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On "genomenclature": A comprehensive (and respectful) taxonomy for pseudogenes and other "junk DNA"

(genomic nomenclature/genomic potential/adaptation/exaptation/nonaptation)

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ABSTRACT **Genomic nomenclature has not kept pace with the levels and depth of analyzing and understanding genomic structure, function, and evolution. We wish to propose a general terminology that might aid the integrated study of evolution and molecular biology. Here we designate as a "*nu*on" any stretch of *nu*cleic acid sequence that may be identifiable by any criterion. We show how such a general term will facilitate contemplation of the structural and functional contributions of such elements to the genome in its past, current, or future state. We focus in this paper on pseudogenes and dispersed repetitive elements, since their current names reflect the prevalent view that they constitute dispensable genomic noise (trash), rather than a vast repertoire of sequences with the capacity to shape an organism during evolution. This *pot*ential to contribute sequences for future use is reflected in the suggested terms "*pot*onuons" or "*pot*ogenes." If such a potonuon has been coopted into a variant or novel function, an evolutionary process termed "ex*apt*ation," we employ the term "*xapt*onuon." If a potonuon remains without function (*nonapt*ive nuon), it is a "nonaptation" and we term it "*napt*onuon." A number of examples for potonuons and xaptonuons are given.**

The term gene "evolved" from gemmule in Charles Darwin's theory of pangenesis in 1868 (1) via pangen (Hugo DeVries, ref. 2) to gene (Wilhelm L. Johannsen, ref. 3) at the beginning of this century. While Johannsen (3) used gene as a mere concept, 80 years later we know, in great detail, the structures and actions of thousands of genes. The gene has been dissected into smaller units, such as exons, introns, and a variety of regulatory elements, which have been named when they were anticipated, discovered, or characterized. However, genomes do not only consist of genes. Sequences located between and also within gene boundaries, accounting for a large portion of genomes in higher Eucarya, are not being addressed in a similar manner, partly due to the widespread opinion that these sequences are without function. As even more genomic sequences will accumulate, mainly through various genome projects, we will continue to be confronted with many structures where the name gene is not appropriate. The need for more generalized as well as more specialized (i.e., accurate) terms to address those sequences arises.

Here we propose to name all identifiable structures represented by a *nu*cleic acid sequence (DNA or RNA) as "*nu*ons." A nuon can be a gene, intergenic region, exon, intron, promoter, enhancer, terminator, pseudogene, short or long interspersed element (SINE or LINE, respectively), or any other retroelement, transposon, or telomer—in short, any unit from a few nucleotides to thousands of base pairs in length. This nomenclature is open-ended, for when a nuon becomes better defined (structurally, functionally, or by its origin) it can be specified by a prefix.

We do not propose to rename all existing elements, for example, to call a promoter a "promonuon." We would like, though, to address the process of gene amplification. On one hand, gene duplication by recombination has long been recognized as an important mechanism for evolutionary increase in complexity (4). On the other hand, genes duplicated or amplified by the tens to the thousands via retroposition (an event where RNA is reverse-transcribed into a DNA copy followed by insertion into the genome) mostly appear to lead into evolutionary dead ends. Consequently, they have been named in an ambiguous or even derogatory manner (e.g., pseudogene or "junk DNA"). Such names do not reflect the significance of retroposed sequences as large valuable assets for the future evolvability of species; and, as a result, it is more difficult to contemplate their significance, impact, and function (5–8).

