The highly-variable enhancers in the intra-specific morphological diversity

Minkina Elena, Akberova Natalia, Shagimardanova Elena

Institute of Fundamental Medicine and Biology, Kazan Federal University, Kazan, Russian Federation
e-mail: minkinaea@gmail.com

Adameyko Igor

Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden

Department of Molecular Neurosciences, Center for Brain Research, Medical University Vienna, Vienna, Austria

Gusev Oleg

Institute of Fundamental Medicine and Biology, Kazan Federal University, Kazan, Russian Federation

RIKEN, Yokohama, Japan

Enhancers are a short DNA regions that increase the transcription level of certain genes. To date, increased interest in enhancers has caused an increase in the amount of data on their localization, target genes and the functional role of enhancers in different tissues or conditions. Also become clear that genetic variants associated in enhancers can lead to diseases. However, sequence changes in the enhancer are mostly less critical, as in protein-coding or promoter regions, since a change in the function of the enhancer can be compensated for by functionally overlapping of cis-regulatory elements [1]. Therefore, it is believed that the fine-tuning of the gene expression patterns carried out by enhancers can lead the morphological divergence between related species. This implies that enhancers that are hyper-variable within a species must also could be involved in intraspecific variability, such as the craniofacial shape in humans.

The variety of the face shape is one of the distinctive features of a human, and understanding of normal variability in the face morphology have significant implications in social, clinical and criminology fields. The human craniofacial morphology is largely inheritable, but the genetic variants in genes likely contribute with relatively small effect size to the normal face variation [2]. A recently studies of craniofacial [3] and neural crest [4] enhancers in humans, chimpanzees and mouse has provided a promising platform for understanding such human morphological features and the contribution of enhancers variability to phenotypical changes.

In the current study we combined polymorphisms data with the predicted human enhancers

from two fundamental projects, as well as a enhancers set identified in a study of human embryonic craniofacial tissues. We combined overlapped enhancers to get non-redundant set (1,515,955 in total) and linked them with protein-coding genes (Gencode v19), using known enhancer-target pairs and Chia-Pet, HiChip and eQTL data. In total we found 2,771,146 enhancer-gene links with 56.1 % enhancers and 98.6 % protein-coding genes.

We next measured the SNP density in enhancers, defined as the ratio of the variants number to the enhancer length, and normalized to the average variants ratio for the whole genome to evaluate enhancers intraspecific variability. The Spearman's correlation tests between enhancers properties showed no correlation for the intraspecific variability of enhancer regions with the interspecific conservation between vertebrates and between primates, as well as with number of linked genes per enhancer, that can imply the presence of some positive selection for variable enhancers in human population. It also supports the idea that hyper-variable enhancers can participate in fine tuning of traits without disrupting the functionality of essential regulatory networks.

We expect that a subsequent systematical and in-depth analysis of the structure of these enhancers in various human populations will provide an additional understanding of their role in the development and shaping of facial features.

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