This Month in Genetics

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MeCP2 Keeps Neurons from Getting Too Jumpy

Approximately 17% of the human genome is thought to be composed of L1 elements, a small fraction of which maintain the capacity to move to another location. This movement was thought to be restricted to germ cells early in development, but it turns out that L1 activity can be detected in neuronal precursor cells. One can even find evidence of this activity in vivo in that quantitative PCR indicates that there are more copies of L1 in the adult human brain relative to other tissues from the same individual. The increased L1 activity during brain development has led to the suggestion that these jumping genes could contribute to somatic mosaicism and may influence expression of neuronal genes in healthy individuals. Could L1 elements also influence variability in a neurodevelopmental phenotype, namely Rett syndrome? Muotri et al. recently found that the absence of MeCP2, the protein that is defective in Rett syndrome, is associated with increased L1 activity in neural stem cells, and this adds to our understanding of the regulation of L1 activity. They report that *Mecp2* knockout mice exhibit, in several areas of the brain, increased neuronal L1 retrotransposition relative to that of wild-type mice. These results appear to hold true in patients with Rett syndrome, who also have increased L1 copy number in brain samples relative to age-matched controls. Although it is plausible that these jumping L1s may give rise to some variability in the Rett syndrome phenotype, they cannot be the key to disease pathogenesis because we know that we can reverse symptoms in mature *Mecp2* mutant mice if we turn the gene back on and this would not be expected to reverse the L1 movements.

Muotri et al. (2010). Nature 468, 443–446. 10.1038/nature0954.

Modulating Histone Aceylation to Alter *FMR1* Transcription

Transcriptional silencing of *FMR1* gives rise to fragile X syndrome. This occurs when large expansions of the CGG repeat tract in the 5′ untranslated region of *FMR1* are hypermethylated. On the other hand, excess transcription of this gene occurs when there are smaller, premutation alleles of this CGG repeat, and this "toxic" mRNA is believed to cause the fragile X tremor ataxia syndrome (FXTAS). Why are premutation alleles overexpressed? Todd et al. recently found evidence that increased histone aceylation at the CGG repeat is responsible, and these histone modifications can be manipulated to reduce the level of the toxic RNA species. In a *Drosophila* neurodegeneration model of FXTAS, overexpression of various histone deacetylases (HDACs) suppresses the toxicity due to RNA containing repetitive CGG sequences; knockdown of the same HDACs worsens the phenotype. In cell lines from patients with premutation-sized alleles, drugs that block histone acetylation—including one that is a natural compound derived from cashews—decrease *FMR1* mRNA expression to control levels. Thus, chromatin remodeling is instigated by premutation alleles, and this process appears to be central to premutation-associated disease. If you read on further in this column, you'll see that this work has implications for a significant number of people; recent estimates suggest that FXTAS could occur in more than 1 in 5000 individuals.

Todd et al. (2010). PLOS Genetics. Published online December 9, 2010. 10.1371/journal.pgen.1001240.

Eating Less to Eat More

Ullrich congenital muscular dystrophy (UCMD) and Bethlem myopathy are muscular disorders on the same continuum and are due to collagen type VI defects. Muscle from affected individuals exhibits mitochondrial dysfunction and apoptosis, which leads to degeneration of myofibers. Grumati et al. recently found evidence that this downward spiral is at least partly due to defects in the stimulation of autophagy, which should normally be used to get rid of dysfunctional mitochondria in order to maintain cell viability. One way to stimulate autophagy is through short-term starvation, which did, in fact, stimulate autophagy and decrease apoptosis in collagen VI-deficient mice. Obviously, this is not a sustainable therapeutic approach, so the authors move to a low-protein diet to stimulate autophagy and demonstrate recovery of dystrophic changes in muscle and improved muscle strength in the same mouse model. Although it remains to be seen whether dietary manipulation can alleviate muscle weakness in patients with UCMD or Bethlem myopathy, this work hints that in the context of collagen type VI deficiency, eating less stimulates muscle cells to increase their consumption of defective organelles, which could alleviate muscle atrophy.

Grumati et al. (2010). Nature Medicine 16, 1313–1320. 10.1038/nm.2247.

