

THE AMAZING PLACENTA: EVOLUTION AND LIFELINE TO HUMANNESS

by Graeme Finlay 

Abstract. The placenta arose during mammalian evolution, which is recent in evolutionary terms. Genetic changes underlying placental development remain identifiable by the new science of comparative genomics (approximately post-2000). Randomly arising features of genomes including endogenous retroviruses and transposable elements have provided structural genes and gene-regulatory motifs responsible for innovations in placental biology. Stochastic genetic events indeed contribute to new functionality. Theologically, random mutations are part of the strategy by which the divine purpose for humanity is attained. Placental function critically underlies human brain development, and suboptimal function, associated with environmental conditions and maternal distress, contributes to mental health deficits in the offspring. Many enter life with handicaps arising from contingent events *in utero*, mandating understanding, compassion, and socioemotional support, imperatives native to moral including biblical values. The extended period of development afforded by placenta enables prenatal parenting, with implications for sensitive and devoted parental commitment.

Keywords: evolution; mutations; neurodevelopment; placenta; prenatal parenting; providence; purpose

People may raise various objections to theological interpretations of evolution. In older evolutionary models, it was axiomatic that most mutations were disruptive, and it was hard to see how they might contribute to new functionality. Only a vanishingly small number might increase the fitness of living creatures, but there was almost infinitely much time, so evolution was able to blindly proceed, staggering from chance to chance—or so it was thought. Phylogenetic novelty arises from mutations; and from a theological perspective, the apparent genuine randomness of the genetic processes involved has been difficult to reconcile with divine intentionality. New models of evolution, however, raise all sorts of new and interesting

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questions for theology, while considerably softening the difficulties associated with random mutation. Viruses have often been seen as just a problem, a threat, coming from the liminal world at the edge of life. They are now known to be crucial to life on Earth, appearing sometimes still as threat and intrusion and at other times eventually adding usable content to DNA, and hence new functionality to the phenotype. What does this mean, theologically? How can this liminal stuff be a part of what generates all animal species, but humans in particular? What does this mean about our status as unique and image-bearing creatures? Finally, placental contributions to the uniquely developed human social brain call for ethical reflection.

The placenta and the mammary gland are required to sustain human life (Guernsey et al. 2017). The placenta manifests a diversity of morphologies, depending on taxonomic grouping (Chavatte-Palmer and Tarrade 2016), but despite this variety, there is a uniformity among mammalian species in the way it performs multiple essential functions to support fetal development *in utero*. The placenta provides nutrition. It offers protection from pathogens, from toxins (by excluding or metabolizing them), and from maternal immunity. It secretes hormones. And, it sequesters the fetus within the body of the mother, providing the capacity for early neural development, learning, and bonding or relationship (Soares et al. 2018).

The history of the placenta is recent in evolutionary terms, giving credence to the expectation that discrete genetic events underpinning placental evolution will be discernible in mammalian genomes. Genetic novelties may be identified by aligning and comparing the genomic texts of multiple species. Comparative genomics has indeed established that what appears to be random additions to the genome have contributed repeatedly to functions that are specific to the placenta. In particular, parasitic units of genetic material, that replicate semiautonomously within host cell genomes, and that are *often* disruptive, have nevertheless also made enormous contributions to the evolution of placental form and function.

This essay is based on Christian presuppositions. It was undertaken in order to illustrate how mutations (1) establish human evolutionary descent from primate precursors and (2) reconfigure genomes so as to generate complex new functionality. Both of these concepts remain disputed widely in the general population. Retroviruses and transposable elements (TEs) are genome-disrupting agents that have contributed to the evolutionary development of the placenta, and so provide illuminating demonstration of evolutionary descent and the generation of innovation. Having established these scientific findings, pressing questions may present themselves to people with theological interests. These include the issues of how random genetic processes might serve divine action, how the pathogenic potential of such process may be reconciled with divine goodness, and how such molecular genetic processes connect with human relationality.

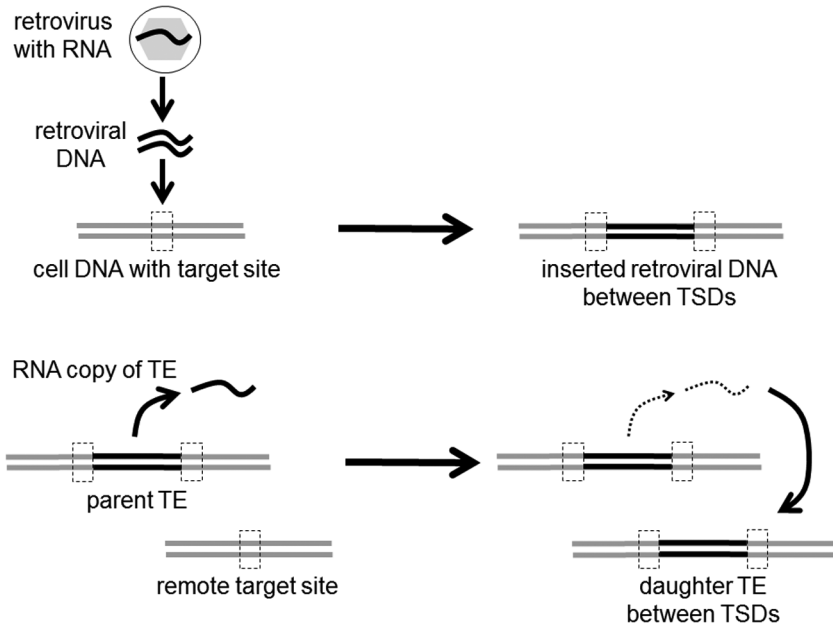


Figure 1. How retroviruses and TEs colonize genomes.

