

# The 'VIGE-first hypothesis'—how easy it is to swap cause and effect

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Transposable and transposed elements are present in all genomes and contribute to generate variation in offspring. Hence, they qualify as variation-inducing genetic elements (VIGEs). Here, I will discuss the 'VIGE-first hypothesis'—which holds that RNA viruses originate in the genomes from genetic elements commonly known as endogenous retroviruses—in the context of the origin and evolution of the syncytin gene locus. I will argue that the most parsimonious explanation for understanding the syncytin locus involves the assumption of only two integrations of derailed VIGEs. The 'VIGE-first hypothesis' implies that the functional syncytin gene present in the human genome was not derived from the envelope gene of an ancient RNA virus. Rather, the mobile genetic elements that contain a syncytin-like gene are secondary and originated after uptake of the syncytin gene from the genome. Importantly, this vision also indicates that HERV-W may be on its way to becoming a full-blown RNA virus.

The origin of genes is the topic of a particular discipline of historical science: evolution. Since nobody was present to observe the formation of functional genetic novelties, the actual sequence of events can only be inferred, never known. The method of inference is, however, highly biased by the premises and prejudices about the origin of the universe, and cause and effect may easily be swapped. In the current secular paradigm, several functional genetic novelties ('genes') are made up of transposable and/or transposed element sequences. The consensus nowadays is that such "genes were originally formed from mobile elements and that in some process of molecular evolution a coding sequence was derived that could be translated into a protein that is of some importance to human biology."<sup>1</sup>

The human genome contains approximately 3 million transposable and transposed elements (short: TEs), together making up 45% of the entire genome. TEs can be subdivided into two groups: DNA transposons (3% of the genome) and retro-elements (42% of the genome), which require RNA-mediated transposition mechanisms. Among the latter, the so-called endogenous retroviruses (ERVs) are an interesting class of TEs, because they very much resemble disease-transmitting RNA viruses at the genetic level. Like RNA viruses, ERVs contain *gag* and *pol* genes, which code for eight proteins, including reverse transcriptase (RT), ribonuclease H, and integrase. These proteins are required for the conversion of RNA into complementary DNA and facilitate insertion into the genome. The double-stranded DNA forms through the action of RT, which is then inserted back into the genome at a different location. The result of this copy-paste

mechanism is two identical copies at different locations in the genome. More than 300,000 sequences (8% of the genome) that classify as ERVs have been found in the human genome.<sup>2</sup> In the naturalistic paradigm, ERVs have long been thought of as the remnants of ancient invasions of RNA-viruses and they have long been regarded as selfish (even parasitic) genetic elements. The parasitic view of TEs is wrong and the non-functional presence of TEs in the genome is increasingly challenged by scientific observations.<sup>3,4</sup> Biologists increasingly appreciate TEs as an important functional and regulatory part of the genome, and a more positive, even symbiotic, role for mobile genetic elements has recently been proposed.<sup>5</sup> The activity and expression of ERVs are stringently controlled, clearly demonstrating the design features of these genetic elements. The major part of ERVs may be degenerate and defunct due to the inherent redundant character of literally hundreds of thousands of copies.

## VIGE-first hypothesis

Previously, I have argued that in order to understand the origin of RNA viruses, it is imperative to completely ignore the mainstream view that a major part of our genome is made of the genetic debris of ancient invasions of RNA viruses. Instead, I have hypothesized that transposable and transposed elements might have been originally designed to generate variation in offspring and should therefore be renamed *variation-inducing genetic elements* (short: VIGEs).<sup>6</sup> Hence, the major part of genomes contains VIGEs and their degenerate remnants. As mentioned above, ERVs are mobile genetic elements

The ‘VIGE-first hypothesis’ postulates that RNA viruses have their origin in *gag-pol* elements. Within an ID-framework, *gag-pol* elements may be interpreted as a particular class of variation-inducing genetic elements (VIGEs) specifically designed to induce variation in offspring. The hypothesis assumes that the original baranomes contained high numbers of distinctly different *gag-pol* elements, which can still be distinguished today and commonly known as endogenous retroviruses (ERV) families.

