This Month in *The Journal*

Kathryn D. Bungartz[1] and Robin E. Williamson[2]

Shake, Rattle, and Roll

Tao et al., page 138

The prickle proteins are highly conserved and are involved in the regulation of intracellular calcium release and planar cell polarity. Previously, a mutation in *PRICKLE1* was found in patients who suffer from an ataxia syndrome with myoclonus and seizures. Here, Tao and colleagues explore whether disruption of other prickle proteins can also lead to seizure phenotypes in humans and other species. As a start, *PRICKLE1* and *PRICKLE2* are examined in patients with myoclonus epilepsy, and several mutations are found. The shared homology between prickle orthologs leads the authors to predict that similar phenotypes would be observed in prickle-deficient models in other species. Tao and colleagues check three different mouse strains with *Prickle1* mutations and one mouse strain in which *Prickle2* is disrupted. They show that all of the mutant mice have a lower seizure threshold than wild-type mice. To move further back the evolutionary chain, the authors then look for a seizure phenotype in flies. The test that they use to evaluate seizures in flies involves trying to stimulate seizures by vortexing the tube of flies and measuring how long it takes the flies to recover and resume climbing the walls of the tube. If seizures result, the flies take longer to recover. In this experiment, the flies with a disruption in the prickle ortholog took longer to recover after vortexing than did the wild-type flies. Interestingly, this delay disappeared if the mutant flies were treated with the antiepileptic medication valproic acid. With this work, the authors are able to demonstrate the conservation of the effect of prickle disruption in seizure disorders.

If You Stay Close, We'll Make It Through Together

Browning and Browning, page 173

Two people are said to share a genomic region identically by descent if the segment of DNA is the same in the individuals because it was inherited from a common ancestor. In general, closely related individuals will share longer regions that are identical by descent (IBD) and more distantly related individuals will share IBD regions that have been shortened via recombination through the generations since the common ancestor. It is this phenomenon of the inheritance of unbroken segments of DNA that has led to the linkage disequilibrium that is fundamental in linkage and association studies. To properly perform such studies, it is important to detect regions that are IBD in the set of tested individuals to avoid the biases introduced by utilizing samples who are too related to each other. Although methods for doing this do exist, those that are precise are too computationally intensive to be used in a genome-wide manner on a large number of samples, and those algorithms that can handle all such data do not produce reliable results. In this issue, Browning and Browning present their answer to this problem: fastIBD. The authors demonstrate the utility of this method by comparing fastIBD to other algorithms currently used for detecting shared genomic regions and show that the new methodology is particularly improved in its ability to identify shorter regions that are IBD. When they apply fastIBD to the Wellcome Trust Case Control Consortium bipolar disorder data, Browning and Browning are able to detect shared regions that are not obvious via other means. The authors have incorporated fastIBD into their Beagle suite.

When Nutrition Is Not the Key to Malnourishment

Cario et al., page 226; Banka et al., page 216

Malnourishment is a common occurrence worldwide. Shockingly, around 19% of adolescents (10- to 19-year olds) have impaired development and growth due to poor nutrition. In a single recent year, over 36 million people died as the result of deficiencies in micronutrients. Micronutrients are nutrients required only in small amounts. Without these trace elements, our bodies do not function properly. Studies of micronutrient deficiencies have led to common practices such as salt iodization and water fluoridation. Iodine is necessary for proper neurologic and thyroid function, and flouride is needed for oral health. Folate is another micronutrient that has received considerable attention in recent years. Folate deficiency can lead to neural tube defects in developing fetuses, prompting women around the globe to take supplements before and after conception. It has also been associated with mental disorders, cardiovascular disease, and anemia. Although folate deficiency can be caused by lacking proper amounts of folic acid in the diet, defects in folate metabolism can also be at fault. Dihydrofolate reductase (DHFR), encoded by *DHFR*, is a key

[1]Science Editor, *AJHG*; [2]Deputy Editor, *AJHG*
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player in the regulation of folate homeostasis. Although mutations in *DHFR* have been suspected in cases of folate deficiency, they have not been previously shown. In this issue, Cario and colleagues and Banka and colleagues identify separate families having *DHFR* mutations and diseases of folate metabolism. Both groups are able to treat the phenotype of their patients with folinic acid, a chemical that does not require DHFR for its conversion to folic acid derivatives. These studies emphasize that although malnourishment can occur even in the presence of adequate micronutrients, when the genetic cause is known, it may still be easily treated.

Flying High with a New Approach to GWAS

Shulman et al., page 232

Model organisms have been used to understand human biology for decades. Fish, rodents, insects, yeast, and worms are among the most commonly utilized species. From identifying likely members of signaling pathways to understanding color perception to mimicking aspects of a human genetic disease, model organisms have helped researchers make breakthrough discoveries applicable to humans. In the age of genome-wide association studies (GWAS), researchers are finding new ways to benefit from model organisms. Numerous genetic associations for many different diseases and traits have now been identified in different human populations. Some might argue that way too many associations have been recognized, making it difficult to separate the functional variants from the incidental ones. In addition to the variants associated with genome-wide significance are the associations falling just short of the significance threshold. In this issue, Shulman and colleagues use a model organism to help ferret out associated variants with functional significance for Alzheimer disease (AD). Nineteen genes harboring candidate AD variants in an initial GWAS were found to have conserved *Drosophila* orthologs. Using a transgenic fly model of AD, Shulman and colleagues knock down the expression of all 19 orthologs. Taking advantage of the well-characterized eye phenotype of the Tau AD fly model, this team identifies six genes that interact with Tau toxicity and further investigates variants in the six human genes in a second cohort. This study demonstrates an innovative means of screening for significantly or nominally associated variants worthy of further investigation.

Are You My Mommy?

Soares et al., page 239

A great deal of what is known about the history of human origins, migrations, and evolution comes from analyses of genetic data. mtDNA from individuals of different populations has often been used for this purpose, but earlier studies that looked only at certain sequences within the mtDNA did not always have enough resolution to allow reliable conclusions to be made. Complete sequencing of the entire mtDNA genome in representative individuals has yielded a larger amount of data, and in this issue, Soares and colleagues apply such a strategy to settle an ongoing controversy regarding the origins of the people who colonized Polynesia. Archaeological, linguistic, and some earlier genetic evidence supports that the maternal lineage found in most Polynesian individuals is of Taiwanese origin. Other work has suggested that older voyages between Near Oceania and Island Southeast Asia contributed to Polynesian ancestry and precluded a significant direct contribution from Taiwan. To delve deeper into the problem, Soares and colleagues use the mtDNA sequencing data to estimate when the Polynesian motif was introduced into certain geographical regions. The authors report that Taiwan did not serve as the direct origin of the predominant maternal ancestry in Polynesia and that instead, the lineage is of ancient Asian ancestry with some stops made through Island Southeast Asia and Near Oceania before ending up in Polynesia. The timing and distribution of the lineage not only have implications for the understanding of the colonization of Polynesia but also provide additional insight into how the Austronesian languages were introduced and expanded throughout the region.