



The core transcriptome of mammalian placentas and the divergence of expression with placental shape



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ABSTRACT

Introduction: The placenta is arguably the most anatomically variable organ in mammals even though its primary function is conserved.

Method: Using RNA-Seq, we measured the expression profiles of 55 term placentas of 14 species of mammals representing all major eutherian superordinal clades and marsupials, and compared the evolution of expression across clades.

Results: We identified a set of 115 core genes which is expressed (FPKM ≥ 10) in all eutherian placentas, including genes with immune-modulating properties (*ANXA2*, *ANXA1*, *S100A11*, *S100A10*, and *LGALS1*), cell-cell interactions (*LAMC1*, *LUM*, and *LGALS1*), invasion (*GRB2* and *RALB*) and syncytialization (*ANXA5* and *ANXA1*). We also identified multiple pre-eclampsia associated genes which are differentially expressed in *Homo sapiens* when compared to the other 13 species. Multiple genes are significantly associated with placenta morphology, including *EREG* and *WNT5A* which are both associated with placental shape.

Discussion: 115 genes are important for the core functions of the placenta in all eutherian species analyzed. The molecular functions and pathways enriched in the core placenta align with the evolutionarily conserved functionality of the placenta.

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1. Introduction

Even though the placenta's primary function is conserved among mammals, the placenta varies widely in terms of shape, degree of intimacy between fetal tissues and maternal tissues, and degree of interdigitation of maternal and fetal tissues in different species of mammals [1] (Supplemental Table S1). Mammals also differ drastically in the number and size of their offspring, as well as the length of gestation; these traits are often associated with specific aspects of placental morphology [2] (Supplemental Table S2). Although the morphology of the mammalian placenta has been well characterized in a number of species [1], the diversity of the molecular environment is only beginning to be understood from a genetic perspective [3].

These observations lead to two related questions: 1) what are the genes which are responsible for the **core functions of the placenta** and 2) which genes are associated with **changes in placenta morphology**?

Previous studies of some species (i.e., *Homo sapiens*, *Mus musculus*, *Bos taurus*, and *Loxodonta africana*) have provided some preliminary answers to these questions. They revealed a stunning divergence in the genetics of the placenta, especially in later stages of pregnancy [3–6]. For example, each superorder (Euarchontoglires, Laurasiatheria, Afrotheria, and Xenarthra, Fig. 1) has evolved expansive placenta-specific gene families with expression patterns that can vary in space and time [7]. These include independent expansions of the prolactins in *Mus musculus*, *Spalax carmeli*, *Spalax galili*, and *Bos taurus*, Pregnancy-Specific Glycoproteins in *Homo sapiens* and *Mus musculus*, Pregnancy-Associated Glycoproteins in *Bos taurus*, genes related to the thymus-specific serine protease *PRSS16* (protease, serine 16) in *Loxodonta africana*, and the expansion of the growth hormone and chorionic gonadotropin beta gene families in anthropoid primates [8,9]. Expression patterns of specific genes can also vary widely between species. For example, the expression of orthologous genes in the placenta have been found to vary substantially between *Homo sapiens* and *Mus musculus* [5].

To address our questions we sequenced and quantified the total RNA of mammalian placentas at term, including *Pan paniscus*

[bonobo], (the sister species to *Pan troglodytes*), *Ateles fusciceps* [spider monkey], *Mus musculus* [mouse], *Spalax galili* [blind mole rat from Upper Galilee], *Spalax carmeli* [blind mole rat from northern Israel], *Canis familiaris* [domestic dog], *Bos taurus* [domestic cow], *Loxodonta africana* [African savanna elephant], *Dasyurus novemcinctus* [nine-banded armadillo], and *Monodelphis domestica* [gray short-tailed opossum]. These species represent four major branches of eutherian mammals (Euarchontoglires, Laurasiatheria, Afrotheria, and Xenarthra) as well as marsupials (Fig. 1). These placentas also represent a wide array of placental morphologies as well as traits such as number and size of offspring and length of gestation (Supplemental Table S2). We use these data, along with existing RNA-Seq data from *Mus musculus* [10], *Homo sapiens* [11], *Equus caballus* [horse] [12], *Ovis aries* [sheep] [13], and *Sus scrofa* [domestic pig] [14] to: 1) identify the non-housekeeping genes which are expressed in the placentas of all eutherian species analyzed and therefore represent the **core functionality of the placenta**; 2) identify genes whose expression level changes significantly in each of the placenta morphology types.

2. Methods

2.1. Collection of placental tissue and RNA extraction

Fetal tissue was collected from the placenta of eight mammalian species (*Pan paniscus* [bonobo], *Ateles fusciceps* [spider monkey], *Canis familiaris* [domestic dog], *Bos taurus* [domestic cow], *Loxodonta africana* [African savanna elephant], *Monodelphis domestica* [gray short-tailed opossum], *Spalax galili* [blind mole rat from Upper Galilee], *Spalax carmeli* [blind mole rat from northern Israel] [15]; n = 1 for all collected species). Information on specimen ID, number of specimens, and collector is shown for each sample in Supplemental Table S3. In the case of *Pan paniscus*, *Bos taurus*, and *Loxodonta africana*, the placenta was collected at term upon expulsion from the mother following delivery. Near-term placental tissue from *Canis familiaris* was collected upon the death of the mother and fetus from a car accident. Placental tissue from *Monodelphis domestica* was sampled at fetal stage 32, roughly one day

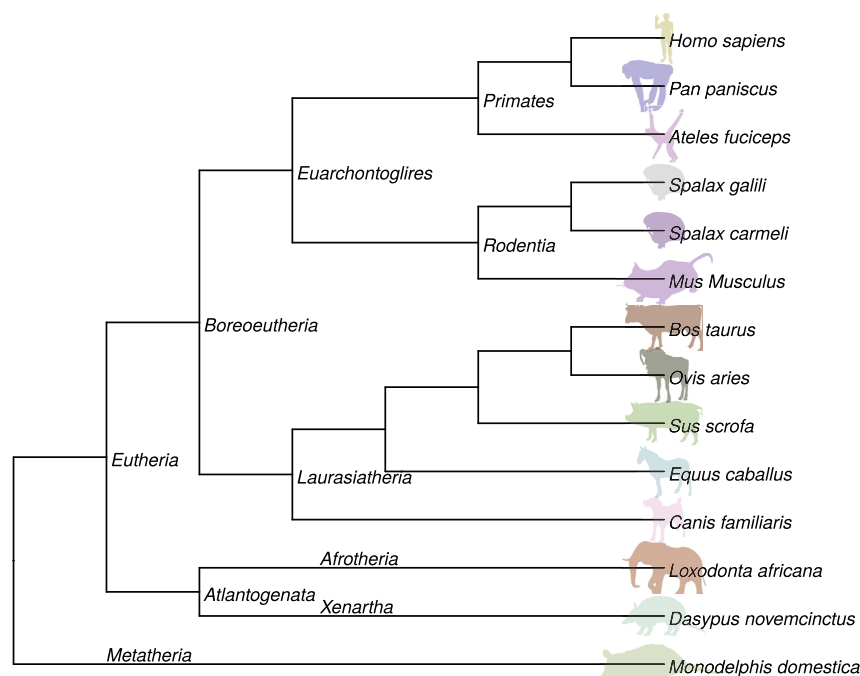


Fig. 1. Species tree for organisms studied showing the relationship between species. Branch lengths are not to scale. Silhouettes of species were obtained from <http://phylopic.org>.

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