Note. The upper scheme depicts how an invading retrovirus copies its genetic material from RNA to double-stranded DNA, and then selects (largely at random) a target site in the genome of the host cell into which the viral DNA is inserted. During the insertion event, the target site is duplicated, so as to bracket the viral sequence with target-site duplications. The lower scheme depicts how TEs replicate by a copy-and-paste mechanism within cells. A parent TE is transcribed into an RNA copy that is copied into DNA and inserted at a target site, selected largely at random. The daughter TE is bracketed by target site duplications.

PART I

Retroviruses and TEs

Two broad classes of such genetic parasites are retroviruses and TEs (or, colloquially, jumping genes). The classification of these genetic parasites is complex, but they share the feature of replicating in genomes, and so expand genome content. The genetic material accreted from retroviral and TE activities comprises at *least half* of the human genome. When retroviruses infect cells, they insert their genetic material into that of the host cells at a site in the DNA that is selected largely at random (the target site) (Figure 1, upper scheme). TEs, on the other hand, exist only inside cells and those germane to this discussion replicate by a copy-and-paste process (Figure 1, lower scheme). The multistep insertion events are catalyzed by retroviral- and TE-specified enzymes, which generate small duplications of the target site at each end of the inserted unit of DNA

(Engelman and Cherepanov 2017). If retroviral infection or TE replication occurs in germ cells, the inserted segments of DNA are transmissible to future generations. Inherited segments of retroviral DNA are called *endogenous retroviruses* (ERVs). Thus, evolution occurs partially by the inclusion of certain “foreign” retroviral elements and TEs, which become adopted and co-opted by the host organism, and partly by the duplication or transposition of existing genetic material.

Retroviral Contributions to Placental Evolution

The genes present in ERVs usually decay with time after insertion into their host genomes. But contrary to past and commonsense expectation, a few ERV genes have retained their integrity over large expanses of primate history; and several of these strikingly durable genes have been assimilated into the functioning of the placenta. That means that without these unscheduled and potentially disruptive processes, humans would not have their distinguishing organ of reproduction, the placenta, in its current form.

But precisely, how have ERVs made their contributions to placental biology? Retroviruses possess *envelope* (*env*) genes, the products of which enable virus particles to stick to cells during the infection process. But in the case of the unique *ERVW-1* insert, the *env* gene has been domesticated (*or co-opted*) to specify a protein that serves human reproduction. The modified *env* protein enables cells called cytotrophoblasts to stick together and fuse into a layer, the syncytiotrophoblast, which forms the critically important interface between fetal and maternal placental tissues. The repurposed *env* protein has been renamed syncytin-1. The *ERVW-1* insertion site, with its trademark target site duplications, is depicted for hominoid primate species in Figure 2. The insertion event occurred in an ancestor of Old World monkeys and apes, but the ERV decayed in the Old World monkey group (such that only fragments remain), and was preserved and retained functionality in apes, including humans. New World monkeys retain the undisturbed target site (Bonnaud et al. 2005).

But can a randomly inserted viral gene be regulated so as to conform to the demands of a complex, dynamically changing organ? The regulation of the *ERVW-1/syncytin-1* gene is effected by DNA sequence motifs present in a more ancient ERV (called an *MLT1L* element) into which the *ERVW-1* inserted itself (Prudhomme et al. 2004). And, the activity of the syncytin-1 protein is balanced by a protein called suppressyn, which is a domesticated *env*-derived product of a third ERV—one that entered the primate germline in an Old World monkey-ape ancestor (Sugimoto et al. 2013). These findings demonstrate both that an essential gene (*syncytin-1*) has arisen in primates from the seemingly haphazard but fortuitous insertion of an ERV, and that regulatory functions that operate in both genetic (*MLT1L*) and

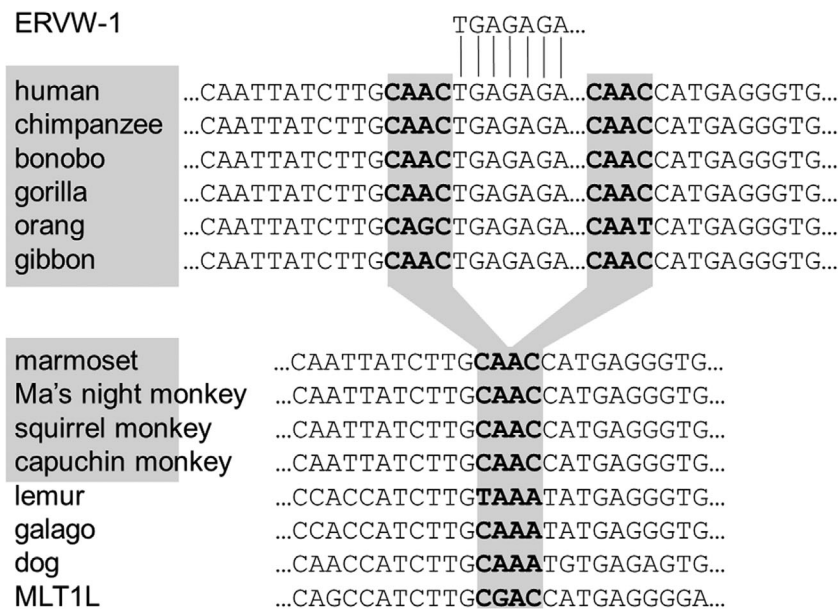


Figure 2. The insertion site of an ERV in the genomes of hominoid primates (apes).

