METRO CONNECT

THE DIAGNOSTIC NEWSLETTER FOR CLINICIANS

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TRINUCLEOTIDE REPEAT DISORDERS

INTRODUCTION

- A kind of mutation where trinucleotide repeats in certain genes exceeds the normal, stable threshold which differs per gene.
- It is also called ***trinucleotide repeat expansion disorders***, ***triplet repeat expansion disorders*** or ***codon reiteration disorders***.
- A single gene is responsible for the manifestations of Trinucleotide Repeat Disorders. Eg: *htt* gene in Huntingtons disease.
- **GENETIC ANTICIPATION** is the hallmark of Trinucleotide repeat disorders. In Anticipation, a genetic disorder is passed on to the next generation; the symptoms of the genetic disorder become apparent at an earlier age with each generation.
- Large expansions (full mutations) are penetrant in all males & many females. Small expansions (premutations) are seldom associated with cognitive deficits in males&females,but, if present in symptomatic individuals it confirms clinical diagnosis.
- Extensive study of family history and pedigree analysis assist in the diagnosis of Trinucleotide Repeat Disorders.[1]

Polyglutamine (Poly Q) diseases

Autosomal dominant

- 3 – 10 / 100,000 ≈ *Huntington's Disease*
- 1 – 2 / 100,000 ≈ *Spinocerebellar Ataxia*
- 1/8000 ≈ *Mytonic Dystrophy*

Non-Polyglutamine (Poly Q) diseases

- *Friedreich Ataxia* ≈ 1 / 50000 — Autosomal recessive
- *Spinobulbar Muscular Atrophy* ≈ 3 / 100000 — Autosomal recessive
- *Fragile X syndrome* ≈ 1 / 4000 — X-linked

Facial Features
Large protruding ears (both)
Elongated face(vertical maxillary excess)

Vision
Cataracts
Retinal damage
Double vision and Abnormal eye movements

Respiration system
Breathing difficulties and Sleep apnea

Gastrointestinal tract
Lower digestive tract, colon, Rectum, anus and irritable bowel syndrome

Endocrine system
Insulin dependent Diabetes mellitus

Balance and coordination
Hand-flapping and flat feet
Seizures
Incoordination of gait
Chorea
Waddling gait
Aggressive scoliosis (curvature of the spine)

Cognitive function
Intellectual impairment
Dementia
Psychological disorders
Motor neurons degeneration of brain stem & spinal cord

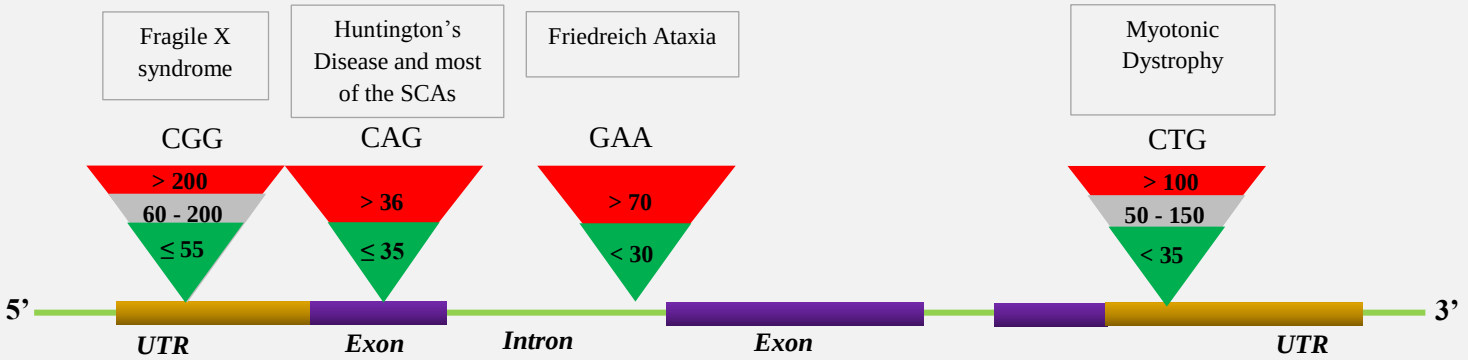
Cardiovascular system
Arrhythmias & Cardiomyopathy
Cardiac muscle impairment

Reproductive system
Low testosterone levels & Weakened uterine muscles
Larger testes (macroorchidism)
Erectile dysfunction
Low sperm count & Gynecomastia (breast enlargement)

Muscles
Muscle tightness (Spasticity)
Loss of coordination (ataxia) in arms and legs
Muscle loss (Atropy)
Dysarthria
Muscle contracture (dystonia)
Weakness of tongue and mouth muscles &Muscle cramps
Large calf muscles
Muscle Weakness

