in the following two frames, and a new set of frozen domain structures (bottom frame). This partial flux flow, first described by Kramer (*7*) more than 20 years ago, was believed to occur in the technically useful strong-pinning superconductors; Matsuda *et al.* (*1*) provide direct evidence supporting this view.

In order to better understand the factors that control the formation of the vortex rivers observed (*1*), it is advantageous to analyze computer simulations (see figure), where, unlike in experiments, material parameters can be continuously varied. Indeed, both Lorentz microscopy and computer simulations are valuable tools for the analysis of the microscopic spatiotemporal dynamics of individual flux lines in superconductors, which are not easily observed by other means, lending insight to commonly measured bulk macroscopic quantities such as the magnetization and the critical current. These approaches can help elucidate the topological ordering of a driven plastic lattice interacting with a rigid one, a problem that has recently attracted considerable attention (*3*–*6*).

The figure here and figure 6 of (*1*) show paths through which vortices move, producing dynamically generated flux lattice defects or phase slips. This plastic flow is in contrast to the coherent motion predicted by elastic models. In both the figure here and in (*1*), the increasing external field provides the pressure that forces the vortices to move into the sample (*8*). The figure herein shows the top view of a small region of a larger sample. In part A of the figure, where the pinning force is strong, the vortex transport is characterized by trails of interstitial vortices that move around regions with flux lines that are strongly pinned at defects, indicating that the interstitial vortices are flowing through the energy minima created by the strongly pinned flux lines. In part B, where the force is 10 times weaker, vortex transport proceeds in a different manner: pin-to-pin vortex motion, as well as interstitial, is possible, and the previously narrow vortex trails become considerably broader.

Although most experiments only focus on the effects of random pinning distributions, some investigations (*9*) have used samples with periodic arrays of pinning sites (PAPS). These can greatly enhance pinning when parts of the flux lattice become commensurate with the underlying PAPS. Under such conditions, high-stability vortex configurations are produced that persist in an increasing current or external field. Flux lattice domains attributable to commensurate effects are visible in figures 3 and 4 of (*1*). Other vortex matching effects also have recently been observed in a variety of different superconducting systems, including Josephson junctions, superconducting networks, and the matching of the flux lattice to the crystal structure of $YBa_2Cu_3O_7$ due to intrinsic pinning. Nonsuperconducting systems also exhibit magnetic field–tuned matching effects, notably in relation to electron motion in periodic structures where unusual behaviors arise as a result of the incommensurability of the magnetic length with the lattice spacing. Commensurate effects also play central roles in many other areas of physics, including plasmas, nonlinear dynamics, the growth of crystal surfaces, domain walls in incommensurate solids, quasi crystals, Wigner crystals, and spin and charge-density waves. The magnetic motion pictures obtained in (*1*) allow one to easily visualize such commensurate effects, which otherwise can rarely be directly resolved in both space and time.

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The Expanding World of Trinucleotide Repeats

Stephen T. Warren

It is not every day that new kinds of mutations in the genetic material are discovered. Nevertheless, 5 years ago the first examples of mutations resulting from the unstable expansion of trinucleotide repeats were reported in individuals with fragile X syndrome and spinal and bulbar muscular atrophy (*1*). In both cases, a normally polymorphic triplet of nucleotides (CGG in fragile X syndrome and CAG in spinal and bulbar muscular atrophy) increases in copy number in individuals with these disorders. For fragile X syndrome, this change could be extraordinary; patients can exhibit hundreds and sometimes thousands of the CGG triplet at this site (locus), whereas normal individuals contain only about 30 repeats. Although the normal CAG repeat at the site mutated in spinal and bulbar muscular atrophy is similar in length to the fragile X triplet (about 20 CAGs), in affected individuals the expansion is more modest, exhibiting only a two- to threefold increase (38 to 66 repeats). Ten additional human loci are now known to have alleles with expanded trinucleotide repeats of either the massive or modest variety (*2*) (see figure). Although at some of these loci expansion is benign (except causing a chromosomal variation called a fragile site), most result in disease, including such disorders as Huntington's disease, myotonic dystrophy, and a number of hereditary ataxias. There are certain similarities among these repeats that have implied some simplifying generalizations. The most recent addition to this growing list of genetic diseases caused by trinucleotide repeat expansion, Friedreich's ataxia, reported by Campuzano and co-workers in this issue, now shows that some of these generalizations may have been premature (*3*).