Every duplicated gene (or nuon), whether generated by recombination or retroposition can become an active gene, or part thereof, potentially giving rise to a variant or even a gene with novel function—but may also become an inactive pseudogene (multiplications generated by recombination stand a better chance of active "life" since, in most cases, not only the coding region of a gene but also its control elements are duplicated). Recruitment of a variant gene into a new function may take millions of years and occur at various stages via transcriptionally or translationally inactive intermediates (see, e.g., ref. 9). In the silent stage, such genes would be termed "nonaptations" since they do not contribute to fitness at the time of their inactivity. However, the term nonaptation evokes uneasiness, for it is a "negative definition and can only record a feeling that the subject is lesser than the thing it is not" (5). Gould and Vrba (5) argued that "this feeling is wrong, and that the size of the pool of nonaptations is a central phenomenon in evolution," but stopped short of proposing a term for features without current fitness. Since such features have the option or *pot*ential of becoming functional in the course of evolution or, alternatively, may remain nonaptations, we will here introduce the term "*pot*-aptation." It follows that any duplicated or amplified gene or nuon is a "*pot*ogene" or "*pot*onuon." If over evolutionary time, as is indeed the case for most LINEs, SINEs, and pseudogenes, such potonuons never acquire a function in genomes (so far as we know), eventually becoming obliterated as genomic noise, they can be termed *non*apt*i*ve (5) nuons or "*napt*onuons." In contrast, potonuons that have been coopted for a function are ex*apt*ations (5) and can be termed "*xapt*onuons" or "*xapt*ogenes."

Gould and Vrba (5) coined the term exaptation for a vital concept that, curiously, had never received a name: functional features of the phenotype that were not built by natural selection as adaptations for their current role but were rather coopted from structures either built as adaptations for other

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Abbreviations: LINE or SINE, long or short, respectively, interspersed repeated element.