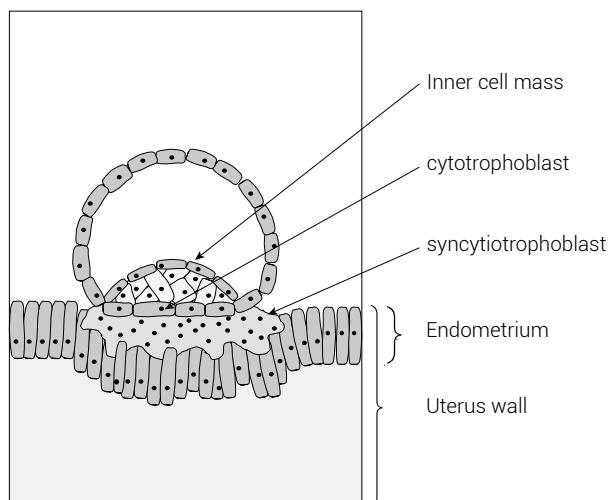
characterized by *gag* and *pol* genes that closely resemble full-blown RNA viruses, such as influenza and human immunodeficiency viruses. The origin of such RNA viruses can therefore be understood as a transformed ERV. In other words, RNA viruses may form in genomes from ‘*gag-pol* elements’.<sup>7</sup> *Gag-pol* elements may transmute into RNA viruses through sequential uptake and/or recombination of genomic genes (‘host genes’), which serve to further the virus envelope (to wrap up the RNA molecule derived from the VIGE) and genes that enable them to leave and re-enter host cells. Once such derailed VIGEs become shuttle vectors between different hosts, they have converted into full-blown RNA viruses.<sup>6</sup> This view, the ‘VIGE-first hypothesis’, solves the RNA virus paradox, i.e. the observation that all families of RNA viruses found today “could only have appeared very recently, probably not more than about 50,000 years ago”.<sup>8</sup> In addition, it provides a plausible explanation for the origin of RNA-virus-driven diseases.<sup>6</sup>

Still, a challenge to the ‘VIGE-first hypothesis’ is presented by naturalistic philosophers claiming that novel genes derived their sequence from endogenous retroviruses.<sup>1,9</sup> An interesting example is provided by syncytin, a protein critically involved in the development of mammalian placenta. The coding sequence of the syncytin gene seems to be made from an endogenous retrovirus envelope gene. The ‘VIGE-first hypothesis’ now says that it must be the other way around, i.e. the syncytin gene was captured by a *gag-pol* element. I will argue that the most parsimonious explanation to understand the syncytin locus is by assuming the integration of two such elements. This novel vision implies that the functional syncytin gene present in the human genome was not derived from the envelope gene of an ancient RNA virus. Instead, the *gag-pol* elements that contain a syncytin-like gene (known as HERV-W provirus) are secondary and originated after uptake of the syncytin gene from the genome. Importantly, this vision also

indicates that HERV-W may be on its way to become a full-blown RNA virus.<sup>10</sup>

### Functions of syncytin

The placenta is a prominent source of virus-like particles. Early electron microscopy studies were consistent in showing them budding from the plasma membrane of the cells making up the syncytiotrophoblast.<sup>11</sup> After isolation and further characterization of the particles it became evident that they contained genetic material identified as typical for retroviral elements, including sequences coding for reverse transcriptase and RNaseH.<sup>12</sup> Syncytin proteins are found on the outer envelope of the virus-like particles, and the syncytin gene is therefore also sometimes referred to as the *env* gene of HERV-W. Syncytin proteins are exclusively expressed by the syncytiotrophoblast, an epithelial cell-derived tissue that attaches itself to the uterus wall to initiate the embryonic placenta (figure 1). The syncytiotrophoblast is a homogenous, multinucleated, tissue that is formed through cell fusions, which are mediated by syncytin. Without syncytin’s fusogenic properties the formation of the syncytiotrophoblast would be impossible and a placenta could not be formed. The importance of syncytin

