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Molecular networks and the evolution of human cognitive specializations

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Inroads into elucidating the origins of human cognitive specializations have taken many forms, including genetic, genomic, anatomical, and behavioral assays that typically compare humans to non-human primates. While the integration of all of these approaches is essential for ultimately understanding human cognition, here, we review the usefulness of coexpression network analysis for specifically addressing this question. An increasing number of studies have incorporated coexpression networks into brain expression studies comparing species, disease versus control tissue, brain regions, or developmental time periods. A clearer picture has emerged of the key genes driving brain evolution, as well as the developmental and regional contributions of gene expression patterns important for normal brain development and those misregulated in cognitive diseases.

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Introduction

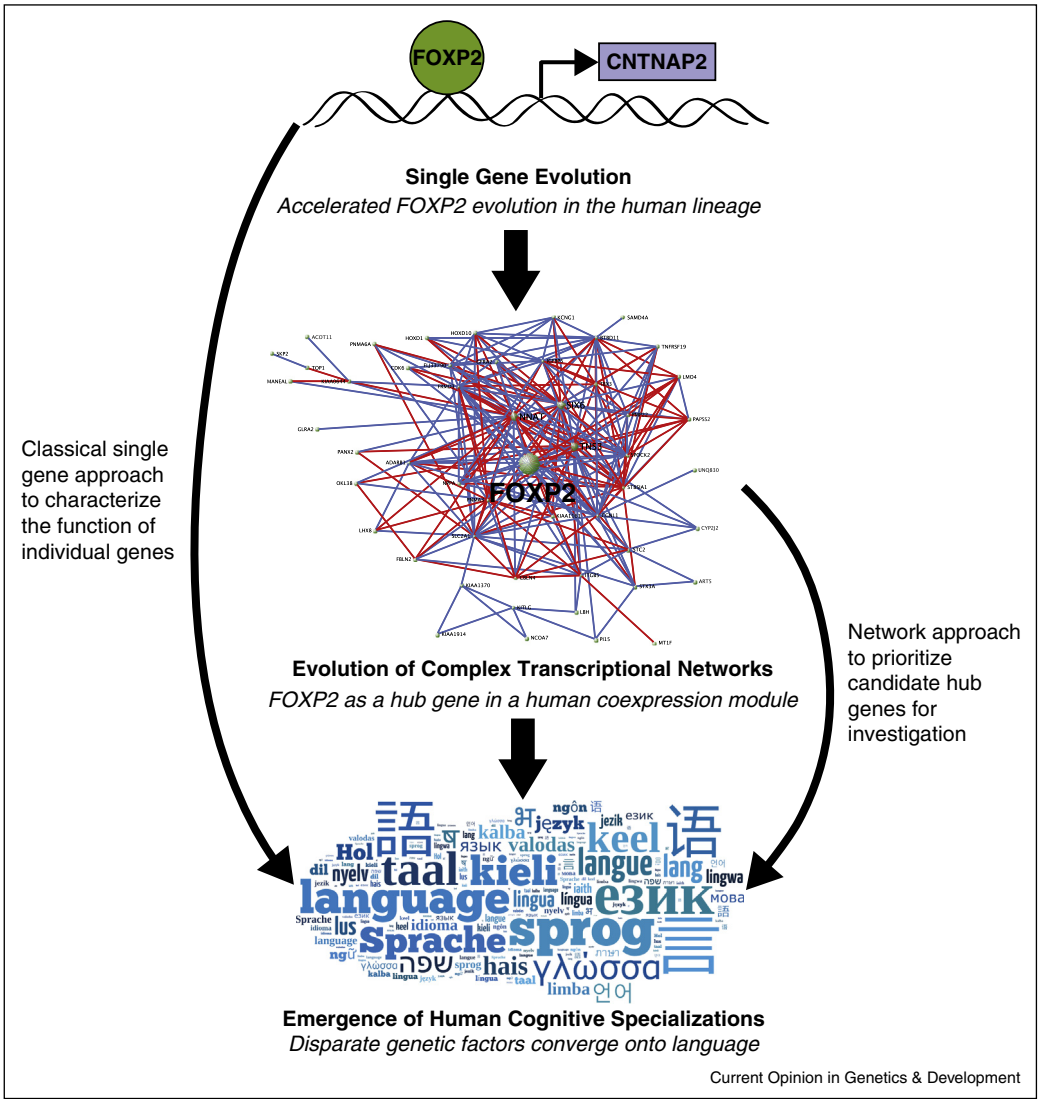
The evolution of human cognitive specializations has been the subject of human ruminations for perhaps as long as the evolution of self-reflection itself. Here, we consider some of the outstanding questions in the field of human cognitive evolution that can be addressed through the comprehension of evolved molecular networks in the brain. An important unanswered question is how genes and, perhaps more importantly, how gene networks have evolved to impart cognitive specializations in humans. What are the key players in human gene networks that are important for specific specializations, such as language?

