This Month in the *Journal*

This month in the *Journal,* Jonathan Rees discusses human variation in sensitivity to UV radiation. Some physiological determinants of this trait are the level of melanin pigmentation and the inflammatory and DNA-repair responses to UV exposure. On the genetic level, the key locus is the melacortin 1 receptor, *MC1R*. Think beyond the question of who's going to sunburn more quickly, though; this is an important issue for risk of skin cancer, and Dr. Rees discusses why it's difficult to tell whether this is as simple a relationship as pale people being more likely to get skin cancer.

ADAMTS10 ***Mutations in Weill-Marchesani Syndrome,*** *by Dagoneau et al.* (*p. 801*)

Weill-Marchesani syndrome (WMS) is a connective-tissue disorder characterized by eye anomalies, joint stiffness, short stature, and brachydactyly. Mutations in the gene encoding fibrillin-1 have been reported in the autosomal dominant form of this syndrome, and the autosomal recessive form has been mapped to a different location, on chromosome 19. Dagoneau et al. now report that the recessive disease is caused by mutations in *ADAMTS10*. This gene encodes a metalloprotease associated with the extracellular matrix, but its substrate is unknown. A previous report found unusually large bundles of microfilaments in skin fibroblasts from an affected individual. Dagoneau et al. now expand this cytoskeletal phenotype to include abnormally large actin filament bundles, and they wonder whether this reflects an impaired connection between the extracellular matrix and cytoskeleton.

Analysis of Genetic Variation in COMT, *by Chen et al.* (*p. 807*)

Catechol-O-methyltransferase (COMT) plays an important role in the inactivation of catecholamine neurotransmitters, including dopamine. Genetic associations of *COMT* have been reported for a number of phenotypes, but particularly with schizophrenia. The association of schizophrenia with a common coding SNP, Val158Met, is believed to occur as a result of differences in activity between the alleles, and measurements of COMT activity in blood and liver have supported this theory. The key tissue for schizophrenia, though, is not the blood or liver, so Chen et al. measured COMT activity in brain. They collected postmortem dorsolateral prefrontal cortical tissues from >100 individuals and found that COMT activity was nearly 40% higher in individuals who were homozygous for the Val allele at position 158, compared with Met homozygotes. In contrast, other *COMT* polymorphisms that have been reported to be associated with schizophrenia as part of a haplotype with the Val allele did not have a significant effect on enzyme activity in brain. The activity differences between the Val and Met alleles are smaller than have been reported previously, but the authors argue that their assays may be more physiologically relevant. These data support the theory that the Val allele is associated with increased risk of schizophrenia because it increases COMT activity and therefore decreases prefrontal dopamine signaling.

WNT5B ***and Type 2 Diabetes,*** *by Kanazawa et al.* (*p. 832*)

Because members of the WNT family of signaling proteins are thought to play a regulatory role in adipocyte differentiation and because LRP5, a mediator of WNT signaling, is involved in glucose-induced insulin secretion, Kanazawa et al. favored the *WNT* genes as candidates for involvement in type 2 diabetes (T2D). They performed a case-control association study with SNPs in 11 *WNT* genes and found an association with *WNT5B*. To determine the role of this gene in T2D, Kanazawa et al. examined its relationship with adipogenesis. First, they show a peak of *Wnt5b* expression during early adipogenesis. Second, they found that overexpression of *Wnt5b* in preadipocytes accelerates their differentiation to adipocytes and is associated with increased expression of two genes essential for adipogenesis, *Cebpa* and *Pparg*. These cells also overexpress at least two adipocytokines, molecules involved in insulin sensitivity that are secreted by differentiated adipocytes. Together, these results implicate WNT5B in the regulation of adipocyte function and possibly in pathogenesis of T2D.

LIT1 ***Microdeletion in BWS,*** *by Niemitz et al.* (*p. 844*)

Beckwith-Wiedemann syndrome (BWS) is an overgrowth syndrome that also includes embryonal tumors and umbilical abnormalities as part of its phenotype. The locus relevant to this disorder is on chromosome 11p15 and

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includes several genes and two imprinted domains. Within this region, several primary defects have been associated with BWS, including loss of imprinting (LOI) for *IGF2* or mutations in $p57^{KIP2}$. The most common defect is LOI of *LIT1,* a gene encoding an antisense transcript that appears to regulate genes in *cis,* including $p57^{KIP2}$. Niemitz et al. report the first BWS-associated *LIT1* deletion, which helps them to further discern the role of this gene in BWS. Normally, the maternal allele of *LIT1* is methylated and silenced. In the proband of the study family, the *LIT1* deletion was inherited maternally. The proband's mother, on the other hand, carried the deletion on her paternal allele, which made for a nice comparison. As expected because he carries a normal copy of the expressed paternal allele, the proband exhibits normal *LIT1* RNA levels, whereas the mother has no detectable *LIT1* transcript. Then, why does the proband have BWS, whereas the mother does not? It turns out that *LIT1* RNA is not the key to BWS in this situation; rather, it seems to be the effect of the deletion on $p57^{KIP2}$. Expression of this gene is reduced in the proband but not in the mother, a finding that leads the authors to conclude that the deletion removes an enhancer of $p57^{KIP2}$ expression. These data provide the first evidence that the *LIT1* gene itself contains regulatory elements for neighboring genes.

IR-Induced Expression Phenotypes, *by Correa and Cheung* (*p. 885*)

It isn't easy to study genetic control of certain exposure responses, because appropriate samples of exposed individuals are difficult to collect. Correa and Cheung, for example, were interested in responses to ionizing radiation (IR), but finding families who have all been exposed to IR in known doses would be very difficult. Instead, Correa and Cheung decided to look at these responses at the cellular level, through gene-expression studies. They exposed lymphoblastoid cells from several individuals to IR and determined, both before and after exposure, the variability in expression of a set of genes known to be induced by IR. In a set of normal individuals, they found extensive variation in the transcription of these genes. Through use of a set of twin pairs, they found evidence for a genetic influence on this variability at baseline and post exposure. The cellular IR response therefore seems amenable to genetic dissection in this system, especially because one can do controlled exposures on as many different samples as necessary. It is likely that this approach will also be a useful way to study responses to other types of toxic exposures.

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