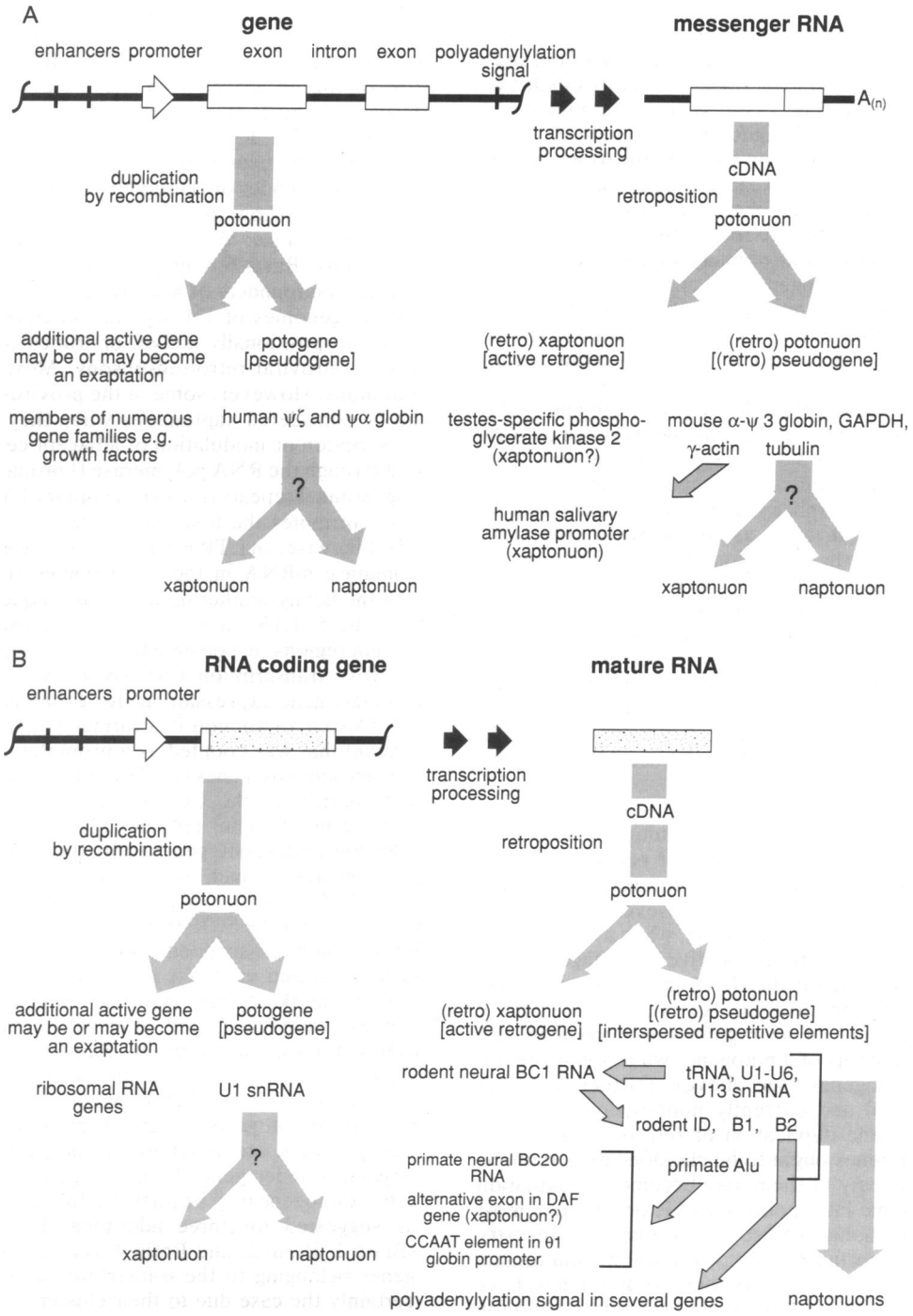

FIG. 1. Multiplication of genes and generation of additional nuons. (*A*) Protein coding genes. Any gene can be multiplied either directly via recombination (to the left) or indirectly via a transcribed RNA intermediate and reverse transcription into cDNA and subsequent integration into the genome (retroposition; to the right). The term nuon is more general than gene (see text) and in many cases these terms are interchangeable. However, a gene is always a nuon; a nuon is not always a gene. Any mechanism of gene multiplication creates a potonuon. Either the original gene or the duplicated one can potentially give rise to gene variants (therefore, initially both copies are potogenes or potonuons). In the case of duplication, for example, either copy may be exapted into a novel or variant function. The other then is usually conserved. Alternatively, at some point after duplication, a potonuon can become inactivated. It remains a potonuon, since it may be exapted at a later time (see lightly shaded double-headed arrow with question mark: any potonuon can either become a xaptonuon or naptonuon). Generally, the route of retroposition leads to more naptonuons than xaptonuons as indicated by the thinner part of the branched arrows leading to xaptonuons. Some of the previous designations are given in square brackets. In the lower third, examples are listed. An example for exaptation is indicated with an outlined arrow (e.g., contribution of a γ-actin potonuon to a promoter). It is not clear yet whether the product of the intronless testes-specific phosphoglycerate kinase gene (*Pgk-2*) has, in that tissue, already been exapted into a different function or whether it still possesses an identical function as the product of the intron containing *Pgk-1* gene; hence the question mark after xaptonuon. (*B*) RNA coding genes. Scheme is identical to that in *A*. Processed and nonprocessed RNAs can yield retroposons. In some cases, retroposons correspond only to part of the RNA template, such as the ID element. Although the majority of retro-nuons will end up as naptonuons (broad arrow, to the lower right), a number of examples are indicated where retro-nuons may avoid their usual fate of becoming naptonuons and instead are coopted into novel functions as xaptonuons (outlined arrows). For example, most likely a $tRNA^{Ala}$ potogene gave rise to BC1 RNA (outlined arrow pointing from right to left). This neuron-specific RNA also became, in some cases via intermediates, the founder of ID retro-potonuons (outlined arrow pointing to the lower right).

functions (feathers as initially thermoregulatory, but later coopted for flight) or arising nonadaptively. The term adaptation is then restricted, as Darwin himself had advocated and many evolutionists followed ever since, to features built by selection for their current role. In our genomic terminology, such conventional ad*apt*ive changes are "*apt*onuons," "*apt*ogenes," etc. We do not focus on them in this paper, since we are treating duplications that arise as redundancies (potonuons) and are then available for cooptation (xaptonuons). But we mention their status here for completion's sake.

