This Month in Genetics

Kathryn B. Garber[1,*]

Treatment for Vascular Ehlers-Danlos Syndrome

If you try to blow up a balloon with a weak spot, the weak spot gets bigger and—if you keep blowing—it's likely to burst. This is basically a simplified model of the connective tissue disorder vascular Ehlers-Danlos syndrome (EDS); the pressure and mechanical stress put on fragile tissues with defective type III collagen can lead to vascular or hollow organ rupture. This model led to the underlying premise of the BBEST trial, a prospective study to determine the effect of beta-blockers on vascular EDS: would reducing the heart rate and pulsatile pressures decrease the vascular complications associated with vascular EDS? The trial, in which affected individuals were randomly assigned to a group who received the hypertension drug celiprolol or to a control group, was planned as a five-year trial. Ong et al. recently reported the results of the trial, which was stopped early because of treatment benefit. Celiprolol treatment resulted in a 64% reduction in the risk of a major complication of vascular EDS, such as arterial rupture or dissection. The effect of celiprolol occurred despite the fact that the original rationale for the trial did not hold true; the drug did not reduce the heart rate or blood pressure of treated patients. This does not negate the risk reduction conferred by celiprolol treatment; it simply means that there is more to learn about the pathogenic process of vascular EDS.

Ong et al. (2010) Lancet. Published online September 7, 2010. 10.1016/S0140-6736(10)61155-5

When a Loss Is a Gain

Contractions of a D4Z4 repeat sequence in the subtelomeric region of chromosome 4q cause facioscapulohumeral muscular dystrophy (FSHD), a progressive muscular dystrophy that affects the upper body. However, the contraction alone is not sufficient to cause disease, something that has puzzled researchers studying FSHD genetics. A simple loss-of-function model doesn't explain the fact that patients with FSHD must have at least one copy of the D4Z4 sequence present and that contraction has to occur in the context of certain haplotype backgrounds. The major transcript in the repeat is produced from *DUX4*, which encodes a double homeobox protein, although the transcripts from the repeat are reportedly unstable. Lemmers et al. recently discovered evidence that contraction of D4Z4 on a permissive background actually leads to a gain, rather than a loss, of function. They find increased stability of a distal *DUX4* transcript produced from FSHD-permissive haplotype backgrounds, due to the creation of a polyadenylation signal. What does the repeat contraction have to do with this? The contraction is associated with DNA modifications that open the chromatin structure and could be associated with increased transcription of genes in this region. Thus, cells from patients with FSHD would theoretically produce more of the relevant *DUX4* transcript and it would stick around longer. The missing piece of this pathogenesis puzzle is to figure out how more of this *DUX4* transcript leads to muscle wasting.

Lemmers et al. (2010) Science Express. Published online August 19, 2010. 10.1126/science.1189044

Structural Polymorphism at 16p12.1 Influences Microdeletion Risk

The large-scale methodologies that were used to sequence the human genome made the project feasible but did not have the finesse to unravel the true structure of some of the more complicated segments of the genome. Antonacci et al. create a better map of one such region, the segmental duplication-rich 16p12.1, which they realized was assembled in the wrong orientation in the human reference assembly. The orientation was not the only issue; there are, in fact, two common human haplotypes in this region that differ by more than 300 kb of duplicated sequence, making it one of the largest copy-number polymorphisms identified to date in the human euchromatin. Beyond the correction to the human reference assembly, this discovery alters the locations of structural elements relative to the breakpoints of a recurrent microdeletion that predisposes one to intellectual disability. In fact, only the larger of the two common haplotypes at 16p12.1 appears to be susceptible to this deletion, because it alone contains directly oriented duplications that could serve as substrates for nonallelic homologous recombination.