Before this most recent discovery, all the known expansion loci contained either CGG or CAG repeats, although they have been reported in permutations that vary with strand and frame. When expansion results in disease, the disorder transmits as a dominant trait with the repeats found within the exons of their respective genes (although they may or may not be coding for amino acids). Furthermore, the repeats at these loci, despite being stably transmitted in normal families, exhibit marked instability when abnormally expanded, with siblings often showing unique repeat lengths distinct from that of the transmitting parent. In addition, these "dynamic mutations" show a predilection for gaining repeat units when transmitted through subsequent generations. Concomitant with this increase in repeat number with subsequent generations is an increase either in disease severity, frequently revealed by decreasing age of onset, or in penetrance. This phenomenon is called genetic anticipation and is considered a hallmark of such dynamic mutations.

These similarities have become viewed as mechanistically significant points. The relatively high CG content of the repeats appeared pertinent, and a number of models were proposed in which such trinucleotide repeats assumed hairpin or triple helical

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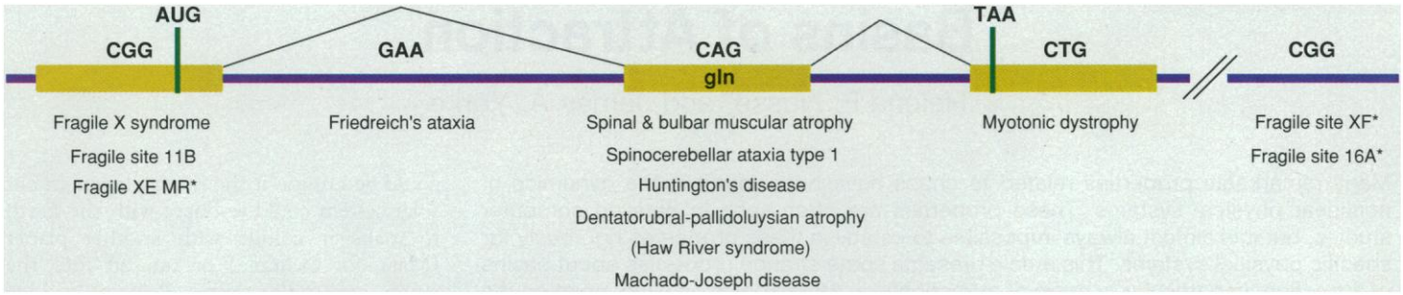

Location and type of triplet repeats in humans. This factitious gene of three exons (green boxes) and two introns (intervening blue line) depicts the location and type of expanded triplets. The repeats of fragile X syndrome, fragile XE mental retardation (MR), and fragile site 11B are found within the 5′ untranslated region of the first exons of their respective genes and are CGG repeats. Friedreich's ataxia repeats are within the first exon of the *X25* gene and are GAA. Five loci responsible for neurological diseases contain CAG repeats that are coding and result in lengthening of a normal polyglutamine tract in their respective gene products. Haw River syndrome repeats are at the same locus as those for dentatorubral-pallidoluysian atrophy and similarly involve expansion of the same CAG repeat but with slightly different phenotypic results, possibly because of modifying genes. Myotonic dystrophy is caused by a 3′ untranslated CTG repeat (CAG on the other strand) in the final exon of the DM protein kinase gene. Two fragile sites, XF and 16A, are not known to be in the vicinity of any genes and, like fragile site 11B, are not known to result in any disease phenotype. * Location inferred but not proven.

structures, widely interpreted as relevant to the instability (*4*). Moreover, the dominant inheritance with genetic anticipation of these disorders initiated a search for disorders with these attributes as likely candidates for trinucleotide repeat expansions (*5*). The observations made in Friedreich's ataxia now suggest that these interpretations are perhaps too narrow.

