MCT-1 Expression and Hypoglycemia, *by Otonkoski et al.* **(*p. 467*)**

Blood glucose levels are regulated by the β cells in the pancreas, which control the release of insulin. When circulating glucose levels are high, insulin is released to stimulate glucose uptake and metabolism. Conversely, when glucose levels drop, insulin secretion is stopped to avoid hypoglycemia. A dominant disorder, exercise-induced hyperinsulinism (EIHI), has previously been identified in which this delicate glucose/insulin balance is disrupted and affected patients suffer from hypoglycemia after short periods of anaerobic exercise. It was noted that the β cells in EIHI-affected patients inappropriately released insulin after injection with pyruvate. This suggested that, unlike in the β cells of unaffected individuals, insulin release from EIHI β cells could be stimulated by pyruvate. Otonkoski et al. performed linkage analysis for the EIHI-affected pedigrees and, after screening several candidate genes in the most significant locus on chromosome 1, they identified three different mutations in the regulatory regions of *SLC16A1,* the gene that encodes MCT1, the monocarboxylate transporter 1 protein. These variants were expected to alter gene expression through the disruption or addition of binding sites of transcription factors or repressors, and, indeed, two are shown to cause a significant increase in *SLC16A1* expression. It is predicted that this increased expression could lead to aberrant activity of MCT1 and improper transport of pyruvate into β cells, which leads to subsequent inappropriate insulin release.

Functional Impairment from* RMRP *Mutations, *by Thiel et al.* **(*p. 519*)**

Mutations in *RMRP,* the gene encoding the untranslated RNA in RNaseMRP, cause a wide range of skeletal dysplasias, including cartilage hair hypoplasia (CHH) and anauxetic dysplasia (AD). Although AD is more severe than CHH in terms of bone dysplasia, AD is restricted to a skeletal phenotype, whereas CHH often also involves immunodeficiency, hematological dysfunction, and hair hypoplasia. In a first step to establish a genotype-phenotype correlation, Thiel et al. looked at the conservation of *RMRP* regions affected by 13 mutations. Because the gene is not translated, it has been difficult to predict the functional consequences of mutations. The authors noted that most of the mutations were in highly conserved regions and were predicted to disrupt stem-and-loop features of the two-dimensional RNA structure. The effect of each of the *RMRP* variants on the ability of RNaseMRP to cleave mRNA and ribosomal RNA (rRNA) was then compared with that of the wild-type gene. There was a relationship between cleavage ability and the phenotype observed. Those mutations that caused the more severe AD decreased the ability to cleave rRNA, but their effect on the ability of RNaseMRP to cleave mRNA was minimal. Conversely, the variants involved in the milder CHH phenotype somewhat decreased rRNA cleavage activity but also disrupted mRNA cleavage. The dual functions of *RMRP* help to explain how mutations can result in different phenotypes.

Flexible Design for Follow-Up Studies, *by Yu et al.* **(*p. 540*)**

Because replication has become the gold standard for establishing an association between a phenotype and a genetic marker, it has become important to develop methods to most efficiently design the second stage of analysis, to make best use of sample size and markers. Although many studies design the first and second stages before any work is done, there are advantages in implementing a flexible design in which the second stage is designed on the basis of the results of the first stage. An important consideration for determining the parameters of the second stage is the effect size of the proposed association in the first stage. Unfortunately, because of the "winner's curse," directly applying the first measured effect size can lead to significant bias. Yu et al. extend previously described methods to incorporate a corrected estimate of effect size in the flexible design. This allows the authors to efficiently predict the sample size needed for stage 2, to ensure that they have enough power to detect an association if one is present, and they established a selection criteria for which markers should be carried into the second stage of analysis. Using their method on association data from a non-Hodgkin lymphoma study, they demonstrate that, compared with the naive measurement of the effect size, the two most significant SNPs had an effect size that was almost half what was predicted. This would lead to a great underestimate in the number of study-participant samples needed for the second stage. The authors also explore the power gains associated with combining results from the two stages into one analysis.

Family Aggregation of Congenital Amusia, *by Peretz et al.* **(*p. 582*)**

Because of the innate ability of the majority of people to recognize and make music, it has been assumed that such functions are potentially controlled by genetic factors. To determine which genes are involved in musical ability, previous work has studied subjects with congenital amusia (a

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lack of musical ability since birth). The phenotype is very homogeneous and involves no cognitive dysfunction other than the musical disability. Previous twin studies have demonstrated heritability of amusia, and unrelated cases have been reported, so Peretz et al. prepared to study this defined phenotype in families. A precise series of tests was used to evaluate the ability of probands with congenital amusia and their relatives to identify melodies containing notes in the wrong key, notes that were out of tune, or a disruption of meter. When compared with control families, the amusia-affected probands were able to identify the meter disturbances but could not detect when notes were in the wrong key or out of tune. This inability was seen in a larger proportion of the proband relatives than in controls and their relatives, which demonstrates a clustering amusia in families and provides additional evidence that genetic factors play a role in determining musical ability.

Admixture Selection in Puerto Ricans, *by Tang et al.* **(*p. 626*)**

Admixed populations are formed when two or more ancestral populations combine and, through subsequent generations, regions of the genome mix together so that new regions of mixed background are formed. During this process, it is likely that genomic regions of one of the ancestral populations may be maintained at a disproportionate level because of selective pressures of the environment in which the new population lives. Tang et al. searched for such regions in Puerto Ricans, an admixed population with a mixture of European, West African, and Native American ancestry. Using genomewide markers, the authors sought to determine whether any genomic regions of the ancestral populations were present in amounts that diverged from the genomewide average of that ancestry throughout the genome. (Some variation is expected through random genetic drift.) One region was identified that contained an excess of African ancestry, whereas two other regions contained an excess of Native American ancestry. These regions are presumed to contain sequence that conferred a selective advantage to the Puerto Rican population by increasing survival or by conferring a more desirable mating phenotype.

This Month on the Cover

The ability to determine the sequence of DNA segments became a reality in 1977 with the introduction of Maxam and Gilbert's chemical-modification method (Proc Natl Acad Sci USA 74:560–564) and Sanger's dideoxy-sequencing method (Proc Natl Acad Sci USA 74:5463–5467). Both Walter Gilbert and Fred Sanger received the Nobel Prize in Chemistry in 1980 for the development of their techniques. On the cover is an example of radioactive dideoxy sequencing. By including low concentrations of one of the chain-terminating dideoxy bases in four separate polymerase extension reactions, DNA segments of varying lengths are created. By visualizing each of the reactions on a size-separation gel, the sequence of the template DNA can then be determined by noting which base terminated the smallest band on the gel, followed by the bases terminating the subsequent larger bands. Special thanks to Nancy Robertson for the image.

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