To begin, one must address whether genetic and/or genomic changes are important for cognition. Most cognitive diseases (e.g. autism and schizophrenia) have a strong genetic component, and there is significant evidence that the evolution of the human genome has been permissive for both cognitive evolution as well as increased risk for developing cognitive diseases [1–5]. Are these genes disrupted in cognitive diseases under selective pressure, and are they important from an evolutionary standpoint?

There are precedents for changes in single genes at the DNA level affecting cognitive specialization. For example, it has been suggested that two human-specific amino acid changes in the transcription factor *FOXP2* are under positive evolutionary selection due to the role of FOXP2 in human speech and language [6]. When the human-specific modifications of FOXP2 were knocked-into the endogenous mouse *Foxp2*, these animals displayed a number of behavioral and pathological changes including alterations in ultrasonic vocalizations [7]. These two amino acids are also sufficient to direct an altered transcriptional program [7,8]. Furthermore, beyond evolution of protein sequence, changes in the regulation of gene expression will likely have profound consequences relevant to cognitive function [9]. For example, recent analysis of differential DNA promoter methylation between humans and chimpanzees has implicated epigenetic control of genes associated with disorders highly prevalent in humans such as autism, neural-tube defects, and alcohol dependency [10].

We propose that studying the emergence of altered gene networks may provide greater insight into cognitive evolution than considering the modifications to only a handful of genes. Scale-free networks exist across multiple domains, ranging from bacteria to the Internet [11,12]. The prevalence of such networks across nature reinforces the idea of using gene networks as an improved model for understanding relationships among gene expression changes. In contrast to differential expression approaches, which focus on how single genes change between conditions, a network approach allows for the rapid prioritization of the most interconnected genes, or hub genes, from complex datasets, such as those often generated across tissues and species (Figure 1). In addition, the importance of these hub genes has been validated through the assessment of network structure upon removal of expression of a hub gene [13]. In other words, if one attempts to build a network using expression data from a knockout animal for one of the hub genes, the network essentially falls apart [14]. While the majority of this review will focus on one particular technique, Weighted Gene Coexpression Network Analysis (WGCNA, see Box 1), for building

Figure 1



Understanding the interaction of individual genes at a network level in the evolution of cognitive specializations. Here, we illustrate that compared to a single gene approach (e.g. *FOXP2* regulation of specific cognitive-related genes such as *CNTNAP2*, contactin associated protein-like 2), network analysis can uncover more subtle and additional candidate genes which could exert important influence on the higher-order function in question (e.g. language). Thus, the incorporation of a coexpression network approach in evolutionary comparisons provides increasingly more information than single gene approaches.
The network image is modified from Konopka *et al.* [8].

genomic networks, there are many other methods for achieving a similar goal, such as the transcription-factor-focused weighted topological overlap (TF-wTO), Detecting Association With Networks (DAWN), Pearson, Spearman, or Kendall correlations, and Rank Theil-Sen [15,16,17•,18•,19,20,21] (see Box 2).

Comparative networks across species

Although hundreds of differentially expressed genes between human and other species have been identified by directly comparing gene expression in the brain [22–25] (for more details see the review by Somel in this issue), translating these findings into meaningful functional distinctions between species has been difficult. Comparing genomic data in humans with those of our closest genetic relatives on a network level, in contrast, may provide a more straightforward approach to identifying networks important for human-specific cognitive specializations. WGCNA offers an unbiased view of relationships within gene networks and has been used to directly test this idea.

The first application of WGCNA to address human cognitive evolution compared gene coexpression networks in human and chimpanzee brains [26•]. By using data from