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Revealing gene regulation and associations through biological networks

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ABSTRACT

Traditionally, over the last 10,000 years, agriculture has relied on natural biological evolution and careful selection of plant varieties by farmers that was used as the founder material by plant breeders in the last 150 years for further genetic improvement. Plant breeders played an important role mainly by introgression of a trait of interest, through the transfer of genetic loci, into an elite crop line that exhibits high-yield performance across a wide range of conditions. Modern agriculture has relied on the use of biotechnologies and molecular biology to improve marker development and aid in the discovery of candidate loci or genes associated with desirable traits, thereby reducing the time required for selective breeding.

In this review, we briefly describe the evolution of the methods used to identify candidate leads (gene, loci or regulatory regions) for crop improvement, starting by quantitative genetic methods. The development of co-expression and molecular networks will be described. It will be shown how network analysis can reinforced the discovery of candidate genes/loci more rapidly and with higher confidence. These improvements will serve to accelerate genetic engineering and molecular breeding as modern agriculture confronts the challenging times ahead, with the increase of abiotic stresses for crops as drought, heat, soil high salinity or waterlogging.

Without taking in account possible losses due these growing stresses, the increase in crop yields needs to be significantly accelerated to feed the growing world population, following the FAO previsions.

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1. Period preceding network analysis

1.1. Methods used before the advent of network analysis

To increase yield and stress tolerance, it is essential to understand how crop phenotypes were improved during the domestication process. To this end, researchers have investigated how early societies domesticated wild plants, e.g., by adapting teosinte into a high-yield crop like maize [1]. During domestication, diversity was dramatically reduced, as rare alleles in the population declined in favor of more frequent ones [2]. Awareness of the reduction in the size of the gene pool led to the idea that exploring the wild ancestors of crop plants could help to recover rare alleles. These rare alleles might be useful in improving modern crop varieties. According to simulation studies in maize, only 2–4% of the genome has been actively selected over the course of domestication [2]. This finding highlights the tremendous potential of using the wild varieties or ancestors of extant crop plants to recover lost genetic diversity. Such (re) discovery of lost alleles could help meet challenging breeding goals such as conferring tolerance to drought, salinity, and other stresses [1,2].

Historically, the methods of choice for identifying candidate loci/genes primarily involved identification of quantitative trait loci (QTLs). In such analyses, phenotypic observations are associated with genetic region segregation, taking advantage of linkage disequilibrium.

In crop species, one aim of QTL analysis is to define genetic regions responsible for architectural and stress-related phenotypes, e.g., the response to water deficit and the efficiency of nitrogen use [3–5]. However, these genetic regions can be very large, due to the size of the QTL confidence intervals. To discover the causal genes, it is required to manually parse ~100 candidate genes per locus. Sometimes, the number of candidate genes can be reduced using fine mapping, by finding additional makers within the QTL interval. Nevertheless, the process of narrowing a QTL is highly time-consuming [6]. Moreover, the outcome is not always guaranteed, as it depends upon the rate of crossing-over in the