Friedreich's ataxia certainly does not fit the mold of a dynamic mutation. It is an autosomal recessive disease with little evidence for genetic anticipation. Although the age of onset may vary, most patients exhibit signs of the disease in adolescence, and, quite unlike other triplet diseases with anticipation, onset in middle age or later is exceedingly uncommon (*6*). Thus, as is clear from the report by Campuzano and coworkers, no one was more surprised than the authors that an expanded repeat causes Friedreich's ataxia. What began as a routine positional cloning effort led to the identification of a single gene (*X25*) in a 150-kb critical region on chromosome 9, within which the responsible gene must lie. Despite the fact that *X25* was the only gene identified in the critical region and that the pattern of *X25* expression matched that of the tissues involved in Friedreich's ataxia, only three point mutations were found in a series of 249 patients. Moreover, those harboring the mutations did so in a heterozygous state, quite unexpected for a recessive disease. However, further study revealed that a fragment of the *X25* gene appeared to be about 2.5 kb larger in patients, which led to the discovery of an expanded GAA trinucleotide repeat within intron 1. In normal chromosomes, 10 to 21 copies of this repeat are seen, but among Friedreich's ataxia chromosomes, nearly 95% contain anywhere between 200 and 900 GAA repeats. Although nearly 90% of patients are homozygous for the expanded repeat, it is important that almost half of the remaining patients were compound heterozygotes carrying one allele with a repeat expansion and the other with point mutations predicted to be null alleles. This finding establishes *X25*, which codes for the protein frataxin, as the gene responsible for Friedreich's ataxia. These investigators further demonstrated that the expanded GAA repeat in intron 1 may interfere in frataxin heterogeneous nuclear RNA processing, resulting in the absence of a mature message in the cytoplasm. It is tempting to speculate that the massive number of consecutive AG splice acceptor sites formed by the expanded GAA triplet might be responsible. Nevertheless, the end result appears to be a loss-of-function expansion mutation in Friedreich's ataxia.

Besides the obvious importance of uncovering the gene responsible for one of the most frequent forms of hereditary ataxias, this work represents a departure from what has become expected for dynamic mutations. The implications of CAG or CGG repeats, including the influence of their unusual structures on instability, seem less important, because GAA repeats appear unable to form these structures (*3*). Indeed, CG-rich repeats no longer appear unique, opening up the possibility for any of the remaining possible triplet repeats expanding at other loci. Also no longer valid as consistent characteristics of disorders resulting from repeat expansions are the location of the repeats within exons, the features of genetic anticipation, and dominant inheritance. The latter point is particularly important because the loss-of-function expansion seen in recessive Friedreich's ataxia suggests that many similar examples exist among the large number of autosomal recessive diseases that remain uncharacterized at a molecular level in humans.

Similarities, however, still remain among these disorders. Although this latest addition continues a trend of attributing neurological diseases, frequently ataxias, to expanded triplets, it is difficult to understand any biological basis for this supposition. The modestly expanded triplets in the ataxias are in coding regions (expanding polyglutamine tracts) that produce a gain- or change-of-function, or in noncoding portions of genes—such as the intron involved in Friedreich's ataxia, or the 5′ untranslated region of the *FMR1* gene in fragile X syndrome (*7*), both resulting in loss-of-function changes. Therefore, depending on the location of the unstable repeat, the consequence of expansion can be quite different and should not be expected only in neurological diseases. Another consistency among these disorders is the involvement of a triplet repeat, as opposed to a di- or tetranucleotide repeat. The case for triplets being distinct in their propensity toward expansion increases with every additional example. However, not until the mechanism of the expansion is understood will this curious association be understood. Indeed, it is difficult at this juncture to even predict a mechanism by which triplets of the varieties now described become unstable. Nevertheless, one prediction that is not difficult to make is that further examples of these remarkable mutations will undoubtedly be uncovered in the future.

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