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OPINION ARTICLE

Tripartite genome of all species [version 1; peer review: 1 approved, 2 approved with reservations]

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Abstract

Neutral theory has dominated the molecular evolution field for more than half a century, but it has been severely challenged by the recently emerged Maximum Genetic Diversity (MGD) theory. However, based on our recent work of tripartite human genome architecture, we found that MGD theory may have overlooked the regulatory but variable genomic regions that increase with species complexity. Here we propose a new molecular evolution theory named Increasing Functional Variation (IFV) hypothesis. According to the IFV hypothesis, the genome of all species is divided into three regions that are 'functional and invariable', 'functional and variable' and 'non-functional and variable'. While the 'non-functional and variable' region decreases as species become more complex, the other two regions increase.

Keywords

Increasing Functional Variation hypothesis, Maximum Genetic Diversity theory, Neutral theory, Evolution, Genome architecture, Gene regulation

Open Peer Review

Approval Status ? ✓ ?

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version 1	?	✓	?
19 Feb 2016	view	view	view

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Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

The structure and function of the genome have been a major question that all researchers want to solve. The current popular view of the genomic structure is represented by the neutral theory. The neutral theory states that the majority of the genome is variable and neutral¹. The variable property of these genomic regions would not change as the complexity of species increases (Figure 1).

Figure 1. Comparison of IFV, MGD, and neutral theory. While the neutral theory and MGD theory analyze genome structure as bipartite, the IFV hypothesis adds an additional region which is the variable and functional gene regulatory region. As species complexity increases, the variable region of the genome would stay as variable according to neutral theory. While in MGD theory, as species complexity increases there would be less variable region. Unlike MGD theory, IFV hypothesis states that the functional variable region which contains gene regulatory elements would also increase with species complexity.

While in recent years, another theory called Maximum Genetic Diversity (MGD) provided unprecedented insights into the genome structure²⁻⁵. The MGD theory originated from blasting some conserved proteins such as cytochrome C and hemoglobin of different species. By computing the changeable sites of each species³, Huang found that more complex species have less changeable sites in certain regions of the genome. Thus, MGD theory states that as the complexity of species increases, the genome would have more invariable regions and less variable regions (Figure 1).

IFV hypothesis

Here we proposed the Increasing Functional Variation (IFV) hypothesis inspired by both the MGD theory² and our recent work on human genome architecture⁶. Recently, based on co-localization of various genomic features we divided the human genome into three parts, referred to as gene enriched (Genic) zones, gene regulatory elements enriched (Proximal) zones and non-functional features enriched (Distal) zones⁶. We regard the Genic zones as mainly functional and invariable, and the Distal zones as mainly non-functional and variable. The Proximal zones that compose 31% of human genome contain the majority of gene regulatory elements including transcriptional factor binding sites (TFBSs) and are at the same time enriched with conserved indels. These features make Proximal zones functional and variable. It has been proven that as the complexity of species increase, there would be more gene regulatory region in the genome. Based on these two points, we propose that as the complexity of species increases, this variable part of the genome which contains functional regulatory elements would also increase. We call it the Increasing Functional Variation (IFV) hypothesis. Besides the variable gene regulatory region, the other part of the genome can be divided into two parts, the functional and invariable region and the non-functional and variable region. The alteration of these two parts with species complexity can be explained by MGD theory (Figure 1). What the MGD theory lacks and IFV hypothesis complements is the existence of the variable and functional gene regulatory region in the genome. And according to the IFV hypothesis, as species complexity increases, the variable part of the genome would not simply decrease as stated by MGD theory. The differences between IFV hypothesis and MGD theory have been illustrated in Table 1.

Table 1. Comparison of IFV hypothesis and MGD theory.

	IFV	MGD
Genome architecture	Tripartite	Bipartite
Types of variable region	Two	One
Alteration of variable region as species complexity increases	Functional variable region increases while non-functional variable region decreases	Decreases

Conclusions

MGD theory has refuted the idea stated by the neutral theory that the majority of the genome is neutral and variable among all species. Instead, it proved that the variable region of the genome would decrease as species become more complex.

However, MGD theory has its own limitation as pointed out by Ho shortly after the publication of MGD. As Ho has mentioned in her book⁷, more complex species have more sequence diversity, which is needed for precise regulation of local somatic expression. Ho also stated that although MGD theory solved the paradoxes in molecular evolution, the diversity of complex species at somatic level can't be explained by it. Our recent study⁶ on human genome architecture discovered not only variable but also functional regions of the human genome. In an attempt to provide a more comprehensive view of genome structure and molecular evolution, we developed the IFV hypothesis based on our discovery of the variable property of the gene regulatory region.

Why would we develop this tripartite model of genome architecture across all species? As the ancient Chinese philosopher Lao Tzu

stated in *Tao Te Ching* thousands of years ago that “three engenders the myriad things”, which means “three” is the root of all things. If the truth of the universe is universal, we believe that the consistency between our tripartite genome architecture of all species and Lao Tzu's philosophical thinking is not a coincidence.

Author contributions

TBH & MPL jointly conducted this work and wrote the manuscript.

Competing interests

The authors declare there is no conflict of interest.

Grant information

MPL & TBH are recipients of MD-PhD scholarship from Hong Kong University of Science and Technology. This work was supported by the grant to TBH from Central South University, China (2282013bks118).

I confirm that the funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Alfredo Pulvirenti

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The paper, in its current version, presents several major limitations.

The authors should provide more details about the theories.

Furthermore, the rationale behind their IFV hypothesis should be given in a deeper way. Examples supporting the conclusions are strongly needed. The authors should also highlight the limitations and the opportunities of this hypothesis.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 03 May 2016

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Rahul Banerjee

Crystallography and Molecular Biology Division, Saha Institute of Nuclear Physics, Kolkata, India

The manuscript by Long and Hu is of considerable interest in the field of evolution of genomes. However the authors could consider the following points to improve the quality of the manuscript

:

1. Is there any numerical measure of species complexity ?

2. On page 2, column 2, line 6

'Huang found that more complex species have less changeable sites in certain regions of the genomes.'

It would be nice if some more details could be included with regard to these sites.

3. The authors should be more elaborate as to why they considered the Genic zones to be mainly functional and invariable and the Distal zones as mainly non-functional and variable, and the Proximal zones functional and variable.

4. The note about Lao Tzu was also quite attractive and added some philosophical charm to the scientific note.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 29 March 2016

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Shaillay Dogra

Vishuo BioMedical Pte Ltd, Singapore, Singapore

It would be nicer for the readers if there was more explanation and discussion in the text on the various different theories, what they imply, their pros and cons etc. Currently, it requires some background reading on these topics for the not so well-informed reader.

A detailed discussion of the basis of the IVF hypothesis, the basis of the proposals, its criticism etc. is suggested for a greater understanding of the author's ideas.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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