This Month in Genetics

Kathryn B. Garber[1,*]

Exome Sequencing Yields Gene Mutations for Kabuki Syndrome

Although sought in several investigations, genetic mutations associated with Kabuki syndrome has remained elusive because of the relative rarity of the syndrome and the fact that most cases are sporadic, thereby hindering traditional gene-hunting strategies. This syndrome, which gets its name from the characteristic facies that are reminiscent of the makeup used in traditional Japanese Kabuki theater, is a multiple-malformation syndrome that includes intellectual disability. With the identification of *MLL2* mutations in patients with Kabuki syndrome, Ng et al. demonstrate again the power of whole-exome sequencing for the identification of rare genetic mutations. Their sample consisted of ten affected individuals of various ethnic backgrounds. Although their initial analysis did not yield a probable candidate gene, the allowance for genetic heterogeneity in their sample, as well as a system of ranking the individuals in the sample according to how well their phenotype matched the Kabuki syndrome gestalt, highlighted *MLL2* as a candidate gene. Ultimately, nine out of ten cases in the initial cohort had inactivating *MLL2* mutations, as did 66% of affected individuals in a larger sample. Although *MLL2* mutations may not be the only mutations responsible for Kabuki syndrome, they certainly are a major contribution to this phenotype.

Ng et al. (2010) Nat Genet. Published online August 15, 2010. 10.1038/ng.646.

The *PARK2* Tumor Suppressor?

PARK2 is most famously associated with familial Parkinson disease, the disease from which it gets its name. But deletion of this gene has most recently been linked to the development of sporadic colorectal cancers (CRCs). Poulogiannis et al. were seeking small copy number changes in sporadic CRCs, and their most frequent hit was deletion of an approximately 1 Mb region within *PARK2*, a change that was found in one-third of the sporadic CRCs. Second-hit mutation or inactivating methylation of the remaining *PARK2* allele was only infrequently observed, suggesting that haploinsufficiency, rather than a classic two-hit model, is sufficient for inactivation of *PARK2*'s tumor-suppressing capacity. *PARK2* is located at a chromosomal fragile site, so these deletions might simply be a byproduct of tumor development, rather than a driver of tumorigenesis. However, the authors demonstrate that heterozygous deletion of *Park2* in mice with a mutation in the CRC-associated gene *Apc* increases the prevalence and accelerates the development of intestinal adenomas.

Poulogiannis et al. (2010) Proc Natl Acad Sci. Published online August 9, 2010. 10.1073/pnas.1009941107.

New Congenital Disorder of Glycosylation Caused by Mutations in an Unexpected Gene

Although N-linked glycosylation is an essential posttranslational modification in eukaryotic cells, the biosynthesis of its precursors is not fully characterized. In the process of elucidating the cause of a multisystemic syndrome that includes congenital eye malformations, cerebellar atrophy or vermis malformation, microcytic anemia, and dysmorphic features, Cantagrel et al. better define a crucial component of N-linked glycosylation that comes from an unexpected corner. Extensive consanguinity in the original family indicated that the disorder was likely to be autosomal recessive, and linkage analysis followed by brute-force sequencing uncovered a complex mutation in *SRD5A3*, which—on the basis of sequence similarity—was believed to encode a steroid 5α-reductase. This didn't jive with the fact that the phenotype in affected families was reminiscent of a congenital disorder of glycosylation and that an early step in N-linked glycosylation was defective in patient cells. The authors used extensive biochemical characterization to show that SRD5A3 is actually a polyprenol reductase that is necessary for synthesis of the lipid carrier of the oligosaccharide that will be transferred to proteins in the N-glycosylation process. An open mind and a willingness to look beyond homology-based predictions allowed the authors to define a new congenital disorder of glycosylation and to further outline the process of N-linked glycosylation.

Cantagrel et al. (2010) Cell 142, 203–217. 10.1016/j.cell.2010.06.001.