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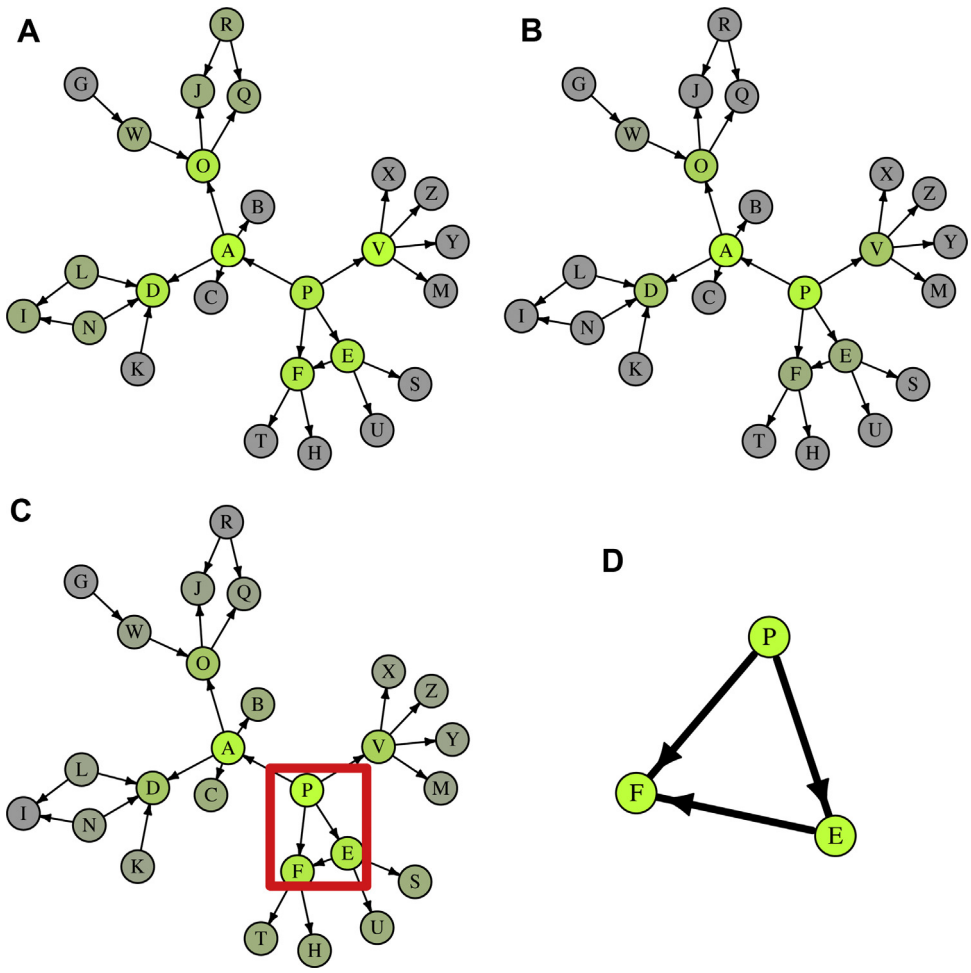

Fig. 1. Centrality and network motifs.
A random network is represented (A–C) mimicking a possible biological network. The greenest nodes represent the genes with the higher connectivity centrality (A), betweenness centrality (B) and Eigen vector centrality (C). Node A has the highest betweenness centrality (B) whereas node P has the highest Eigen vector centrality (C). It shows how a researcher can act on either node A or P in function as the desired action shown (e.g. Fig. 2). The grey nodes have a lower value for each of these respective centralities. A close-up from the red box (C) of a network building block called network motif is shown in D. It represents a Feed Forward Loop.

species under study, as well as the identification of new molecular markers.

1.2. Global expression data

1.2.1. Transcriptomic analysis

Following the emergence of microarrays in the mid-1990s, transcriptomic experiments have become a predominant method for discovering candidate genes related to phenotypes of interests [7]. Next-generation sequencing made the direct count of transcript possible based on the number of sequencing reads. Before, only relative expression levels were obtained in microarray experiments by converting level of fluorescence on chips [8,9]. RNA-seq also enabled the study of the whole transcriptome, independent from a fully sequenced genome, as well as detailed analysis of gene alternative splicing forms [10–16]. One major application of transcriptomic technologies is to reveal genes differentially expressed, potentially responsible for a phenotype change, for instance between mutant and wild type samples. As technology improved, the production of comprehensive gene expression resources across a large catalogue of tissues, developmental stages became possible. Named transcriptome atlases, these resources are used as a base to obtain insights into biological processes and gene function for *Arabidopsis* (e.g. AtGenExpress), maize (Maizeatlas), or rice (e.g. RiceXPro) [17–24]. At a single tissue level, the tissue and longitudinal root atlas was produced using a combination of microarrays, cell type-specific protoplasts and root cross sections [20]. Combining these 2D analyses gives a 3D expression map in *Arabidopsis* roots. Recent work in maize that has used RNA-seq in a combination of time-course and mutant analyses has provided greater insight into the regulation of maize meristems [25,26].

However, these lists derived from transcriptomic analyses, do not immediately provide a clear insight into gene regulation. Rather, they allow selection of candidate genes that can be subsequently validated. Further reverse genetics approaches need to be used to identify mutant phenotypes. If the predicted phenotypes are observed in the mutant, novel variants in this location can be searched for in natural variation or germplasms for plant breeding improvement. Mutant analyses have some drawbacks: for example, non-conditional mutants exert their effects across all tissues and developmental stages, potentially resulting in undesirable interactions that are not directly linked to the phenotypes of interest [27,28].

2. Type of networks

2.1. Network theory

A network comprises all possible links existing between members of a community (Fig. 1). These members could be a group

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