کارگاه‌های آموزشی مرکز اطلاعات علمی

آموزش نرم‌افزار Word برای پژوهشگران

روش تحقیق کمی

آموزش مهارت‌های کاربردی در تدوین و چاپ مقالات ISI

Molecular approaches to neurogenetic disorders involving trinucleotide repeat expansions

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Abstract
A neurogenetic disorder is defined as a clinical disease caused by a defect in one or more genes which affect the differentiation and function of the neuroectoderm and its derivatives. There are more than 25 known neurogenetic disorders involving trinucleotide repeat expansion. Expanded repeats range from small expansions of 20-100 copies to larger expansions of up to several thousand units. These dynamic expansions result in variability in age of onset, degree of severity and clinical presentation. Individuals carrying alleles in the intermediate range, known as premutation alleles, are often asymptomatic, but can potentially transmit a further expanded allele to his/her offspring. For autosomal dominant adult-onset disorders, carriers are asymptomatic prior to disease onset. With current molecular tools, it is now possible to determine the presence and number of expanded repeats for accurate diagnosis, presymptomatic testing and carrier status screening. The discovery that expansion of unstable repeats can cause a variety of neurological disorders has changed the landscape of disease-oriented research for several forms of mental retardation, Huntington disease, inherited ataxias, and muscular dystrophy. The dynamic nature of these mutations provided an explanation for the variable phenotype expressivity within a family. Beyond diagnosis and genetic counseling, the benefits from studying these disorders have been noted in both neurobiology and cell biology. Examples include insight about the role of translational control in synaptic plasticity, the role of RNA processing in the integrity of muscle and neuronal function, the importance of Fe-S-containing enzymes for cellular energy, and the dramatic effects of altering protein conformations on neuronal function and survival.
Disorders such as Huntington's disease, spinocerebellar ataxia type 1, fragile X mental retardation, spinobulbar muscular atrophy and myotonic dystrophy are all known to be caused by the expansion of trinucleotides. Huntington disease, spinobulbar muscular atrophy, and the autosomal dominant cerebellar ataxias are examples of autosomal dominant disorders caused by the expansion of trinucleotides (CAG) within disease genes. The CAG expansions appear to result in a gain of gene function. Prenatal, presymptomatic, and differential diagnostic tests are based on the detection of the repeat expansions. Classification of the repeat expansion disorders could be based upon mutation sequence and pathogenic mechanism. The four types of repeat expansion disorders defined by this approach are 1/ the CAG/polyglutamine repeat diseases; 2/ the loss-of-function repeat diseases; 3/the RNA gain-of-function repeat diseases; and 4/ the polyalanine diseases.
1/ The first class of disorders, the Type 1 repeat diseases, are the ‘‘CAG-polyglutamine disorders.’’ This class of repeat diseases includes nine inherited neurodegenerative disorders (SBMA, Huntington’s disease, dentatorubral pallidoluysian atrophy, and six forms of spinocerebellar ataxia) that all share the common feature of being caused by a CAG repeat located within the coding region of a gene. Upon CAG repeat expansion, a mutant protein with an extended polyglutamine tract is produced, making the protein then adopt an abnormal conformation and misfold to initiate the pathogenic cascade.
2/ The Type 2 repeat diseases are the ‘‘Loss-of-function repeat disorders.’’ These disorders include different repeats that vary in sequence composition and gene location, but share a final common

pathway of disease pathogenesis–a loss of function of the disease gene within which they occur. This group includes various classic trinucleotide repeat disorders such as the two fragile X syndromes of mental retardation (FRAXA and FRAXE) and Friedreich's ataxia – but also encompasses the dodecamer repeat expansion in progressive myoclonic epilepsy type 1, and possibly the CAG repeat expansion in Huntington's disease like-2 (HDL2) gene.

3/ Type 3 disorders, comprise a shared class because all of them have been proposed to involve the production of a toxic RNA species. This category of repeat diseases is thus called the RNA gain-of-function disorders. Included among these disorders are two closely related forms of DM, the common and classic myotonic dystrophy type 1 (DM1) and its uncommon phenocopy, myotonic dystrophy type 2 (DM2).

4/ Type 4 disorders, are the ''GCG-polyalanine disorders'' that are grouped together because all involve short GCG repeat tracts falling within the coding regions of unrelated genes that become expanded to moderately sized GCG repeats. With the exception of oculopharyngeal muscular dystrophy, all are developmental malformation syndromes, and while gain- of-function polyalanine toxicity has been proposed for a number of these disorders, loss of function due to the polyalanine expansion seems more likely for others. It is now apparent that triplet repeat expansion is responsible for a number of genetic conditions, primarily neurologic disease

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