Antonacci et al. (2010) Nature Genetics 42, 745–750. 10.1038/ng.643

Reversal of Mis-Fortune

If DNA mutations randomly occur and can cause a detrimental effect, is it not reasonable that they can also have a positive effect and lead to correction of a defect? Sure, reversion mutation is theoretically possible and has been reported, albeit infrequently. Choate et al. recently

[1]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30322, USA
*Correspondence: kgarber@genetics.emory.edu
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reported a case in which mutation reversion is the rule, rather than the exception. In ichthyosis with confetti (IWC), the skin of affected individuals lacks integrity and proper differentiation of the epidermal layers. However, there are patches of normal-looking skin that can number in the thousands, giving the appearance of confetti. Through comparisons of DNA from the normal skin to that from the blood and abnormal skin of the same affected individuals, Choate et al. demonstrate that each normal patch of skin in every affected individual has loss of heterozygosity of a similar, but not identical, region of chromosome 17q. They use this information to identify mutations in the gene for keratin 10 as the cause of IWC and to prove that each normal patch of skin represents a separate reversion event of the original mutation. The high rate of reversion, as well as the persistence of these clones, indicates that there may be positive selection for the revertant stem cell clones and/or increased mitotic recombination in IWC. The unusual mutant protein produced in the affected skin could play a role in the generation of or selection for revertants; all of the mutations cause frameshifts into the same alternate reading frame, which adds an arginine-rich C-terminal peptide to keratin 10, aberrantly directing it to the nucleolus.

Choate et al. (2010) Science Express. Published August 26, 2010. 10.1126/science.1192280

Plavix, Pharmacogenetics, and Prescriptions

The mainstay therapy for treatment of acute coronary syndrome is a combination of aspirin and clopidogrel (Plavix), a drug that inhibits platelet aggregation. It is estimated that maybe one-quarter of people have a subtherapeutic response to clopidogrel, due at least in part to variation in the genes that govern uptake and metabolism of the drug. The FDA has required a statement to be added to the clopidogrel label that warns that it might be less effective in poor metabolizers, who are at least partly defined by reduced function alleles in *CYP2C19*, a gene encoding the enzyme that activates clopidogrel from its prodrug form. Even so, *CYP2C19* accounts for only a minority of the variation in clopidogrel response, and data suggest that response to the drug might also be governed by variation in *ABCB1*, which encodes a drug transporter. Two recent large studies add to the pharmacogenetic data on clopidogrel and on two newer platelet inhibitors, prasugrel and ticagrelor, but do not clarify the use of pharmacogenetic data in the prescription of platelet inhibitors. These analyses, which are offshoots of the TRITON-TIMI 38 and PLATO trials, provide further support for the influence of *CYP2C19* variation on risk of cardiovascular death, heart attack, or stroke in patients with acute coronary syndrome. Adding genotype information for *ABCB1*, which is an independent risk factor, seems as though it could improve the discrimination between risk groups, but the two studies report opposite risk effects for the same *ABCB1* allele in people treated with clopidogrel, making the utility of this information unclear. What is still lacking for the pharmacogenetic data on clopidogrel is to provide physicians with data that suggest how the information should influence prescription of the drug. Perhaps this will become a moot point, because of the fact that prasugrel and ticagrelor each outperformed clopidogrel in these studies in all genotype groups.

Mega et al. (2010) Lancet. Published online August 29, 2010. 10.1016/S0140-6736(10)61273-1

Wallentin et al. (2010) Lancet. Published online August 29, 2010. 10.1016/S0140-6736(10)61274-3

This Month in Our Sister Journals

Chromosome 16p11.2 Deletions Are Associated with Developmental Delay and Obesity

Chromosome 16p is rife with segmental duplications that make it prone to rearrangement. Among the recurrent mutations of 16p is a ~200 kb deletion at 16p11.2 in individuals with severe early-onset obesity, as reported earlier this year (Bochukova et al. Nature *463*, 666–670). In *Genetics in Medicine* this month, Bachmann-Gagescu et al. find the same recurrent deletion, but the pool of samples from which they draw allows them to more broadly assess the associated phenotype. Whereas the case sample used by Bochukova et al. was defined by severe obesity, Bachmann-Gagescu et al. collect data from a sample of over 23,000 patients referred for comparative genomic hybridization for a variety of reasons, and overlapping 16p11.2 deletions were found in 31 individuals. Although complete phenotypic information was not available for most, four of the six individuals on whom they were able to obtain additional clinical information were found to be obese, further cementing the link between this deletion and obesity. All of the six individuals also had developmental delay, thereby also implicating the deletion in neurodevelopmental phenotypes.

Bachmann-Gagescu et al. (2010) Genetics in Medicine. Published online August 30, 2010. 10.1097/GIM.0b013e3181ef4286