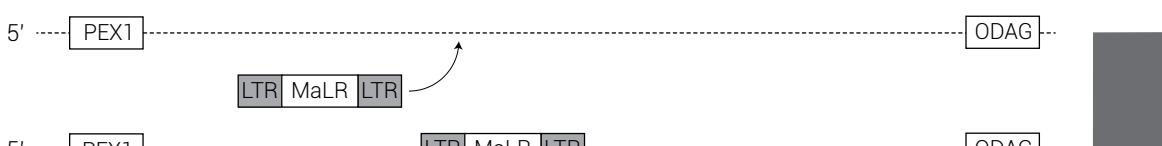


**Figure 1.** The syncytiotrophoblast is the epithelial layer that attaches itself to the uterus wall to form the embryonic placenta. It is a multinucleated, homogenous tissue that is formed through cell fusions mediated by syncytin. RNA viruses may have their origin in the placenta and spread afterwards. Many animals eat the placenta after partition and consume the provirus particles (ERVs). The recycling of previruses may advance the formation of real full blown RNA viruses through several integration and replication events. The abundance of proviruses in the placenta may thus simply reflect the preferred, optimal environment for the origin of RNA viruses.

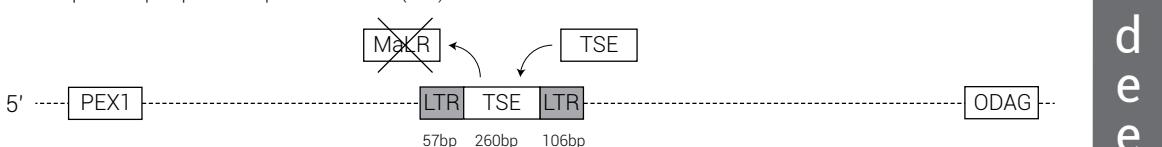
genes is demonstrated in homozygous syncytin-A null mouse embryos ('syncytin knockouts'), which die *in utero* between 11.5 and 13.5 days of gestation.<sup>13</sup> The study submits therefore that the genomes of placental mammals must absolutely contain at least one functional syncytin gene for reproductive success; a gene that is only expressed in placental tissue.<sup>14</sup> Besides its fusogenic role in establishing the syncytiotrophoblast, syncytin has also been shown to have a similar function in the generation of osteoclasts through fusion of mono-nucleated precursors, a key event of bone physiology and bone resorption.<sup>15</sup>

Furthermore, the syncytin proteins have a range of immunological effects to protect the developing embryo from being destroyed by immune cells of the mother. It should be noted here that the embryo, a developing novel human being with immunogenic 'alien' properties, will immediately be recognized by the immune system of the mother as unfamiliar tissue. Natural killer cells and macrophages, which are both part of the mother's immune-response, will then be alarmed in order to get rid of the 'intruder'. Now, in order to safeguard the embryo, one function of syncytin proteins is probably to

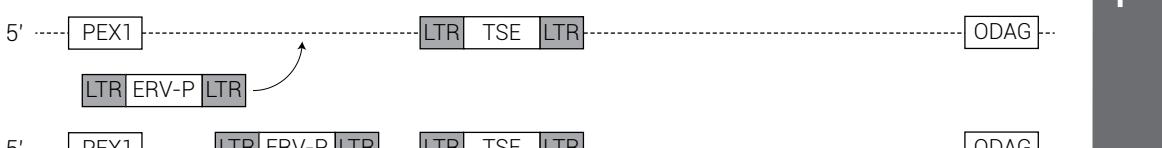
1) Integration of MaLR including the LTR regions



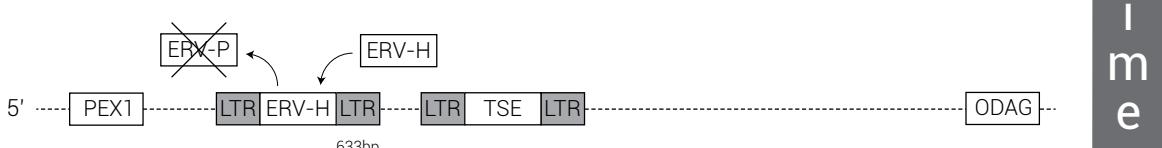
2) Exact excision and loss-without-a-trace of MaLR and acquisition of a unique 260 bp trophoblast specific enhancer (TSE)



