

# Trinucleotide repeat disorders: an interesting interface between psychiatry and medicine

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## SUMMARY

The discovery of conditions resulting from the expansion of unstable trinucleotide repeats, with their neuropsychiatric presentations crossing the boundaries of different specialties, provides ample opportunity for research and liaison work between medical and psychiatric subspecialties. Clinicians' awareness of the presentations and genetic basis of these conditions improves management strategies and the quality of life of patients and their carers.

## DECLARATION OF INTEREST

None

diagnosis will adversely affect future planning, at great financial and emotional cost: for example, the individual may lose their job, be unable to take out a mortgage or life insurance, lose their driving licence and independence.

The psychiatric symptoms that can occur with each TRD vary. However, all have the potential to cause mental health problems and, as with the diagnosis of many serious chronic diseases, this can give rise to profound emotional concerns for the patient. In addition, there is a wider impact on the families, who will require support through the process of diagnosis and management relating not just to the patient, but to family members at risk of developing the disease (Orr 2007).

This brief article aims to stimulate interest among clinicians by focusing on fragile-X syndrome and Huntington's disease, as these are commonly reported at the interface of psychiatry and medicine. However, it summarises common management strategies that are applicable to all TRDs. Readers are advised to refer to other resources for a more comprehensive overview of this topic (Box 1).

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Trinucleotide repeat disorders (TRDs) occur as a result of the expansion of unstable repeats exceeding normal limits (Table 1). Diagnosis of these disorders, in particular Huntington's disease, can be devastating for individuals and families as hopes for the future may be destroyed (e.g. When will they develop symptoms? Will they be able to have an unaffected child?). In addition,

**TABLE 1** Genetics and clinical features of trinucleotide repeat disorders (TRDs)

TRD	Mode of inheritance	Repeats involved	Examples of presentation
Dentatorubral-pallidoluysian atrophy	Autosomal dominant	CAG ≥49 Chromosome 12	Symptom onset is variable and depends on trinucleotide repeat length; can present with ataxia, dementia, depression, anxiety, chorea, etc.
Fragile-X syndrome	X-linked dominant	CGG >200	Intellectual disability, epilepsy, attention-deficit hyperactivity disorder, autistic-like features
Friedreich's ataxia	Autosomal recessive	GAA ≥70 Chromosome 9	Progressive ataxia, dysarthria, depression, etc.
Huntington's disease	Autosomal dominant	CAG ≥40 Chromosome 4	Chorea, dementia, depression
Myotonic dystrophy	Autosomal dominant	CTG >50 Chromosome 19	Intellectual disability or psychiatric symptoms can occur but main presentation is usually with muscle weakness, etc.
Spinobulbar muscular atrophy	X-linked recessive	CAG ≥38	Progressive muscles weakness and atrophy, fasciculation, etc.
Spinocerebellar ataxia	Autosomal dominant	Various, depending on the subtype	Variability in age at onset dependent on trinucleotide repeat length. Psychosis and dementia can occur with some subtypes, but progressive ataxia is the main presentation

A, adenine; C, cytosine; G, guanine; T, thymine.

Information gathered from various areas of The Medical Biochemistry Page leading from <http://themedicalbiochemistrypage.org/trinucleotiderepeatdisorders.php>.

**BOX 1 Charity website addresses**

**Ataxia UK:** information on dentatorubral-pallidoluysian atrophy, Friedreich's ataxia and spinocerebellar ataxia  
<https://www.ataxia.org.uk/ataxia-types1>

**Fragile X Society**  
<http://www.fragilex.org.uk>

**Huntington's Disease Association**  
<https://hda.org.uk>

**HDBuzz:** Huntington's disease research news  
<https://en.hdbuzz.net>

**Huntington's Disease Youth Organization (HDYO)**  
<https://en.hdyo.org>

**Myotonic Dystrophy Support Group**  
<http://www.myotonicdystrophysupportgroup.org>

**Spinal Muscular Atrophy Support UK**  
<http://www.smasupportuk.org.uk>

**Fragile-X syndrome**

Fragile-X syndrome is the leading cause of inherited intellectual disability (McCary 2013), with the phenotype attributed to the full mutation affecting 1 in 3600–8000 of the population (Cornish 2008). The premutation allele is unstable and expands with successive generations – the Sherman paradox (O'Donnell 2002). On reaching adulthood, patients are often transferred from child psychiatry and paediatric teams to intellectual disability services for the management of challenging behaviours, attention-deficit hyperactivity disorder, autistic-like features, epilepsy and psychiatric symptoms.

