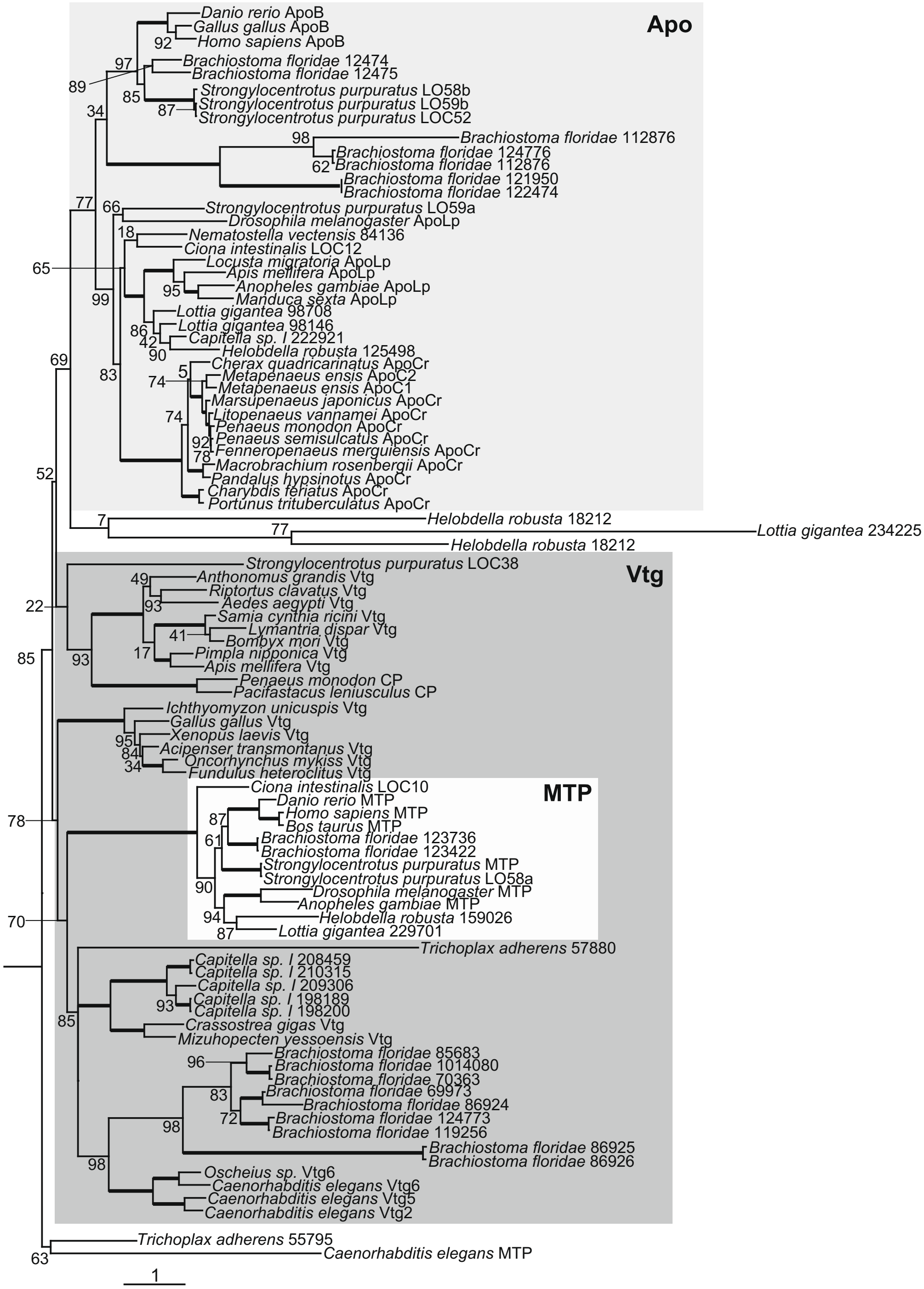

Fig. 1. Phylogenetic tree using Maximum-Likelihood method showing the relationships of LLTP genes.