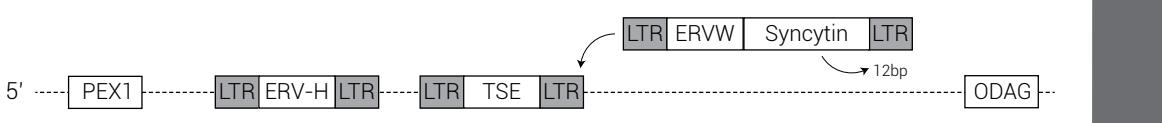
3) Integration of ERV-P including LTR regions



4) Exact excision and loss-without-a-trace of ERV-P only leaving the 633bp LTR behind followed by the acquisition of ERV-H



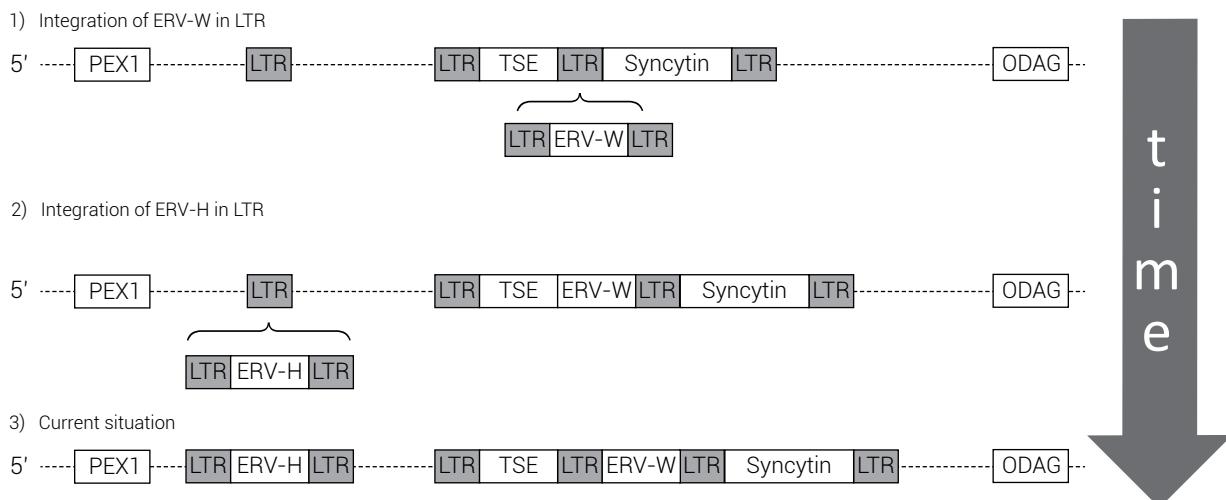
5) Integration of ERV-W including the syncytin gene followed by a 12 bp deletion



6) Current situation



**Figure 2.** The most parsimonious evolutionary scenario for the evolution of the ERWV1 locus involves a number of specific genetic events of which we do not find any evidence in the genomes of extant species. For details see text. (The sizes of the genetic elements (PEX1, ODAG, LTR, TSE, ERV-P, ERV-H, ERV-W) are not represented at scale).



**Figure 3.** Most parsimonious scenario for the evolution of the ERVW1 locus from the VIGE-first hypothesis involves only two steps. The original genetic situation present in the baranomes of man, pan and gorilla was not associated with the gag-pol sequences. Through the sequential uptake of two gag-pol elements, known as ERV-W and ERV-H, the genomes 'evolved' into the current situation. It should be noted that the box designated LTR-TSE-LTR is a highly tissue specific regulatory element known as trophoblast specific enhancer (TSE). Although present in all cells, this enhancer makes sure that the syncytin gene is only expressed in the right place at the right time, i.e. in the trophoblast. (The sizes of the genetic elements (PEX1, ODAG, LTR, TSE, ERV-P, ERV-H, ERV-W) are not represented at scale).

suppress the cytolytic and cytotoxic actions of natural killer (NK) cells.<sup>16</sup> In addition, there is direct evidence that syncytin-like proteins, including human syncytin-2, direct an immunosuppressive response,<sup>17</sup> which may also help to prevent rejection of the embryo. Together, these effects of syncytin seem to be specifically designed in order to advance reproduction of placental organisms.