**Huntington's disease**

Huntington's disease is a neurodegenerative disorder with a prevalence of 4–10 per 100 000 of the population; it has a mean age at onset of 40 years and progression to death within 15–20 years of motor symptom onset (Ross 2011). The expansion of the repeats through successive generations is associated with an earlier onset and a more severe presentation (anticipation phenomena).

Huntington's disease is usually diagnosed by neurologists following assessment of chorea. However, the symptoms are heterogeneous, and undiagnosed patients may initially present to mental health services with psychiatric, behavioural or cognitive symptoms such as depression, aggression, psychosis or dementia (Jauhar 2010).

**Management of TRDs**

Management strategies should include: predictive genetic counselling for family members (Baig

2016); availability of counselling after diagnosis; referral to diagnosis-specific resources (e.g. specialist clinics, charities and patient/carer support groups) to identify any ongoing concerns and to address these early on; opportunity for patients to participate in research and clinical trials; psychological therapies for ongoing emotional distress; and advice on healthy lifestyles, for example exercise, diet, restful sleep and stress reduction strategies. There are also pharmacological interventions to manage chorea and psychiatric symptoms. Psychiatrists are therefore well positioned to promote patients' emotional and mental well-being and optimise prevention or treatment of accompanying mental health problems. Additional input from members of the multidisciplinary and multiagency teams aims to manage symptoms through a patient-centred approach and across the life span. It includes regular input from district nurses for the management of physical health problems such as incontinence and skin breakdown, community psychiatric nurses to monitor patients' mental health and their response to medications, dieticians to maintain weight, speech and language therapists to manage swallowing and communication difficulties, and occupational therapists and physiotherapists to offer advice on environment and mobility aids to ensure safety and reduce the risk of falls.

Psychological interventions can also be extremely helpful in addressing stigma and guilt, as patients often report a fear of having passed the gene on to their children. General practitioners' regular review and treatment of superimposed illnesses such as infection are essential parts of management strategies. The involvement of social services, commissioners, advocacy and charity organisations (Box 1) can help to improve patients' living conditions through appropriate housing, benefits entitlement, supported employment and structured day-time and leisure activities. In some cases, vulnerability and safeguarding concerns necessitate close collaboration with legal authorities.

The nature of TRDs presents challenges to both the patients and the medical professionals looking after them. For asymptomatic patients and their families there is often uncertainty regarding the onset, duration and symptom profile of their disease, particularly in the case of Huntington's disease. Furthermore, owing to the genetic components, this can have far-reaching and devastating effects on families, who at the same time as they are coming to terms with the diagnosis may need to be educated about complex concepts concerning inheritance of the condition.

Clinicians working with this group of patients must be competent in risk assessment, especially as regards risk of suicide. One study (Paulsen 2005) found that there were two critical periods for increased risk of suicide in Huntington's disease: the first was immediately before receiving a formal diagnosis and the second was when independence diminished. It is therefore critical for health professionals to be aware of suicidality and provide support for their patients accordingly.

### The importance of keeping up to date

Our knowledge and understanding of TRDs is constantly evolving, but the exact details of the clinical course of the condition for each patient remain uncertain. This exemplifies the need to remain up to date with the current evidence base.

Furthermore, it is essential to the doctor–patient relationship that patients have confidence in medical professionals' knowledge and feel comfortable asking questions. It is important to empower patients to engage in discussions about their illness and its management, with the realistic expectation that their concerns and questions will be addressed compassionately using current scientific evidence. This is an important concept to convey to patients so that they remain empowered, informed and educated throughout the course of their illness. Equally, patients should be

encouraged to engage with services and participate in joint decision-making regarding their mental and physical health as far as it is practical within the support network provided by members of the multidisciplinary team.

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