Note. The unique *ERVW-1* present at this insertion site contains the envelope gene that now functions in placental development as the syncytin-1 gene. The preinsertion target site and the postinsertion TSDs are in bold type and shaded. Mammal sequences were obtained from Bonnaud et al. (2005) and the NCBI database by BLAST search (<https://www.ncbi.nlm.nih.gov/genome/>). The ERV-W type sequence (LTR17) was obtained from the Dfam database (<http://dfam.org/>). This ERV inserted into an older ERV (MLT1L), the type sequence of which was obtained from RepeatMasker (<http://www.repeatmasker.org/cgi-bin/WEBRepeatMasker>).

protein (suppressyn) networks arose from interactions with other ERVs that were added to primate genomes by the same stochastic (chance) processes (Figure 3).

The retroviral provenance of the syncytin-1 fusion-generating protein is not an isolated story. Yet another ERV-specified *env* gene has remained intact over vast periods of time, and now specifies a protein with cell-fusing functionality necessary for human development (Lu et al. 2017). The unique *ERVFRD-1* sequence was spliced into the genome of an anthropoid primate (simian) ancestor. This *env* gene has been transmogrified to encode what is now known as the syncytin-2 protein, which also induces cell fusion to form the syncytiotrophoblast. But syncytin-2 performs an additional role. It suppresses immune reactivity, and so may contribute to the marvel of immunological tolerance by which the mother's immune system does not destroy the fetus (which expresses paternal proteins) (Lokossou et al. 2020).

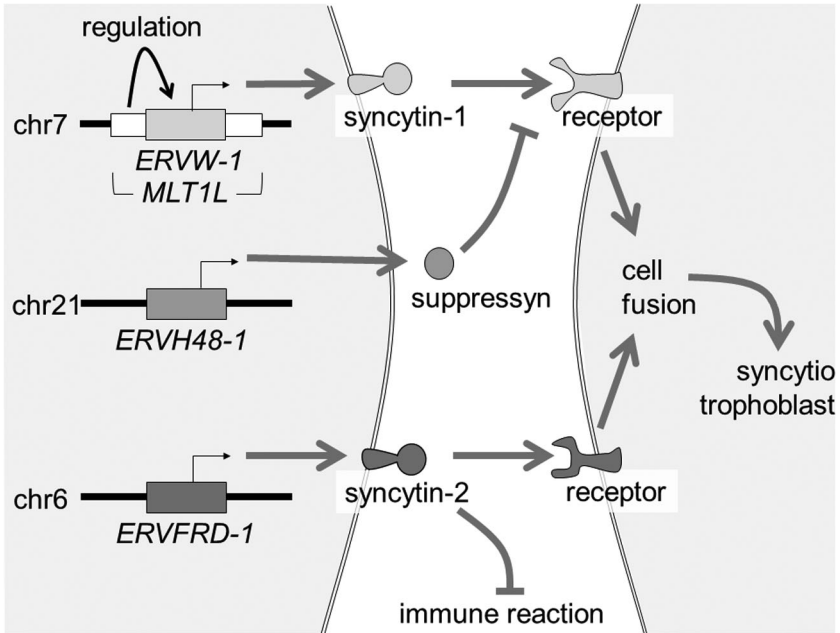


Figure 3. ERV-Derived sequences active in formation of the syncytiotrophoblast.

Note. Lightly shaded areas represent neighboring cells. In the left-hand cell, three genetic loci are represented: in chromosome (chr) 7, *ERVW-1*, embedded in an *MLT1L* element, encodes syncytin-1; in chr21, *ERV48H-1* encodes suppressyn; in chr6, *ERVFRD-1* encodes syncytin-2. Cells stick to each other when the syncytin proteins adhere to receptor proteins on neighboring cells, a process that is balanced by suppressyn.

We should pause here to reflect on the wonder of these random insertions into mammalian DNA. The molecular biological activities of ERVs have become integrated into, and mutually enhancing within, functional networks and have elaborated the fundamental reproductive strategies of many mammals. These events are a part of the architecture of evolvability, not only of what might be seen as peripheral phenotypic characteristics but also of novel and absolutely essential adaptations like the placenta.

But there is more. The incorporation of randomly acquired ERV sequences into regulatory networks is a recurring theme. The *INSL4* gene arose by a gene duplication event early in eutherian history, but it survives in an active form only in Old World primates. The *INSL4* gene is active only in the placenta, and specifies an insulin-related protein that may control life-and-death decisions in cells of the placenta. The gene is regulated by DNA sequence motifs located within a nearby ERV (Macaulay et al. 2011, 2017). This particular ERV was spliced into the primate germline in

an Old World monkey-ape ancestor, and thus dates from the same epoch as the ERVs that provided the antecedents of the syncytin-1 and suppressyn genes. The undisturbed target site is apparent in New World monkeys.

And, there is still more. Placental syncytiotrophoblast tissue of anthropoid primates (but not of other species) produces corticotropin-releasing hormone (CRH) in late pregnancy. Placental CRH contributes to the timing of parturition. Regulation of the *CRH* gene is controlled by sequences within an adjacent ERV that was spliced into the primate germline in an ancestor of anthropoid primates. Prosimians and nonprimates retain the undisturbed target site (Dunn-Fletcher et al. 2018). The left-hand junction between the ERV and flanking DNA provides a binding site for a protein, known as DLX3, that exerts control over *CRH* gene activity. A related ERV sequence, also dating from an anthropoid ancestor, may also partake in placenta-specific regulation of a signaling molecule (the IL-2 receptor β) (Cohen et al. 2011).