The phenotypic contributions of many xaptonuons may be subtle; therefore, many xaptogenes will only be recognized as potogenes. If any of these nuons have been generated by retroposition, the prefix retro, as currently used, can, if needed for distinction, be added to yield the terms retro-potonuon, retro-naptonuon, retro-xaptonuon, retro-potogene, etc. In principle, any string of nucleotides in a genome could be addressed as a potonuon since it may be recruited as part of a novel coding region (10) or regulatory element. For example, in one β-thalassaemia globin gene a point mutation in intron 2 generates a new splice site and leads to the inclusion of 165 nucleotides of that intron as an additional exon (11). Although in this case the alteration of the mRNA has a deleterious effect, similar events can lead to exaptations. Thus the vast undefined sequences in a genome can be considered "potomass." Much of this potomass consists of randomized sequences contributed by naptonuons (never exapted potonuons) whose sequence similarity with their origin was, over time, annihilated by mutations. Here, we define potonuons (including naptonuons) as entities with identifiable ancestry. If the ancestry of a sequence is no longer traceable, it is considered part of the genomic potomass.

The following examples (see also Fig. 1) should clarify this nomenclature: If a gene is duplicated or multiplied, both new and existing copies become potonuons or potogenes, since any of them equally has the potential or option to evolve into a novel nuon or gene. In some cases, however, mere amplification acts as an immediate adaptation, when availability of more gene product constitutes a selective advantage. This is almost certainly the case for the rRNA genes (up to several hundred copies in higher Eucarya). An extreme case occurs when an entire genome of an organism is duplicated and every gene has the status of a potogene, while some already may qualify as aptogenes (see above). Furthermore, the numerous debilitated and currently nonfunctional pseudogenes derived by gene duplication or retroposition from a variety of founder genes ought to be classified as potonuons or potogenes, since any of them may become an adaptation or exaptation at some later point in its history (though most will remain nonfunctional until so altered that their ancestry can no longer be ascertained—i.e., they will be and remain naptonuons until they blend into potomass). Potonuons have been generated both by recombination and retroposition in the case of globin genes (for example, the intron-containing human Ψζ and Ψα potogenes or the mouse α–Ψ3 retropotogene; for review, see ref. 12). Genes transcribing tRNAs and other small RNAs (e.g., small nuclear RNAs U1–U6, 5S rRNA, or 7SL RNA) can be founders, source genes, or master genes for large families of potonuons (for review, see ref. 13), such as primate *Alu*, rodent B1, B2, or ID, and rabbit C repetitive elements. Notably, segments from rodent B2 or rabbit C potonuons (both tRNA-derived; ref. 14) can serve as polyadenylylation signals in new locations at the 3′ end of various genes (15–18) and, therefore, ought to be considered xaptonuons. LINEs (19), such as L1 repetitive elements, are mostly potonuons. However, the U-rich portion of a poly(A) addition signal was contributed to the 3′ end of the mouse thymidylate synthase gene, activating a cryptic poly(A) addition sequence (AUUAAA), by a truncated L1 element (20), which is, therefore, a xaptonuon.

Parts of *Alu* potonuons may also give rise to new protein coding exons (e.g., ref. 21) and, if contributing to fitness, will become xaptonuons. Neural BC200 RNA in primates is a retro-xaptogene derived from one of the *Alu* potonuons (J. A. Martignetti and J. B., unpublished data), which in turn are derived from 7SL RNA (23). A tRNA-derived potonuon is the ancestor of the neural BC1 RNA in rodents. BC1 RNA, in turn, is the founder of ID repetitive potonuons (24). The last two examples show that the process can be cyclical: genes spawn potonuons, the majority of which will end up as naptonuons. But a few may become xaptonuons, which, in turn, can be founders of new waves of potonuons.