### Story one—Independent acquisitions of syncytin genes by RNA viruses & improbable genetic events

Since the discovery of the first syncytin gene, it has become clear that there must have been at least six independent gene-capture events by mammalian genomes. At least two independent syncytin acquisitions must be invoked to explain the syncytin loci found in simians;<sup>18</sup> syncytin-1 entered the primate genome 25 million years ago, whereas syncytin-2 invaded approximately 40 million years before present.<sup>19</sup> Two distinct, unrelated genes (*syncitin A* and *syncitin B*) have been identified in *Muridae*, and a fifth gene has been identified in the rabbit (*Lagomorpha*). Independently acquired fusogenic endogenous retroviral envelope genes have also been proposed for *Carnivora*,<sup>20</sup> as well as for sheep (*Ruminantia*).<sup>21</sup> The syncytin genes identified in different orders of mammals do not show a high level of sequence homology and they map to different genomic locations.

The biological evidence thus demands that evolutionists must invoke the RNA virus-origin of syncytin genes, not once or twice, but at least six times independently (most likely more often<sup>20</sup>).

An algorithm to illustrate the evolution of the ERVW1 locus is even more problematic. As demonstrated schematically in figure 2, the most parsimonious evolutionary scenario relies on a great number of highly unlikely genetic events of which the selective value of individual arrangements remains highly doubtful. First, it requires the integration of a *mammalian apparent LTR-retrotransposon* (MaLR) in the PEX-ODAG intergenic region, which is then lost without a trace leaving only MaLR-like LTR units behind (57 and 106 base pairs, respectively). These LTR units are promoters that drive gene transcription. Strikingly, the 260 base pairs between these LTR sequences, which are independently acquired, make up a functional *trophoblast specific enhancer* (TSE; a genetic switch active only in trophoblastic tissue). The complete absence among species of flanking duplicated sequences, which should be present as vestiges of the original integration, does not support this hypothesis.<sup>22</sup> In fact, this TSE must have been acquired together with the syncytin gene: without having trophoblastic tissue an enhancer specific for this tissue does not make sense at all. Next, an ERV-P element integrated between the PEX1 gene and the TSE, which was then replaced by ERV-H, leaving nothing behind except an ERV-P-like

LTR unit of 633 base pairs. Again, the absence among species of flanking duplicated sequences, which are to be expected as vestiges of such integration events, as well as complete lack of ERV-P sequences in this region, do not support this hypothetical view. In the meantime, an RNA virus containing a syncytin gene invaded the germ line, transformed into the so-called ERV-W provirus, and then integrated in the DNA between the TSE and the ODAG gene. Finally, when the syncytin gene lost 12 nucleotides through a deletion, the locus had transformed into a trophoblast-specific information unit to regulate, control and sustain the establishment of the placenta.<sup>22</sup>

In short, story one communicates that pre-mammalian organisms were infected at least six times by RNA viruses carrying a syncytin gene; Six times these viruses invaded the germ line and six times these viruses transformed pre-mammals into mammals. In addition, the molecular evolution of the ERVW1 locus involved a number of highly improbable genetic events of which we do not find a trace in the genomes of extant mammals.<sup>19</sup> Could it be that the secular scientists mixed up cause and effect? Let's have a look at story two.

### **Story two—non-random integration of VIGEs and independent origin of syncytin proviruses**

The most parsimonious scenario of the ‘VIGE-first hypothesis’ is presented in figure 3. Originally, the region between PEX1 and ODAG contained the syncytin gene plus its global and tissue specific regulatory elements (LTR and TSE, respectively). LTRs are required for global regulation of gene transcription and found throughout the genomes of eukaryote organisms. They can best be described as transcription control centers. It is of note that the genes present in *gag-pol elements* rely on LTR as promoters for their transcription. The original design