TE Contributions to Placental Evolution

TEs in various stages of decay also litter mammalian genomes. In remote mammalian history, two TEs of the *sushi-ichi* type each contributed a gene that, appropriately modified, was recruited into protein networks sustaining placental development. These genes are now known as *PEG10* and *PEG11*. The TE carrying the *PEG10* precursor sequence was spliced into the mammalian germline in an ancestor of marsupials and eutherian mammals. The PEG10 protein functions during the invasion of placental trophoblastic cells into the uterus (Chen et al. 2015). The TE carrying the *PEG11* precursor sequence was spliced into the genome of an ancestor of eutherian mammals. The PEG11 protein contributes to placental blood vessel development (Kitazawa et al. 2017).

Glycoprotein hormone-alpha (GPH α) is a subunit of the hormone chorionic gonadotropin (CG), which is secreted by the syncytiotrophoblast and has essential roles in reproduction, including placental development. GPH α exists in two forms. The larger form has an extra polypeptide chain, and possesses novel properties in the context of placental function. The extra polypeptide is encoded by a stretch of DNA sequence that is part of a TE (specifically of the Alu-J element subtype) that was inserted into the genome of an ancestor of anthropoid primates. Prosimians retain the undisturbed target site (Chen et al. 2017). Randomly arising mutations do hone protein function.

Other TEs have provided “start” sites of genes that are active in the placenta, and so affect the way in which those genes are regulated. A family of TEs called L1PA2 elements includes multiple instances involved in the activation of nearby genes that specify nonprotein-coding RNAs. An example of this L1PA2 subclass entered the primate germline in an ancestor

of the African great apes (Chishima et al. 2018). Another example is of an Alu-Y element that drives placenta-specific expression of the growth-promoting gene *KCNH5* that is active in many other tissues, but under independent regulatory influences (Macaulay et al. 2014).

Finally, there is the wonder of the decidua, the maternal (endometrial) part of the placenta. Gene regulatory networks have been reorganized to orchestrate the remodeling of this remarkable tissue. The hormone progesterone regulates decidualization, and in decidual cells, many binding sites for the progesterone receptor are located in TEs (Lynch et al. 2015). A tripartite binding site for three gene regulatory proteins (bZIP, oestrogen receptor, PAX) occurs *exclusively* in Alu elements. The insertion site of one such element dates from an anthropoid primate ancestor (Vrljicak et al. 2018). Randomly accrued parasitic strips of DNA have been co-opted repeatedly to rewire placental regulatory circuits.

PART II

Providence: Chance and Purpose

The study of comparative genomics has demonstrated that random mutations generate novel functionality. The random activities of ERVs and TEs have contributed to new genetic information and to the formation of *Homo sapiens*, the one biological creature dignified with the epithet, the *image of God* (Genesis 1:26–28). It is no longer credible to assert, as many do in the wider society, that mutations exert only deleterious effects and that they cannot produce innovations in function. Nevertheless, the fact of randomness and the postulate of purpose seem to sit uneasily with each other. However, scholars have pointed to ways of bridging the apparent divide. To physicist Paul Ewart (2009), “the operation of chance in evolution is entirely consistent with a creative purpose. It [chance] is seen as the most efficient and effective way of realizing the potentialities inherent in the nature of the created material.” The physicist John Polkinghorne provided theological perspectives on the formative role of chance in evolution before the era of comparative genomics. Specific randomly arising genetic events that have generated placental form and function illustrate his ideas, as discussed below.

First, *biological (evolutionary) history* possesses analogies to *human history*. This is true even though the former involves impersonal molecular processes and the latter involves personal human agency—because our biology embodies our personhood. Polkinghorne (1994, 46–47) has stated that “We’re characters in the cosmic play who have emerged from the scenery. Animate beings have evolved from inanimate matter, and our nature is tied to the physical world which gave us birth.” The operation of minds is connected with molecular processes in brains, so the processes involved

in biological and human histories cannot be entirely dissimilar. Historian Peter Harrison (2016, 278) argues that theological objections to evolution would not have arisen “if the history of nature [evolution] were understood to be more akin to human history at the time Darwin published the *Origin*.” Christians may say of biological history what is fundamental to their interpretation of human history that, despite its bewildering contingency, God’s ends are achieved through it.

Polkinghorne (1988, 47–50) argues in this way that the progression of both biological and human history seems to reflect the interplay of *chance* (randomness, happenstance) and *necessity* (consistency, structure). Similarly Thomas Oord (2015, 151) argues that reality is permeated with randomness, whether we consider genetic mutations (in biological history) or human interactions (in social history), and both histories show law-like regularities. John Haught (2008, 228–29) writes that the unity of chance, necessity, and deep time entails that biological history can be read as story, with all that implies for purpose: “contingency, consistency and temporality are the stuff of story . . . Nature is narrative to the core.” Holmes Rolston (1999, 23, 348) states that biology, including its genetic cycles, is historical. With the advent of genes, the biological story became memorable: “cumulative and transmissible, that is, historic” (Rolston 1999, 52). Biological history, these writers are arguing, is like human history; it is storied and thereby invites metaphysical interpretation: each history is contingent but arguably end-directed. It seems to follow that Christians should see the hand of God in biological history in the same way as they see the hand of God in human history—in all its meanderings and dead ends.

