and shape, the simplicity of Maire and Youks' mechanism could make it of general importance in natural systems.

Establishing spatial collectives may be of importance in the structural formation of tissues, bacterial communities, and ecosystems. The presented framework shows how individuals can tune their role in those processes and thus the processes themselves and therefore provides a path toward understanding those complex systems.

REFERENCES

Albert, R., Jeong, H., and Barabási, A.-L. (2000). Nature *406*, 378–382.

Camazine, S. (2003). Self-organization in Biological Systems (Princeton University Press).

Conradt, L., and Roper, T.J. (2003). Nature *421*, 155–158.

Couzin, I. (2007). Nature *445*, 715.

Ermentrout, G.B., and Edelstein-Keshet, L. (1993). J. Theor. Biol. *160*, 97–133.

Maire, T., and Youk, H. (2015). Cell Syst. *1*, this issue, 349–360.

Meuer, S.C., Hussey, R.E., Cantrell, D.A., Hodgdon, J.C., Schlossman, S.F., Smith, K.A., and Reinherz, E.L. (1984). Proc. Natl. Acad. Sci. USA *81*, 1509–1513.

Miller, M.B., and Bassler, B.L. (2001). Annu. Rev. Microbiol. *55*, 165–199.

Parrish, J.K., and Edelstein-Keshet, L. (1999). Science *284*, 99–101.

Youk, H., and Lim, W.A. (2014). Science *343*, 1242782.

Studying Autism in Context

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Studying autism genes in the context of the protein complexes to which they belong illustrates the potential of network-centric approaches for understanding complex genetic disease.

Autism spectrum disorders (ASD) are a set of related neurodevelopmental diseases with shared phenotypes such as impaired language skills and social cognition. Although ASD is quite prevalent, having been reported to affect ~1% of the population (Miles, 2011), its causes remain poorly understood. This can be largely attributed to the complexity of the disease, which so far has been linked to a diverse set of associated genes. In this issue of *Cell Systems*, Li et al. (2015) examine ASD-associated genes in the context of protein complexes to explore underlying mechanisms of the disease and to suggest shared etiologies between forms of ASD associated with other conditions (syndromic ASD) and those forms for which the cause is unknown (idiopathic ASD).

The genetic basis of autism is highly complex and heterogeneous. In an attempt to identify risk genes, recent efforts have used increasingly large cohort sizes (De Rubeis et al., 2014; Iossifov et al., 2014) and sophisticated statistical techniques to integrate transmitted, de novo, and case-control genetic variation (De Rubeis et al., 2014). While this has led to the discovery of key ASD genes, including voltage-gated ion channels, histone modifiers, and chromatin remodelers (De Rubeis et al., 2014), the physical organization of these genes, especially in relevant cell types, remains unknown. Furthermore, since the observed number of mutations in individual genes is only slightly higher than expected, polygenic models are needed to accurately identify ASD risk genes (Neale et al., 2012). Because it has been shown that ASD genes form highly interconnected protein networks (Neale et al., 2012; O'Roak et al., 2012), Li et al. take the next step and carefully elucidate these networks in neuron-like cells used as models in autism research.

The authors characterize protein complexes involving previously identified ASD genes. Using a published resource of human protein complexes, they find that histone deactylases HDAC1 and HDAC2 in the NuRD chromatin-remodeling complex interact with orthologs of ASD genes in the embryonic mouse brain and positively regulate downstream ASD genes during early brain development.

Next, Li et al. extend this result by using *HDAC1* as well as five idiopathic ASD risk genes (*ANK2*, *CHD8*, *CUL3*, *DYRK1A*, *POGZ*) and a syndromic ASD risk gene (*FMR1*) as "baits" to pull down protein complexes, which were then identified using mass spectrometry. This is the first systematic study to identify protein complexes involving autism-related genes in a cultured neuronal cell line, yielding 119 high-confidence interactions. Comparisons to two independent gene expression datasets confirmed that the interacting proteins are in fact co-expressed in human brain tissue, supporting the idea that this cell-type-specific network may be highly valuable in understanding the physical basis of how ASD genes work.

As an example, the authors find that the I304N mutation on the *FMR1*-encoded RNA-binding protein FMRP significantly perturbs the underlying interactome network. Since FMRP-regulated

genes are known to be very important in ASD (Iossifov et al., 2014), the observed interaction-specific disruptions could be used to generate testable mechanistic hypotheses regarding the modes of action of a master regulator in autism.

The authors also show that many physical and regulatory interactions are shared between the idiopathic and syndromic forms of ASD. This link between these two forms of ASD helps to explain why they share many symptoms and suggests common underlying mechanisms. Since syndromic forms of autism are linked to related genetic disorders such as Rett syndrome and Fragile X syndrome, future studies may be able to extrapolate mechanistic insights from these diseases with better-understood etiologies to the idiopathic form of ASD.