An initiative by:
METROPOLIS The Pathology Specialist

TRINUCLEOTIDE REPEAT DISORDERS



Full mutation

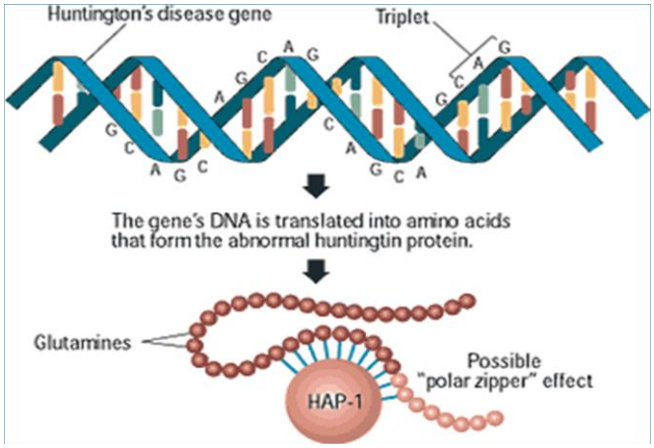
Premutation range (may expand to a full mutation in the next generation)

Normal alleles

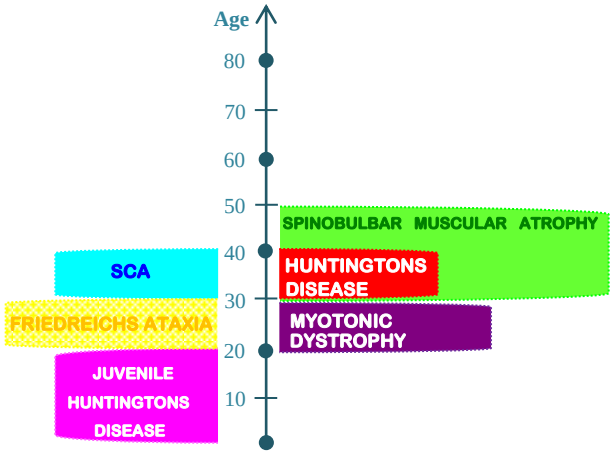
UTR = untranslated region
SCA = spinocerebellar ataxia

MECHANISM OF TRINUCLEOTIDE REPEAT DISORDERS [2]

Many hypotheses have been proposed to understand mechanism of trinucleotide repeat disorders. Most studied mechanism is of Huntingtons Disease.



AGE OF ONSET OF TRINUCLEOTIDE DISORDERS



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Management of Trinucleotide repeat disorders | Spinocerebellar ataxia | Huntington's disease | Mytonic Dystrophy | Fragile X syndrome | Friedreich Ataxia | Spinobulbar Muscular atrophy

Detailed clinical & physical examination	**Motor symptoms** tests like reflex, muscle tone, coordination, balance **Sensory symptoms** like sense of touch, hearing and eye movement **Neuropsychological testing** like memory, reasoning, language function and spatial reasoning **Psychiatric evaluation** like patterns of behaviour, quality of judgement, signs of disordered thinking
Baseline tests	Nerve conduction velocity tests (NCV) and Electromyography (EMG)
Cardiac evaluation	Electrocardiogram and echocardiograph
Brain Imaging tests	MRI and CT scan
Confirmatory tests	***Molecular Genetic Testing (GOLD STANDARD)***

*** *Detailed evaluation of family history, consanguinity and pedigree analysis is essential in management of trinucleotide repeat*

*** *Pre and Post Genetic counselling help understand genetic diseases, explain risks-benefits of genetic testing for patient &relatives.*

TESTS OFFERED BY METROPOLIS HEALTHCARE LTD. FOR TRINUCLEOTIDE REPEAT DISORDERS	
Spino Cerebellar Ataxia ***Comprehensive panel*** (SCA-1,2,3,6,7 and 12)	Fragile X Mutation detection
Spino Cerebellar Ataxia (SCA-1,2,3,6,7,12 and 17) – ***Individual tests***	DRPLA gene analysis
Spinal bulbar Muscular atrophy	Friedreich ataxia Mutation Analysis
Huntington Disease Mutation Analysis	Myotonic Dystrophy Type 1 and 2

References:
1. Huntingtons Outreach Project, Stanford, 2010.
2. Diverse Mechanisms of Trinucleotide Repeat Disorders: An Exploration of Fragile X Syndrome and Huntington's Disease, Cara Strobel, 2013.
3. EMQN/CMGS best practice guidelines for the molecular genetic testing of Huntington disease, Losekoot M, 2013.

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