Many genomes of Eucarya are interspersed with intact, even transpositionally active, or truncated copies of endogenous retroviral retrotransposons. Most of the latter are potonuons. However, some of the provirus-related elements can be considered xaptonuons when they contribute to the transcription or modulation of adjacent cellular genes mediated through the RNA polymerase II promoter of the proviral long terminal repeats (LTRs). A solitary LTR is the promoter and contributes the first exon of the rat oncomodulin gene (25). Likewise, an LTR is part of a new promoter transcribing aromatase mRNA in the extragonadal tissues of chickens with the henny-feathering trait (26). Sequences downstream from the 5′ LTR on *gypsy* retrotransposons in *Drosophila* contain regions responsible for positive and negative control of *gypsy* transcription (27); some *gypsy* xaptonuons may modulate gene expression at, for example, the yellow locus (28). Also a xaptonuon is a former γ-actin potonuon (pseudogene) that was coopted as a promoter element for human salivary amylase genes (29, 30) or the truncated *Alu* element that contributes the CCAAT promoter element to the θ1 globin gene of higher primates (31).

Protein coding potogenes (sometimes addressed as "active pseudogenes"‡) such as the rodent insulin I gene, *Pgk-2*, *Pdha-2*, *Zfa*, and *N-myc2* (for summary, see ref. 8), as well as the gene for the SCIP transcription factor (32) and the gene for carcinoma-associated antigen GA733-1 (22), have also been generated via RNA intermediates, since they still exhibit hallmarks of retroposition. After this, they remained active or were reactivated, often with amino acid changes and different tissue distribution. Should it turn out that the increased gene dosage, or expression in different cell types, has lead to a different functional phenotype, one may define these retro-potogenes as retro-xaptogenes, even if their protein products are functionally indistinguishable from the original founder gene. Like any gene, a retro-potogene or retro-xaptogene may be further duplicated via recombination as suggested for three additional POU domain proteins (Brain-1, Brain-2, and Brain-4; ref. 33) and genes and potogenes belonging to the α-interferon gene family (34), as is certainly the case due to their clustered arrangements.

An interesting case involves eye lens crystallins (35, 36, 40) and major soluble proteins of the corneal epithelium (37, 46, 47). For example, although many taxon-specific crystallins have structural roles in the refractive properties of the lens, they can be identical to house-keeping enzymes such as lactate dehydrogenase B4/ε-crystallin, α-enolase/τ-crystallin, or argininosuccinate lyase/δ2-crystallin and, occasionally, as in the three examples above, still be products of a single gene (38, 39, 48, 49). Although in that case the corresponding gene is neither a xaptogene nor a potogene, as

‡This occasional oxymoronic use illustrates the previous gap in terminology and the need for a well-articulated concept of exaptation. How can such a "negative" entity as a pseudogene be active? Once we acknowledge the idea of cooptation, the paradox disappears. The negative terminology of pseudogenes and junk DNA should also disappear. Junk for what? For now perhaps, but for all conceivable future time and modification?

the gene has not yet been duplicated, the corresponding lens protein can be termed a "xaptoprotein."