Second, some authors have argued that chance represents genuine freedom. Polkinghorne (1991, 82–83) proposes that, theologically, *chance* represents the divine gift of freedom, and *necessity* represents the divine gift of faithfulness or consistency. To Polkinghorne, the unpredictabilities of history “are signs of a genuine ontological openness” (quoted by Oord 2015, 128). As Oord says (2015, 40), “Many believe randomness is not just epistemic but also ontological . . . The world is not a determined machine; the spontaneity inherent in existence generates chance. Chance is irreducible.” Other physicists emphasize this idea. “Randomness is often portrayed as some sort of defect or problem. But randomness could also be named openness. It is freedom from micromanagement” (Briggs et al. 2018, 203). And, (Rolston 1999, 208) agrees that “Life is destined to come as part of the narrative story, yet the exact routes it takes are open and subject to historical vicissitudes.” One can argue that biology is largely nonsentient and human history largely sentient, but the parallels are interesting, nevertheless. Biological history reflects the operation of creaturely freedom (of physical action) in the context of divinely upheld consistency (physical law). Human history reflects the operation of creaturely freedom

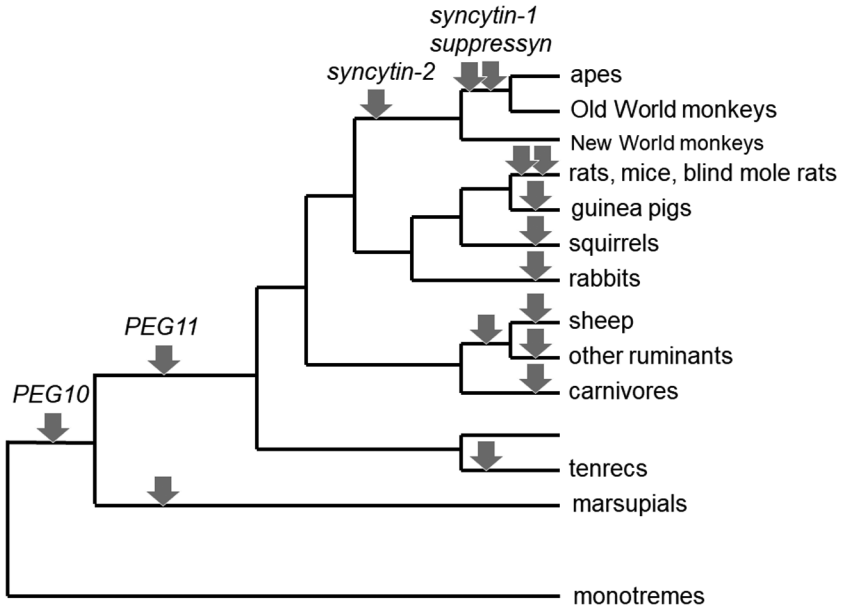


Figure 4. The repeated co-option of ERV-Derived genes in the biology of the placenta. Note. The dendrogram depicts a partial mammalian phylogenetic tree showing those branches on which ERV genes have been domesticated to serve functions in placentation. Based on Denner (2016) and Imakawa and Nakagawa (2017).

(the often-arbitrary expression of human volition) in the context of divinely upheld consistency (moral law).

Third, evolution is typified by convergence and directionality. Chance molecular events and human volition (representing God's gift of freedom) are so constrained by physical law and moral law (our formulations of God's ever-present gift of consistency) that histories move directionally to their divinely purposed consummation. As Oord argues (2015, 188), God uses randomness and chance to bring history to its fulfilment.

We can see this directionality and constraint in the phenomenon of evolutionary convergence. Insertion of each retrovirus is a stochastic event; but retroviruses have contributed *independently* and *repeatedly* to formation of the placenta in mammals (Figure 4) (Denner 2016; Imakawa and Nakagawa 2017). Of particular interest is the case of the rudimentary and transient marsupial placenta. This undeveloped structure shares the TE-derived *PEG10* gene with placentas of eutherian mammals, and also expresses a marsupial-specific *env*-derived syncytin gene of ERV provenance. Even this functionally and taxonomically distant placenta shows convergence (Cornelis et al. 2015). Indeed, the depth of convergence is disclosed

by retroviral contributions to placentation in live-bearing lizards (Cornelis et al. 2017), and TE activity in placental tissue of live-bearing fish (Jue et al. 2018). Simon Conway Morris (2004) has argued at length that the phenomenon of evolutionary convergence reveals hidden processes, which show that evolution has a direction and a purpose. To Andrew Steane (2014, 65–71, 149), “Random seeking has led to non-random finding,” and “the randomness serves chiefly as a mechanism to discover the niches that are made available by the environment.” It is now widely recognized that, in biology, phenotypic changes arising from chance events are *directed* or *constrained* along certain trajectories, as encapsulated by a comment in *Science* that evolution rolls the dice, but physics makes the rules (Camargo 2018).

The strategies involving random mutations and selection (*genetic learning*) are analogous to the problem-solving strategies that involve the production of variant ideas followed by “the selective testing of these in experience” (*neural learning*). “The genetic mutation is a ‘trial’ idea.” The biological organism is a “learning center.” Speciation is a drift “through an information search.” Analogously, “the entire scientific enterprise moves by throwing forward hypotheses on the forefront of experience, by testing these, and by preserving only those few that succeed” (Rolston 1999, 169–70). Software engineers have exploited the strategy of random mutation with natural selection to develop genetic algorithms. These programs generate random variations and retain the best surviving solutions (Rolston 1999, 34–37). Genetic processes involving ERVs and TEs constitute powerful strategies for improving fitness and developing new functionality—compellingly exemplified by that of the placenta.