of the syncytin locus did not contain *gag-pol elements*. The TSE is a trophoblast-specific enhancer, a genetic regulatory element (or: genetic switch) that ensures the syncytin gene is only expressed in the trophoblast, but not in other cells or tissues. After the fall, two *gag-pol elements* (known as ERV-H and ERV-W) sequentially integrated in this locus. Both genetic elements can still be recognized, because they are characterized by *gag* and *pol* sequences. It was only after the integration of ERV-W that the locus was able to produce syncytin-containing VIGEs (or: proviruses). The spread of the HERV-W family into the genome essentially results from events of intracellular retrotransposition of transcriptionally active copies, a phenomenon mediated either by their own reverse transcriptase (RT) machinery or by RT from LINE elements.<sup>23,24</sup> For obvious reasons, the only surviving active provirus was the one that lost a functional copy of the syncytin gene. Shortly after integration, the *gag* and *pol* genes of ERV-W were inactivated due to several debilitating mutations and the remainders of the genes are not functional.

Through recombination at the LTR units already present in the original ERVW1 locus, ERV-H and ERV-W integrated non-randomly in the same location in man, as well as in the great apes. The nested hierarchy we observe in human-hominoids is hence explained as sequence dependent integrations of the same VIGEs present in distinct baranomes (man, chimpanzee, gorilla and orangutan), similar to what has been described for the independent acquisition of the H6S ALU.<sup>25</sup>

### **The reality check**

In humans, the only functional syncytin gene is present on chromosome 7 (locus 7q21.1; HERW1).<sup>26</sup> The locus also harbors sequences for *gag* and *pol* genes, which

|               |     |     |     |     |     |     |     |     |     |     |     |     |
|---------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| ERV-W (hu)    | GCT | GTA | AAR | CTA | CAA | ATN | RTT | CTT | CAA | ATG | GAG | CCC |
| Amino acid    | A   | V   | K   | L   | Q   | M   | V   | L   | Q   | M   | E   | P   |
| Syncytin (hu) | GCT | GTA | AAA | --- | --- | --- | --- | CTA | CAA | ATG | GAG | CCC |
| Syncytin (ch) | GCT | GTA | AAA | --- | --- | --- | --- | CTA | CAA | ATG | GAG | CCC |
| Syncytin (go) | GCT | GTA | AAA | --- | --- | --- | --- | CTA | CAA | ATG | GAG | CCC |
| Syncytin (or) | GCT | GTA | AAA | --- | --- | --- | --- | CTA | CAA | ATG | GAG | CCC |

**Figure 4.** The human-specific ERV-W consensus and the syncytin-1 genes in human, chimpanzee, gorilla and orangutan showing the 12 nucleotides specific insertion in ERV-W (adapted from Bonnaud *et al.*<sup>19</sup>).

are typical for RNA-viruses, but both genes have been disabled by non-sense and frame shift mutations.<sup>27</sup> The fact that the functional syncytin gene is found with gag and pol genes in the same context as these genes appear in HERV-W has prompted the idea that the syncytin gene is of viral origin. If it is so, it must have been delivered by an ancient, now extinct RNA virus, because RNA viruses related to HERV-W are currently non-existing. This is because the coding frame of the syncytin gene present in HERV-W is unique and does not show any similarity to sequences of other RNA viruses, an observation in full agreement with the ‘VIGE-first hypothesis’.

The human genome contains a family of *gag-pol elements*, which belong to the HERV-W family. This family consists of collections of heterogeneous elements, ranging from full-length defective proviruses to isolated long terminal repeats (LTR)<sup>28</sup> derived from recombination events. The provirus members of this family are defined by a DNA sequence that is almost identical to the functional syncytin gene found in the ERVWE1 locus, except that it has an additional 12 nucleotides inserted into the sequence coding for the cytoplasmic tail of the syncytin protein. It is exactly this tail that is responsible for protein’s fusogenic activity and it is the essential part involved in the formation of the syncytiotrophoblast. The insertion of the 12 nucleotides, which may indicate an *in frame* duplication event, adds four amino acids to the protein thereby disrupting its fusogenic function. The proposed duplication event may be reflected in the first three amino-acid codons (LQM), which are merely a repetition of the three amino-acids found in the sequence (figure 4). The contemporary HERV-W family of transposable elements thus harbors a slightly longer but defunct copy of the syncytin gene.