Making the Switch

As a result of developmental regulation, fetal hemoglobin (HbF) is gradually replaced by HbA and generally makes up only $< 2\%$ of all hemoglobin in an adult. Stimulation of HbF expression in patients with β-thalassemia alleviates their anemia and can reduce their dependence on blood transfusions. However, the pharmacological agents that have been used to induce HbF expression are not ideal and can have side effects, such as cytotoxicity and

[1]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30322, USA
*Correspondence: kgarber@genetics.emory.edu
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inhibition of erythropoiesis. Two recent papers uncover a new regulatory mechanism for globin chain switching that could have implications for this therapeutic approach. Borg et al. identify mutations in *KLF1* in individuals with hereditary persistence of HbF. This transcription factor is expressed in erythroid cells and their precursors and is known to regulate many aspects of erythroid differentiation, including activation of *HBB* expression. What was not previously appreciated is that KLF1 also activates expression of *BCL11A*, which, in turn, represses expression of the fetal *HBG1/HBG2* genes. Thus, in addition to direct stimulation of HbA production, KLF1 also indirectly represses production of HbF. This model is further supported by the work of Zhou et al., who demonstrate that in mice, reductions in *Klf1* expression increase the relative production of HbF through reductions in Bcl11a production. These experiments outline two potential new targets for pharmacologic stimulation of HbF production in the treatment of β-globin disorders.

Borg et al. (2010) Nat Genet. Published online August 1, 2010. 10.1038/ng.630.

Zhou et al. (2010) Nat Genet. Published online August 1, 2010. 10.1038/ng.637.

Long-Term Survivors of Gene Therapy for SCID

The development of leukemia in children who were treated with gene therapy for X-linked severe combined immunodeficiency (SCID-X1) was splashy news. What became of those children and the others who did not develop leukemia? They are now as far as 11 years out from the gene therapy treatment, and results of their longer-term follow up have recently been reported by Hacein-Bey-Abina et al. Although one child who developed leukemia did succumb to the disease, seven of the nine children in the study live normal lives (i.e., not in a bubble) and are growing normally, including three patients who recovered from leukemia with chemotherapy. Only one of the eight survivors did not have sustained reconstitution of his immune system, but three of them do require immunoglobulin-replacement therapy. Certainly, the fact that almost half of the children developed leukemia indicates that this treatment is a risky proposition. However, compare this to long-term data on survival of individuals with SCID-X1 after hematopoietic stem cell transplant, the current best treatment. Of those who are transplanted with cells from a mismatched donor, approximately two-thirds survive.

Hacein-Bey-Abina et al. (2010) NEJM 363, 355–364.

This Month in our Sister Journals

Even Classic Mendelian Diseases Are Not Simple

CFTR mutation identification is an important component of newborn screening for cystic fibrosis (CF). However–even between different individuals with the same reported *CFTR* mutations–there can be wide variability to the phenotype, making outcome predictions for these babies difficult, particularly in terms of pulmonary disease. One underexplored issue related to this variability is the fact that *CFTR* mutation analysis generally concludes when two putative mutations have been identified on opposite alleles, meaning that a truly complete analysis of the gene is not performed. Lucarelli et al. wondered whether additional variability in *CFTR* might influence disease outcome, and they explored this in the context of the controversial L997F variant of *CFTR*. This allele has been reported as everything from a nonpathogenic variant to a mutation associated with pulmonary disease, pancreatitis, or congenital absence of the vas deferens. A comprehensive mutational analysis of *CFTR* was completed in 12 subjects, each of whom had a classic CF mutation on the allele opposite L997F. In the group of subjects as a whole, the CFTR-related phenotype and sweat chloride levels varied widely. The subset of individuals with a simple L997F allele also exhibited a variable phenotype, but—in contrast—a subgroup of individuals with a [R117L; L997F] complex allele developed mild to severe CF in conjunction with high sweat chloride levels, a narrower phenotypic range than the group as a whole. Similar mutational analysis of *CFTR* in additional subjects may yield better predictions of outcome in children with the L997F allele.

Lucarelli et al. (2010) Genet Med. Published online August 11, 2010. 10.1097/GIM.0b013e3181ead634.

Serum Response Factor Regulates Neovascularization

Because of its transparency and the fact that its vascularization is tightly controlled, the cornea has been widely used as a model of angiogenesis. In fact, angiogenesis inhibitors have proven effective for the treatment of some types of corneal disease. Mice that are homozygous for a null allele of the destrin gene (*Dstn*) have corneal abnormalities that include neovascularization, inflammation, and epithelial cell hyperproliferation. A recent paper in *Genetics* identifies the serum response factor (SRF) as a key downstream signal in this pathogenic process. Abrogation of SRF expression in the cornea of mice with corneal disease due to a lack of destrin expression reverses their corneal disease, and it also reduces indicators of the pathologic process. SRF has also been implicated in the development of certain cancers. Because angiogenesis and inflammation are important components of cancer progression, the pathway uncovered in this paper could have therapeutic implications beyond the eye.

Verdoni et al. (2010) Genetics. Published online August 9, 2010. 10.1534/genetics.110.117309.