A compelling and well-documented example of the retropositional route of gene amplification among genetic compartments is the nuclear transfer of the mitochondrial *coxII* gene in legume plants (41), since the organelle RNA undergoes posttranscriptional editing. The new nuclear gene exhibits a much closer resemblance to the edited RNA than to the corresponding mitochondrial DNA. Clearly, this transfer involved reverse transcription of mitochondrial coxII RNA followed by integration into the nuclear genome. The timing of the different phases during this transfer is also well understood, by comparative analysis of the presence and activity of nuclear and organelle *coxII* genes in the Papilionoidae subfamily of legumes. The mitochondrial *coxII* gene has transferred into the nucleus of a common ancestor of pea (*Pisum sativum*) and other legumes (*Glycine max*, *Phaseolus vulgaris*, *Vigna radiata*, and *Vigna unguiculata*), thus initially qualifying both the retroposed nuclear and mitochondrial founder gene as potonuons. Although in pea the nuclear gene is present but inactive (remaining a potonuon, and in the future probably ending up as a naptonuon or, if coopted into a new function, as a xaptonuon), in a common ancestor of the genera *Glycine*, *Phaseolus*, and *Vigna*, it had been switched on with a concomitant inactivation of the mitochondrial gene (and the organelle gene has become a potonuon). The activated nuclear gene in *Glycine*, *Phaseolus*, and *Vigna* has lost its potogene status, since (due to silencing of the original mitochondrial gene), there is selective pressure to maintain coxII function by import of the nuclear gene product into mitochondria. In a further step, the mitochondrial gene was deleted in an ancestor of the two *Vigna* species. In *Vigna*, therefore, the nuclear *coxII* gene started its existence as a potonuon, but instead of becoming a naptonuon or xaptonuon, it ended up as an aptonuon (for its function is apparently unchanged from that of the original mitichondrial ancestor). Now that the *coxII* gene is encoded by the nuclear instead of the mitochondrial genome, its transcript is adapted to nuclear processing and cytoplasmic translation and its product is adapted to intercompartmental transport by acquisition of an intron and an associated transit peptide exon (41) for organellar localization. Analogous adaptational events are well-documented with the gene encoding chloroplast ribosomal protein L22 (*rpl22*), which was transferred from the chloroplast to the nucleus in a common ancestor of all flowering plants. In legumes, the nuclear gene later acquired a second exon encoding a putative N-terminal transit peptide and an intron, separating the 5′ exon from the chloroplast-derived core of the gene (42).

The retropositional transfer of the *coxII* gene and the recent discovery of a human *LINE1* master gene (43), including the demonstration of reverse transcriptase activity associated with the protein encoded by one of the *LINE* open reading frames (44) and the potential use of this reverse transcriptase in retroposition of any cellular RNA, therefore, is of general significance. It is now reasonable to assume that many of the products of intercompartmental gene shuttling as well as numerous functional intronless genes[§] such as members of the guanine nucleotide binding protein-coupled receptor family (8, 45), which are examples of intranuclear transfer, are direct retro-xaptogenes or were generated through a retro-xaptogene intermediate, indicating that the retropositional route of gene amplification may indeed be just as important for generating diversity as conventional duplication by recombination (8).

This nomenclature unifies several processes shaping genomes and renders comprehensible and addressable the significance of exaptation (5) and potaptation and the role of genomic elements that were formerly disregarded. The scientific community will be further alerted to the potential of potonuons and xaptonuons in evolution. We are well aware that terminological papers do not form a popular genre in science (and we recognize that colleagues might tend to ignore our work for this reason). But taxonomies are conceptual structures, theories of order, not mere (and dull) hat racks or pigeonholes for accommodating the obvious facts and phenomena of nature. Such phenomena often become visible only when placed with useful names into proper order. In this case, we have long felt that the current disrespectful (in a vernacular sense) terminology of junk DNA and pseudogenes has been masking the central evolutionary concept that features of no current utility may hold crucial evolutionary importance as recruitable sources of future change. Indeed, such vital notions as evolutionary "breakthroughs," advances in complexification, etc., probably bear little relationship to conventional adaptation (as usually assumed up to now) but are crucially dependent upon the size and extent of currently nonaptive pools of potential exaptation—the very material that now receives derogatory names, thus leading to our inattention. The adoption of our unified, comprehensive, and conceptually neutral taxonomy would foster and speed the current integration of molecular and evolutionary studies—a consummation that all biologists must devoutly wish.

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[§]Genes exhibiting a single intron in, for example, the 5′ untranslated region may also be retro-xaptogenes, generated by reverse transcription of an incompletely processed mRNA or acquisition of an intron after retroposition (see also text and ref. 42). Intron insertion may be advantageous to reduce the size of an otherwise large mRNA. This constellation may be frequent in retro-xaptonuons, since in the new location an active recruitable promoter may only be present at a great distance. Over time, such introns may be reduced in size.

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