At the broadest scales, biological organisms may tolerate ERVs and TEs because their genome-modifying propensities provide necessary variation upon which natural selection can act. That is, they enhance *evolvability*, and their relative activities may be responsive (via epigenetic controls sensitive to environmental conditions) to stressful conditions that challenge existing phenotypes (Finlay 2013, 129–31). Evolvability and environmental stress may be linked through epigenetically regulated ERVs and TEs.

In summary, we may accept that evolutionary histories (such as that of the placenta) are deeply contingent, but their routes are constrained by a deeply embedded order. The directedness of chance (freedom) in the context of lawful anthropic consistency invites us to interpret biological history as carrying purpose and as being directed to a goal. This is wholly consistent with the hope of the individual Christian: that is, we experience the interplay of real freedom (represented by the chanciness or randomness of life) and divine consistency (necessity, reflecting God’s covenant faithfulness).

The Problem of Evil

And here, the story might end, except that these same retroviral and TE insertions are often implicated in disease. The complexity makes us more vulnerable to mishap. The syncytin proteins, either individually or together, are expressed abnormally in various placental pathologies (Bolze et al. 2017). These include abnormalities associated with Down's syndrome; preeclampsia (high blood pressure); fetal intrauterine growth restriction (IUGR); the maternal *haemolysis, elevated liver enzymes, low platelets* (HELLP) syndrome; gestational diabetes; and tumors of trophoblastic tissue. Such correlations indicate (at the least) that the retrovirally derived syncytin proteins are fully assimilated into essential functional networks. Aberrant expression may even *cause* pathologies. For example, a *syncytin-2* gene variant may predispose to preeclampsia (Hua et al. 2018). Total integration of syncytins into molecular pathways entails the risk that aberrant activity will lead to disease, or contribute to its progression.

Optimal placental function is essential for the development of the unique capacities of human brain and mind. Placentation serves mentalization. Expressed negatively, placental abnormalities may have enduring disruptive effects on mental health, affecting cognition, behavior, and mood (Figueiro-Filho et al. 2017b). Fetal development through preeclamptic pregnancies has been linked to long-term neurobiological sequelae including altered brain vascular diameters (Ratsep et al. 2016) and abnormal white matter connections between distant brain centers, as defined both structurally (Figueiro-Filho et al. 2017a) and functionally (Mak et al. 2018). It has been hypothesized that oxygen deprivation, resulting from placental insufficiency, leads to altered secretions from placental tissue, and changes to fetal brain biochemistry and structure (Phillips et al. 2017).

The risk of developing autism spectrum disorder (ASD) may be elevated with atypical features of placental morphology (decreased eccentricity of shape; increased maximum thickness and variability), which may in turn reflect a reduced capacity to adapt to stresses in the placental environment (Park et al. 2018). The risk of developing ASD is affected by diverse complications of pregnancy (Chien et al. 2018; Maher et al. 2020) and more specifically, by placental pathologies such as acute inflammation, chronic vasculitis, and inadequate perfusion (Straughen et al. 2017). Altered expression of ERVs may underlie an inflammation-preeclampsia-ASD axis, although placental involvement is inferred only at this stage (Balestrieri et al. 2019). The risk of developing schizophrenia is affected by genes that are active in the context of prenatal complications affecting placental function (Ursini et al. 2018).

Our mental capacities may be limited by the contingencies of a less-than-ideal placenta, or of co-opted genes that once served a viral pathogenic program. Individuals may be predisposed to enduring struggles with mental

health challenges as a result of maternal hypertension or placental dysfunction. The dependence of human brain and mind on (what might be considered) disposable, single-use plumbing emphasizes our rootedness as physical creatures with an evolutionary history. It is easy to forget that we are anchored in biology. Intrinsic to the human condition is the understanding that we are physically vulnerable anthropoid primates.

But reflection on the pervasive existence of disease and evil in the creation of a good God is always ultimately perplexing. A helpful response to this mystery is that a *free-process defense* applies to biology in the same way as the *free-will defense* applies to human history (Polkinghorne 1991, 84; Oord 2015, 143–49). The physical creation would cease to be authentically historical were God to revoke the freedom that operates within the natural order, just as, according to Steane (2014, 220), humans would lose their essential humanity were God to override or rescind their ability to make choices. Indeed, Oord (2015, 169–75) argues that because of his love for creation, God *cannot* deprive it of freedom.

Despite the presence of disease and suffering, Rolston (2010, 205–46) argues that the radical freedom of biological process has led to phenomena of *caring*. Genes are often anthropomorphized as *selfish* but might be described more adequately as *caring*. “Evolutionary natural history has generated ‘caring’ . . . Sooner or later every biologist must concede that ‘care’ is there” (205). Indeed, “the story of life on Earth is of the generation and regeneration of caring” (207). The co-evolution of species generates complexity, so that “a world of less chance would be a world of less caring” (218). The evolved placenta is an exemplar of such care. In humans, its dependent organ, the evolved brain, acts as a survival instrument “by radically elaborating capacities for caring” (224), encompassing “idealized futures” (229), “universalist creeds” that transcend genetic relatedness (237), and the “global biotic community” (238–39).