As mentioned, the syncytin protein helps to fuse the cells of the syncytiotrophoblast to form the placenta. The fusogenic capacity of the syncytin protein, however, depends on an envelope maturation step consisting of cleavage of the intra-cytoplasmic domain by the protease present in the *gag-pol element* (discussed in Bonnaud *et al.*<sup>19</sup>). To preserve a functional syncytin gene for millions of years would have required a HERV-W active protease and coordinated expression of *pro* and *env* genes in time and space. This does not reflect the HERV-W family portrait, however. First, the ERVWE1 locus expressed in placenta contains a *pro* pseudogene, which is unable to produce a functioning protease. Second, the human genome does not contain any *pro* HERV-W genes in a favorable translational context.<sup>19</sup> As argued by Bonnaud and coworkers:

“The absence of fusogenic property of the LQMV modified envelope [the protein transcribed from the syncytin gene containing the 12 extra nucleotides, PB], proposed to mimic the infectious ancestor, could be correlated with the absence of HERV-W protease activity. Hence, one may speculate that the ERVWE1 *env* cytoplasmic domain evolved so as to bypass the cleavage requirement (constitutive fusogenic envelope) or to adapt cellular protease(s). In addition, contrary to the proposed involvement of a cytoplasmic helical structure in the mechanism of cell-cell fusion, the fusogenic cellular envelope exhibited an altered helix, which was restored in the nonfusogenic LQMV mutants. Further investigations will be required to decipher the respective contribution of the cytoplasmic tail maturation and structure in the fusion process mediated by the cellular envelope.”

The observations indicate that the slightly longer defunct copy of the syncytin gene must have originated in the human genome. Therefore, it should be specific for the human genome. It should not be present in the genome of the chimpanzee; not in the gorilla; not in the orangutan; not in gibbons. Indeed, the only active member of the HERV-W family is the one containing the 12 extra nucleotides in the syncytin gene.<sup>22</sup> It is not present in any of the studied simians. This clearly demonstrates that HERV-W originated in the human genome, further contesting the standard view that an ancient mobile ERV-like RNA virus added the syncytin gene to the genome of a putative common ancestor of man and monkeys. Rather, the mobile member of the HERV-W family found in humans may currently be on its way to become a full-blown RNA virus. Maybe we should no longer call it a provirus, but instead call it a *pre-virus*?

The 12-bp deletion signature of syncytin gene described above has also been detected in old world monkeys, including colobus (*Colobus guereza kikuyensis*) and rhesus monkey (*Macaca mulatta*).<sup>29</sup> This was unexpected, because old world monkeys also possess a distinctly different functional syncytin gene. This observation may, however, reflect the original status of the functional fusogenic syncytin gene frontloaded in the *baranomes* of the original kinds these modern species stem from. In the old world monkeys the human-like syncytin gene never retained an essential function and therefore degenerated. Why? Previously, I argued that baranomes are pluripotent, undifferentiated and uncommitted genomes characterized by an engineering design principle: *genetic redundancy*. Some biological

functions are so crucial to the reproduction of organism that the original created kinds must have contained back-up programs harboring the same or similar genetic information.<sup>30</sup> Obviously, the formation of a placenta is essential to the reproduction of mammals and we might expect more genes to back up placental morphogenesis. Back up genes will easily disintegrate, because natural selection cannot prevent its destruction by debilitating mutations.<sup>31</sup> Indeed, syncytin 1 is currently only functional in a limited number of genera, the ‘hominoids’ (man and the great apes). Syncytin 1 inhibition only reduced fusogenic activity by 40–50%, however.<sup>9</sup> This shows that additional placental-forming genes do exist and may have been independently lost in the course of species formation from baranomes. The remnants of the excess of placenta-forming genes can still be traced back in modern genomes using molecular biological techniques, such as FISH, PCR and DNA sequencing.

Finally, the loss of the fusogenic function of the syncytin gene is a prerequisite for the evolution of the HERV-W family, because an uncontrolled functional fusogenic protein would randomly fuse cells together and upset the development of a multicellular organism from a zygote. HERV-W accomplished this through the insertion of 12 nucleotides. This also implies that the evolutionary literature, which repeatedly refers to a 12 nucleotides deletion, has the order of events up-side-down. The original locus contained a functional syncytin gene, represented by the shorter form. The longer form of the gene is secondary and only present in the provirus (HERV-W). In fact, the defunct syncytin gene is the actual reason for the existence of the HERV-W family *per se*, since the dispersion of functional syncytin gene copies throughout the genome would be incompatible with life.<sup>19</sup> This is supported by the observation that the HERV-W family consists of collections of heterogeneous elements, but none of them contains the functional gene.

