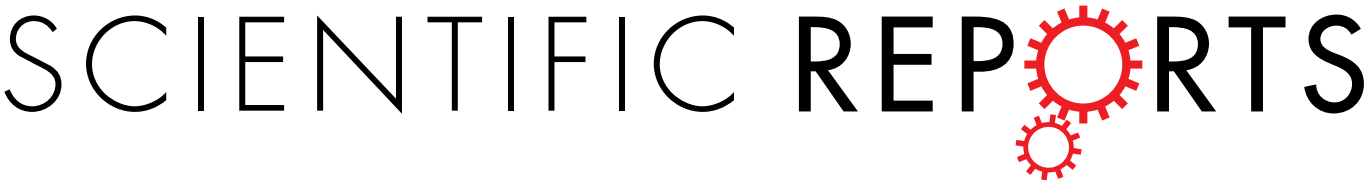

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Comparative genomic analysis of novel *Acinetobacter* symbionts: A combined systems biology and genomics approach

Received: 21 March 2016
Accepted: 08 June 2016
Published: 05 July 2016

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The increasing trend of antibiotic resistance in *Acinetobacter* drastically limits the range of therapeutic agents required to treat multidrug resistant (MDR) infections. This study focused on analysis of novel *Acinetobacter* strains using a genomics and systems biology approach. Here we used a network theory method for pathogenic and non-pathogenic *Acinetobacter* spp. to identify the key regulatory proteins (hubs) in each strain. We identified nine key regulatory proteins, guaA, guaB, rpsB, rpsI, rpsL, rpsE, rpsC, rplM and trmD, which have functional roles as hubs in a hierarchical scale-free fractal protein-protein interaction network. Two key hubs (guaA and guaB) were important for insect-associated strains, and comparative analysis identified guaA as more important than guaB due to its role in effective module regulation. rpsI played a significant role in all the novel strains, while rplM was unique to sheep-associated strains. rpsM, rpsB and rpsI were involved in the regulation of overall network topology across all *Acinetobacter* strains analyzed in this study. Future analysis will investigate whether these hubs are useful as drug targets for treating *Acinetobacter* infections.

Acinetobacter is a Gram negative nosocomial pathogen[1] that causes a variety of infections in humans ranging from respiratory failure, ventilator associated pneumonia, bacteremia and wound infections[2]. The major species of *Acinetobacter* associated with nosocomial infections are *A. baumannii, A. nosocomialis, A. pittii A. johnsonii* and *A. lwoffii*[3]. Systems biology is the study of an organism, viewed as an integrated and interacting network of genes, proteins and biochemical reactions, that form the functional units capable of operations needed for cell and tissue/organ level physiological function[4]. Protein-protein interaction (PPIs) network analysis is a valuable systems biology tool for identifying drug targets and functional mechanisms[5]. PPIs can be used to elucidate the cellular events that maintain physiological stability and integrity. Using whole genome data, we have constructed protein-protein interaction networks for four strains of *Acinetobacter spp.* isolated from different animal intestines to determine the how these networks vary across environments. To delineate differences, we employed hierarchical network theory to quantify the structural properties of each network, such as the emergence of modules/communities and sparsely distributed hubs[6,7], and self-organized working principle[8]. The emergence of modules/communities may correspond to independent functions obeying their own laws, with activities being nonlinear in nature[9]. The sparsely distributed hubs may interfere and control network stability within the community[9] as well as other communities. Hubs and highly connected proteins play a crucial role in biological networks[10].

We have sequenced and assembled the genomes of 3 *Acinetobacter spp.* strains (SFA, SFB and SFC) isolated from sheep feces, and one strain (HA) isolated from the gut of a 5th instar larva of polyphagous insect, *Helicoverpa armigera*. A hierarchical protein-protein interaction network (PPI) was constructed, and subnetwork/modules analyzed, to identify regulatory proteins important for cellular physiological processes. Key proteins are defined as randomly placed, with important functional roles and a high degree of interactions[11,12] in each isolated strain. The STRING v10 database for *A. lwoffi and A. johnsonni* was used to as a basis for building the PPI network of the four novel strains.

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