The onus is on persons to ameliorate suffering. When faced with suffering, humans have the capacity to transcend genetics and demonstrate others-enriching love. “Increased caring, like the increased complexity that supports it, is an ever open niche. That invites us to see such a world, and our task in it, as sacred, even divine” (Rolston 2010, 243). Ultimately “the possibility of disease is not gratuitous, it’s the necessary cost of life” (Polkinghorne 1994, 45). Christian theology anticipates the resolution of suffering only in the Kingdom of God (Wright 2008).

Human Vulnerability and the Need for Compassion

It is significant that to the Maori, indigenous people of New Zealand, the word for placenta, *whenua*, is also the word for land. The Maori bury the placenta, a practice that “reinforces the relationship

between the newborn child and the land of their birth” (<https://teara.govt.nz/en/papatuanuku-the-land/page-4>). Such earthy vulnerability emphasizes the polarities inherent in our humanness. As Richard Holloway said, “I am dust and ashes, frail and wayward, a set of predetermined behavioral responses, programmed by my genetic inheritance and by social context, riddled with fears, beset with needs whose origins I do not understand and whose satisfaction I cannot achieve, quintessence of dust, and unto dust I shall return . . .” We are, however, much more than the product of a genetic history modulated by environment. “Dust I may be, but troubled dust, dust that dreams, dust that has strange premonitions of a glory in store, a destiny prepared, an inheritance that will one day be my own” (quoted by Barker 1991, 162).

In biblical terms, we are Adam from *adamah*; the earthling from the earth; humans from humus. Carol Newsom has said that “we share common ground with the Earth because we are *common ground*” (in Bauckham 2010, 21). God “knows our frame; God remembers that we are dust” (Psalms 103:14). The declaration of God’s knowledge of us as we are formed *in utero* (Psalms 139:13–15), in all our bewildering variety, requires a response that recognizes both the contingencies of our development and the Creator’s supervening care and concern.

The Church then should be a community where people find acceptance despite weakness of cognition and temperament. The congenital limitations that affect the mind are not irreversible, and are sometimes ameliorable to some extent by loving nurture. Sensitive mothering of infants, for example, can prevent some of the damaging effects on cognition of prenatal exposure to the stress hormone cortisol (Glover and Capron 2017). When Jesus said, “Do not judge others” (Matthew 7:1; Luke 6:37), he surely was not proscribing the responsibility to assess moral behavior for its rightness or wrongness; rather he may have been charging his followers to accept the personality quirks—moodiness, anxiety, social remoteness, cognitive dullness—that (for all we know) had their roots in suboptimal intrauterine environments or subsequent equally damaging contingencies like viral infection, environmental toxins, inadequate nutrition, or socioemotional neglect (Monk et al. 2019). We are called to bear one another’s burdens (Galatians 6:2).

The Christian gospel indicates that creatures of such weakness are loved, called and destined for transformation and glory. It puts our hominin physicality into perspective. To elaborate on St Paul: Just as we wear the likeness of the human made of earth—sometimes selfish, with a tendency to aggression in difficult circumstances, but capable of kindness and cooperativity—conditioned *inter alia* by its intrauterine environment—so we will wear the likeness of the human from heaven (1 Corinthians 15:49). Are we just glorified apes? Grace allows us to gladly affirm both terms that constitute the apparent paradox.

Human Relationality: The Ethics of Prenatal Parenting

Placentation allows mother and fetus to influence each other over an extended time frame and this then characterizes mammalian life with its increased propensity to parental bonding and cooperative behavior. Bonding between mothers (and fathers) and children starts to develop prenatally. The strength of both maternal and paternal bonding with their baby *prenatally* anticipates the strength of that bonding *postnatally*. The placenta also plays a central role in mutual maternal-to-fetal, and fetal-to-maternal, programming (Glover and Capron 2017). That is, the placenta participates in influences on physiology and mental state that flow both ways.

The advent of the placenta has provided the conditions enabling “prenatal parenting,” during which parents “can alter the development of their child, even before birth . . . The mother’s emotional state during pregnancy can have a direct influence on fetal development by fetal programming” (Glover and Capron 2017). The significance of such influence is that the uterine environment during sensitive periods alters development with long-term consequences.

Maternal stress, anxiety, and depression during pregnancy may have harmful effects on fetal development. The child’s growth may be retarded, and it may be born earlier than is typical. However, the most widely recognized effects are on the neural system, leading to deficits in emotional state (depression, anxiety), behavior (ADHD, conduct), and cognitive development. The mothers with the 15 percent highest levels of stress have children with double the risk of mental illness. These effects may be mediated by hormones (such as cortisol) and inflammatory cytokines, which modify placental biochemistry and the regulation of genes expressed in the placenta, including *HSD11B2* (responsible for metabolism of cortisol) and *NR3C1* (that encodes the cortisol receptor) (Janssen et al. 2016; Glover et al. 2018). There are, however, differences between populations that may reflect the effects of social environment or of ethnicity (Capron et al. 2018).

Conversely, the fetus conditions the mother. The placenta produces hormones that program the behavior of the mother. The *PHLDA2* gene is active in trophoblastic cells of the placenta. It is subject to precise regulation and may influence patterns of maternal care. In mice, the activity of the *PHLDA2* gene affects the relative effort spent on nest-binding on the one hand, and on direct attention to the pups (licking, grooming) on the other. In humans, the paternally derived *PHLDA2* allele is silenced. It has been hypothesized that the activity of this gene must be minutely controlled to sustain optimal maternal behaviors. The appropriate window of *PHLDA2* activity promotes placental lactogen production, which signals to increase maternal behavior (Creeth et al. 2018).