Overall, the study of Li et al. reaffirms the value of transitioning from gene-centric approaches to network-centric approaches to understand ASD and other complex genetic diseases (Figure 1). Since these diseases are multifactorial, their etiology may be better understood by taking a holistic account of the impact of mutations in the complex cellular interactome. For example, it has been found that germline disease mutations are enriched at protein-protein interaction interfaces (Wang et al., 2012). There also have been recent large-scale experimental efforts to characterize how specific protein interactions are disrupted by mutations implicated in Mendelian disorders (Sahni et al., 2015; Wei et al., 2014), and a similar network rewiring approach has been used to understand how kinase signaling is altered in cancer (Creixell et al., 2015).

Thus, although gene-centric approaches for studying complex disease supply the basic building blocks, network-centric approaches similar to the one adopted by Li et al. are critical for putting together the pieces to produce a more complete mechanistic understanding of how cellular functions are altered in disease.

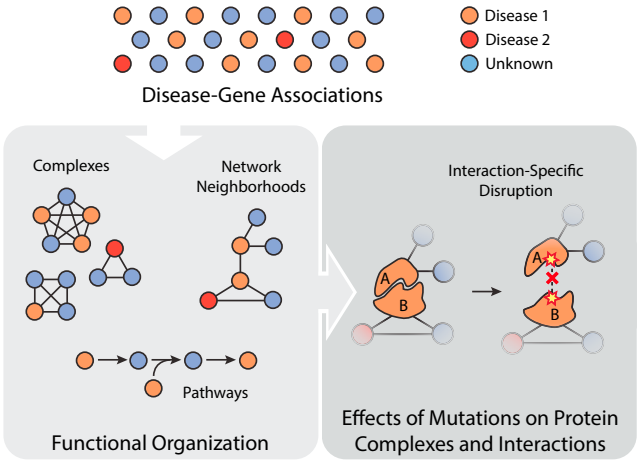

Figure 1. Disease-Gene Associations Are Analyzed in a Functional Context

By identifying complexes, network neighborhoods, and pathways containing genes associated with complex diseases, scientists can search for underlying etiologies and understand the specificity of disease mutations.

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REFERENCES

Creixell, P., Schoof, E.M., Simpson, C.D., Longden, J., Miller, C.J., Lou, H.J., Perryman, L., Cox, T.R., Zivanovic, N., Palmeri, A., et al. (2015). Cell *163*, 202–217.

De Rubeis, S., He, X., Goldberg, A.P., Poultney, C.S., Samocha, K., Cicek, A.E., Kou, Y., Liu, L., Fromer, M., Walker, S., et al.; DDD Study; Homozygosity Mapping Collaborative for Autism; UK10K Consortium (2014). Nature *515*, 209–215.

Iossifov, I., O'Roak, B.J., Sanders, S.J., Ronemus, M., Krumm, N., Levy, D., Stessman, H.A., Witherspoon, K.T., Vives, L., Patterson, K.E., et al. (2014). Nature *515*, 216–221.

Li, J., Ma, Z., Shi, M., Malty, R.H., Aoki, H., Minic, Z., Phanse, S., Jin, K., Wall, D.P., Zhang, Z., et al. (2015). Cell Systems *1*, this issue, 361–374.

Miles, J.H. (2011). Genet. Med. *13*, 278–294.

Neale, B.M., Kou, Y., Liu, L., Ma'ayan, A., Samocha, K.E., Sabo, A., Lin, C.F., Stevens, C., Wang, L.S., Makarov, V., et al. (2012). Nature *485*, 242–245.

O'Roak, B.J., Vives, L., Girirajan, S., Karakoc, E., Krumm, N., Coe, B.P., Levy, R., Ko, A., Lee, C., Smith, J.D., et al. (2012). Nature *485*, 246–250.

Sahni, N., Yi, S., Taipale, M., Fuxman Bass, J.I., Coulombe-Huntington, J., Yang, F., Peng, J., Weile, J., Karras, G.I., Wang, Y., et al. (2015). Cell *161*, 647–660.

Wang, X., Wei, X., Thijssen, B., Das, J., Lipkin, S.M., and Yu, H. (2012). Nat. Biotechnol. *30*, 159–164.

Wei, X., Das, J., Fragoza, R., Liang, J., Bastos de Oliveira, F.M., Lee, H.R., Wang, X., Mort, M., Stenson, P.D., Cooper, D.N., et al. (2014). PLoS Genet. *10*, e1004819.