### Conclusion and discussion

It is well-recognized that many mammalian RNA viruses acquired genes from their hosts, since the captured genes render a reproductive benefit to the virus. For instance, the Rous sarcoma virus (RSV) picked up a piece of the mammalian *SRC* gene and integrated it into its genome.<sup>6</sup> To explain genetic novelties of mammals, such as syncytin, it is likewise argued that viral envelope genes may have been added to the genomes of mammalian hosts, where they adopted novel functions.<sup>9</sup> The latter view requires the existence of full-blown RNA-viruses as vectors to deliver the genes. The problem is

that, if RNA viruses did not form in the genome, nobody knows where RNA-viruses originated. The ‘VIGE-first hypothesis’ solves this problem, by postulating that RNA-viruses originated in mammalian genomes through exogenization of a particular VIGE known as endogenous retroviruses.

RNA viruses need a mechanism to enter (and leave) cells because they require the cellular machinery of eukaryotic cells for reproduction. A mechanism to evade the immune system is also of great help for RNA viruses to become successful replicators. The fusogenic and immune-suppressive genes are highly expressed in the mammalian placenta, which is therefore the perfect environment for RNA viruses to come into existence. The loose chromatin structure of actively transcribed genes is more accessible for molecular machinery and would be the preferred integration site of mobile genetic elements, such as *gag-pol elements*. Therefore, similar ‘proviruses’ may form independently in the same actively transcribed DNA regions of placental tissue of distinct mammals as autonomous integration events of *gag-pol elements*. ERV-W proviruses may hence rather be regarded as *previruses*, not as proviruses, because they are the forerunners of exogenous RNA viruses (not the remnants).

As argued above, the literature indeed reported at least six independent syncytin-acquisition events in the mammalian kingdom. I would like to reinterpret this observation as support for the ‘VIGE-first hypothesis’. Proviruses formed at least six times through integration in the syncytin locus and independent acquisition of the syncytin gene by a *gag-pol* mobile element. The capture of syncytin genes, which vary considerably with respect to their DNA sequences, would be the first step in the ‘evolution’ (or rather: genetic recombination) of novel RNA viruses. The reality of at least six distinctly different syncytin genes, which are not evolutionarily related, supports the independent origin of baranomes and is in full agreement with the creation history recorded in Genesis.

The ‘VIGE-first hypothesis’ may also explain why we find similar, but not the same, ERV-W provirus sequence in the same location of the genomes of the chimpanzee, the gorilla and the orangutan:<sup>19</sup> They integrated via recombination using the LTR present in the original locus and which is required for global syncytin gene expression. ERVs may have been designed including LTRs,<sup>6</sup> which facilitated the integration into DNA sequences containing similar LTRs, such as the one present in the syncytin locus. The observation that the mobile HERV-W, which lacks fusogenic activity, is specific for humans and the fact that all simians have the same DNA sequence reflecting

the functional syncytin gene in humans (which lacks 12 nucleotides), reduce “the problem of a gene attributed by an ancient RNA-viruses” to nothing more than a DNA sequence similarity phenomenon. And, as we all know, DNA sequence similarity (‘having the same genes’) may merely reflect common design, not common ancestry. Once more, the Darwinians were too eager to present ‘not-so-well-understood’ genetic similarity as evidence of universal common descent. And it convinced/confused a lot of our previous proponents. However, the VIGE first hypothesis allows for the complete understanding of the ERVWE1 locus, how it was invaded by transposable elements, and how a unique *previrus* (HERV-W) arose from it. The dynamics, the creativity and adaptive nature of—what is left of—originally created baranomes should never be underestimated. In a fallen world we might expect all sorts of unpleasant things to happen, including the recombination of novel RNA viruses from previously harmless VIGEs.

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