More than 20 human hereditary diseases have been linked to expansions of unstable simple nucleotide repeats. These disorders include several clinically heterogeneous neurological diseases such as the fragile X syndrome (FXS), Friedreich´s ataxia (FRDA1), Huntington´s disease (HD), multiple types of spinocerebellar ataxias (SCA), and myotonic dystrophy type 1 (DM1). The phenotype of these disorders shows wide variability ranging from mild symptoms with late onset to severe congenital forms. The pathogenic mechanism of these expansions depends mainly on the type, localization and length of the repeat. Expansions of tracts of CAG triplets in coding regions cause polyglutamine disorders with abnormal protein function. Expanded non-coding repeats can silence gene expression or produce toxic RNAs which can be engaged in abnormal interactions with RNA-binding proteins [reviewed in 1].

The fragile X syndrome is one of the most common causes of inherited mental retardation with estimated frequency of 1 in 4000-9000 males and 1 in 7000-15000 females [2]. The disorder is associated with the expansion of a polymorphic CGG repeat in the 5´ untranslated region of the *FMR1* gene in Xq27.3 [3-6]. Affected males with full mutations (over 200 CGG repeats) have mental impairment with dysmorphic features (elongated face, prominent jaw, and large protruding ears), hyperextensibility of joints, and large testes in adulthood. Speech and behavioral problems like hyperactivity and autism are also frequent. Affected females with full mutations have highly variable milder phenotype due to the presence of the second, active *FMR1* allele. About 50% have mental retardation and behavioral problems [reviewed in 7]. Alleles with 59-200 CGG repeats represent premutations. They cause low-penetrant neurodegenerative disorder called fragile X-associated tremor/ataxia syndrome (FXTAS) in older males and more rarely also in females [8], or premature ovarian failure (POF) in females [9]. The pathogenesis of these disorders probably involves a toxic effect of the *FMR1* mRNA or a mild reduction of the FMRP protein [reviewed in 10]. Premutations are unstable and can expand into full mutations in the next generation if transmitted by a female.

Myotonic dystrophy (DM) is an autosomal dominant multisystem disorder characterized by muscular dystrophy, myotonia, cataracts, testicular atrophy, frontal balding, and cardiac conduction defect. It is the most common form of adult muscular dystrophy. Its prevalence is estimated to be 1 in 8000 [11]. Myotonic dystrophy type 1 (DM1) is caused by the expansion of a CTG repeat located in the 3´ untranslated region of the *DMPK* gene in 19q13.3 [12-14]. The number of CTG repeats in normal individuals varies among 5-34. These alleles are relatively stable in intergenerational transmission. Intermediate alleles with 35-49 repeats tend to expand in length. Mildly affected patients have mutated alleles with 50-150 repeats, classical DM1 patients have 100-1000 repeats and severe congenital cases, always transmitted from females, can have more than 2000 repeats [15,16]. DM1 shows genetic anticipation, a more severe disease course and earlier onset in successive generations in a family. This phenomenon is usually accompanied by an increase in the number of CTG repeats [17,18]. The second form of myotonic dystrophy (type 2, DM2) is caused by the expansion of a CCTG repeat located in intron 1 of the *ZNF9* gene in 3q21 [19]. Although DM2 is clinically milder than DM1 (no congenital or child forms or mental impairment), the expansion of the CCTG repeat can be much longer than the expansion of the CTG repeat in DM1. Expanded alleles carry 75-11000 CCTG. The repeat also shows higher somatic instability than the DM1 repeat [19,20]. DM1 and DM2 probably share a common pathogenic mechanism leading to a similar phenotype, most likely via the effect of toxic mRNA [21,22].