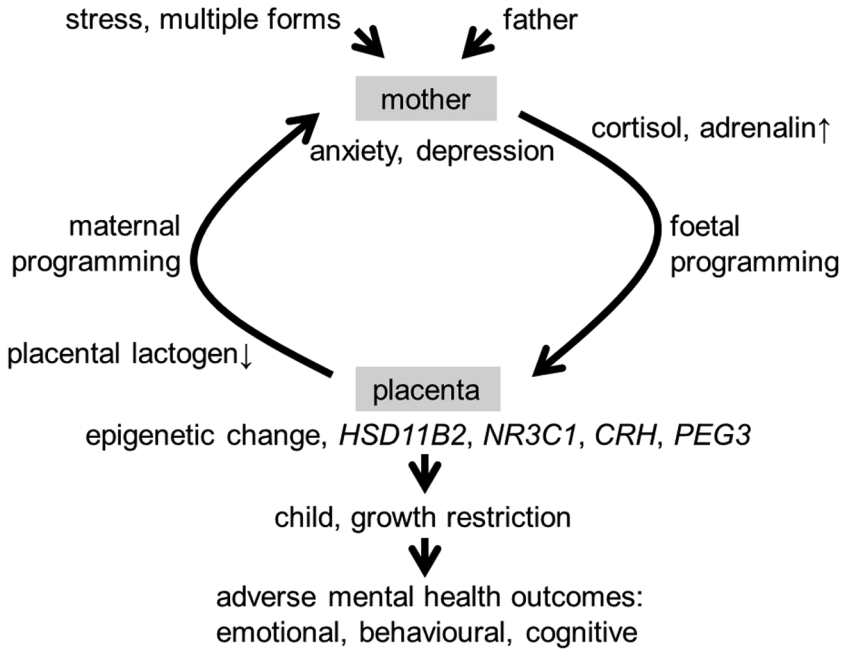


Figure 5. Central role of the placenta in mediating mutual mother-child influences. Source. Based on Janssen et al. (2016), Capron et al. (2018), and Glover et al. (2018).

The father also influences pregnancy outcomes. Paternal depression during pregnancy has been associated with preterm birth. Fathers have an important role in supporting mothers. A significant contribution to maternal stress comes from unsupportive or hostile partners. If fathers were experienced as being hurtful emotionally during pregnancy, children were more likely to score less well cognitively and to show heightened fear responses. Paternal hostility accounts for an estimated three-quarters of the maternal stress-related reduction in infant cognitive and fearfulness scores (Bergman et al. 2007).

Interactions are summarized in Figure 5. The biological environment, including diet, is important for placental growth and function, and for fetal growth (Timmermans et al. 2012). We might say that “we are what we (or our parents) eat.” In addition, there is a seamless interaction between parental love, placental optimality, and fetal mental development. Our status as being placental mammals, rather than (say) being toads or fish, suggests also that “we are how our parents loved.”

The promulgation of a private contractual understanding of human sexuality is common, but incompatible with the cooperative, prosocial, community-oriented life for which the placenta prepares us. At least in the context of parenting, it makes a difference whether human sexuality is

committed and loving. The absence of a profound and sacrificial commitment to the well-being of the partner is inimical to the developing child's safe development through the potential hazards of a nine-month gestation. A *laissez-faire* approach to reproduction carries a high probability of long-term neural damage to the child, even if that damage does not manifest itself until late adolescence. And of course, humans live in states of deep mutual dependencies. Not only a deprivation of love, but also suboptimal diets, exposure to toxins, faulty metabolic pathways, and the presence of wider social strains, all affect developing life through the placenta (Monk et al. 2019).

Women who were pregnant at the time of the terrorist attack on the World Trade Center, and who developed posttraumatic stress disorder, delivered babies who were small for gestational age, and who as infants, had anomalously low cortisol levels (Yehuda et al. 2005). The intensity of stress (arising from a severe ice storm in Quebec) affecting pregnant women has been correlated negatively with the children's "verbal intelligence and language-related abilities" at 5.5 years (Laplante et al. 2008). The authors hypothesized fetal programming as the mechanism linking mothers' exposure to stress and the children's abnormalities. Afro-American women who must cope (in the first two semesters of pregnancy) with police shootings of unarmed (but not armed) black people deliver babies of reduced gestational age and weight. These features correlate with later mental illness. The pain of perceived injustice, that is hypothesized to act through placental CRH, leads to transgenerational disadvantage (Legewie 2019). The effects appear to be generalizable (Dowell et al. 2019). Worldwide, up to 20 percent of children and adolescents struggle with mental illness (Glover et al. 2018).

Being a eutherian mammal with potential for highly honed sociality connects the quality of parental love, to the efficiency of placental function and the vibrancy of mental health. Being a placental mammal has everything to do with the priority of others-directed love.

SUMMARY

In evolutionary terms, the placenta is a recent innovation, for which formative genetic events can be unambiguously identified. Random events—the activities of ERVs and TEs—have featured extensively in this history, demonstrating the positive role of chance in evolution, and providing pointers to the nature of divine providence. The components of matter act freely, in the context of directing divine faithfulness. It is becoming increasingly clear that the operation of the humble placenta greatly influences fetal cerebral development, and with it, a child's later mental health and cognition. The placenta-mind connection emphasizes the imperative of optimizing maternal physical and mental well-being during the prenatal period, a vital element of which is paternal love and support.

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