Genome Architecture

Although the completion of a draft human genome sequence was announced more than ten years ago,

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DOI 10.1016/j.ajhg.2010.12.009.

technical limitations have hampered the delineation of structural variation. Evan Eichler's group has been tackling this through the construction and capillary-based sequencing of genome libraries in fosmid vectors. Discrepancies in the length or orientation of fosmid end sequences, compared to the human reference genome, suggest copy-number variation or inversion. This group recently announced the availability of a set of more than 13 million fosmid clones from 17 individuals, and they characterize more than 2000 breakpoint junctions from structural variants identified through this resource. The three key mechanisms for generating this structural variation, as inferred from this breakpoint analysis, are microhomology-mediated processes, L1 retrotransposition, and nonallelic homologous recombination. Evidence for more complicated events at some junctions is also found, including multiple rounds of gene conversion leading to alternating sequences derived from flanking homologous sequences. The availability of this clone resource should facilitate additional analysis of these breakpoints and lead to an even greater understanding of the structural variation in the human genome.

Kidd et al. (2010). Cell 143, 837–847. 10.1016/j.cell.2010.10.027.

Mutations in *VCP* Cause Familial ALS

The genes disrupted in amyotrophic lateral sclerosis (ALS) largely remain a mystery. For adult-onset neurodegenerative disorders such as this, traditional gene hunting in affected families can be impeded by the lack of surviving affected individuals. To circumvent this problem, Johnson et al. used whole-exome sequencing in an attempt to find the causative mutation in an Italian family with ALS. They sequenced the exomes of two affected family members and used Sanger sequencing in a third affected relative to further limit the potentially relevant shared sequence variants. Their analysis led them to a missense change in *VCP*, a gene that has already been found to be mutated in a different disease phenotype: inclusion body myopathy with early-onset Paget disease of the bone and fontotemporal dementia (IBMPFD). In fact, relatives of some of the probands in this study were given diagnoses of Paget disease and dementia. However, prior to this study, *VCP* mutations were not known to cause ALS, and it was previously believed that an ALS diagnosis in a patient with a *VCP* mutation was an erroneous misinterpretation of the inclusion body myopathy phenotype. Instead, this work indicates that mutations in this gene account for approximately 2% of familial ALS and, in fact, that ALS may be the only phenotype present in an individual with a *VCP* mutation. It further suggests that the broader IBMPFD phenotype should be assessed in pedigrees with familial ALS.

Johnson et al. (2010). Neuron 68, 857–864. 10.1016/j.neuron.2010.11.036; Shaw (2010) Neuron 68, 812–814. 10.1016/j.neuron.2010.11.040.

This Month in Our Sister Journals

To Screen or Not to Screen: That Is the Question

Recent technological advances have made fragile X carrier screening possible through the detection of females heterozygous for premutation-sized alleles in *FMR1*. Hantash et al. used one of the recently developed methodologies, triplet-primed PCR, to screen more than 13,000 anonymized samples for fragile X premutations and use their results to argue for further consideration of population-based carrier screening for fragile X syndrome. The samples, which were gathered in the United States, were originally referred for carrier screening for either cystic fibrosis or genetic diseases that are more prevalent in the Ashkenazi Jewish population. Together with United States Census Bureau data, the authors use the results of their screen to extrapolate an overall premutation-carrier frequency of 1:178, a frequency higher than previous estimates. If one were to argue simply on the basis of estimated carrier frequencies, this number would support population-based screening for fragile X premutation carriers because it is higher than carrier frequencies of other genetic disorders for which screening is already recommended, including cystic fibrosis. The authors also use their data to estimate fragile X premutation-associated diseases in the United States, yielding frequencies of 1:4848 for fragile X-associated tremor and ataxia syndrome and 1:3560 for fragile X-associated primary ovarian insufficiency.

Hantash et al. (2010). Genetics in Medicine. Published online November 24, 2010. 10.1097/GIM.0b013e3181fa9fad.

Location, Location, Location

Is the evolution of a genomic segment due to its sequence or its context? DeBaryshe and Pardue examined this question recently in their comparisons of the same retrotransposon in two different contexts in the *Drosophila* genome. Three retrotransposons maintain the length of *Drosophila* telomeres, and one of these, HeT-A, is also found in the Y chromosome centromere of *Drosophila* and has been maintained there for over 13 million years. This gave them the opportunity to compare HeT-A sequences that have been maintained in a telomeric context with those in a centromeric context. Their analysis suggests that HeT-A gains and loses sequences in different ways in the two different contexts. Whereas the telomeric elements are often found

in their complete form and seem to degrade via gradual erosion and irregular deletions from the terminal end, the centromeric elements have each lost at least 40% of their sequences via internal deletions. On the other hand, the telomere arrays grow via new transposition events, unlike the centromeric arrays, which grow by amplification of internal sequences. Thus, the genome appears to be driving the evolution of these elements on the basis of location and probably on the basis of the function of the telomeric and centromeric regions.

DeBaryshe and Pardue (2010). Genetics. Published online November 1, 2010. 10.1534/genetics.110.122994.