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Huntington's disease (**HD**) also known as **Huntingtons chorea** is degenerative neurological disease arising from irregular expansions of glutamine (CAG) repeats. The number of the repeats are inversely proportional to the on-set of the disease. It is an autosomal dominant disease, hence it does not skip generations.

The mean on-set of the disease is 35-45 years of age. The slow progressive neuronal death associated with HD is phenotypically characterised by progressive motor, cognitive, and physical abnormalities.

Currently, no curative treatments are available for HD.

Aetiology

Mutation

The gene affected is found on chromosome 4, on the p arm 16.3 and is the huntingtin gene (HTT), which codes for the protein product huntingtin (Htt). The wild type (normal) of the the huntingtin gene contains a highly polymorphic CAG nucleotide repeats (which code for glutamine) in the first exon to the 5' end. The disease occurs due to expansion of the CAG repeats in this exon. Different lengths of this area cause different times of on-set of the disease: the wild type contains 10-26 repeats; 28-35 intermediate (unaffected); 36-40 reduced penetrance (the disease may not be fully expressed, so patients may or may not be affected); mutant alleles contain >40 affected.

Phenotype	No. CAG repeats	Features
Normal	<26	Stable throughout meiosis
Normal	27-35	'Premutation' unstable in paternal meiosis
Mild HD	36-39	Late onset or non-penetrance
Adult-onset HD	>40	Symptoms from average age 41 years
Juvenile-onset HD	>55	Symptoms before age 20 years

Of the patients with Huntington's 3% are thought to have developed the disease from a new mutation (de novo), whereas 97% have inherited it from one (or more) of their parents. A possible cause of the extension of CAG repeated sequence in huntingtin maybe slippage of DNA-polymerase during spermatogenesis.

Within cells, huntingtin may be involved in signalling, transporting materials, binding proteins and other structures, and protecting against programmed cell death, the mutated form is cleaved by caspases, which creates a toxic product that kills cells. The CAG repeats promote abnormal aggregation's of polygluatmine near the nuclei of the neurons, mainly in the corpus striatum.

Inheritance

The gene causing Huntington's disease is autosomal dominant, this means that mutant allele (H) masks the effect of the wild type allele (h). Therefore the phenotypes look like this:

- Hh= Affected
- hh= Unaffected
- HH= Affected but very rare

As the HTT gene is on chromosome 4 the inheritance is not determined by sex, however individuals inheriting the mutation from their father have a greater risk of early onset of the disease, approximately 80% of patients with juvenile-onset Huntington's disease inherit the mutant Hd gene from their father.

97% of Huntington's disease suffers have inherited the mutant gene. Due to the dominance of the mutant allele (H) if one parent is heterozygous for the huntingtin gene (Hh) and therefore is affect by the disease each child has 50% chance of inheriting the disease, as shown in this punnet square.

		Affected parent (Hh)	
	gametes	**H**	**h**
Unaffected parent (hh)	**h**	Hh affected	hh unaffected
	h	Hh affected	hh unaffected

If looking at a pedigree for Huntington's, the disease with not skip a generation (unless there is incomplete penetrance). This leads to a characteristic pedigree, and is a valuable tool in diagnose and calculating possible risk for siblings or future children. People with HH genotype are rare due to the rarity of the disease, but may happen with consanguineous families. The effect of possessing 2 mutated genes is thought accelerate the onset of the disease.

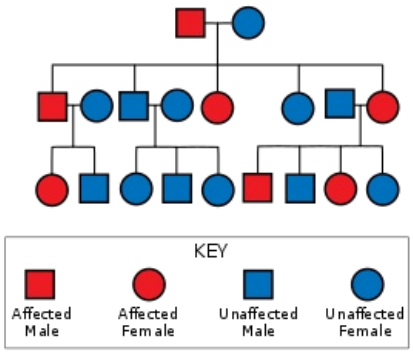

Diagram showing classic pedigree with autosomal dominant trait such as Huntington's. The father possesses the gene thus is affected while the mother is unaffected ;The affected offspring also have affected children. The probability of each offspring inheriting an affected gene is 50%. Inheritance is independent of gender, and the phenotype does not skip generations.

Frequency

Around 1/10-20000 Caucasians have the disease, this is higher than other ethnicities.

Phenotype

The average age of onset is 35-45 years and the mean survival after diagnosis is 15-18 years. Approximately, 25% of patients develop HD after the ages of 50 years and 10% before the age of 20years.

The patient’s age at disease onset is inversely proportional to the number of CAG repeats, although, the number of CAG repeats does not correlate with other features of HD. Hence, tandem repeats do not affect the severity of symptoms in HD. The slow progressive neuronal death associated with HD is phenotypically characterised by progressive motor, cognitive, and physical abnormalities

Motor:

- Involuntary “Choreic” movements is present in more than 90% of patients is characterized by non-repetitive, non periodic jerks that cannot be suppressed voluntarily(i.e. facial grimacing, witching, folding of arms and crossing of legs)
- 30% - 50% of patients experience seizures
- Gait becomes unsteady

Cognitive:

- Begin early in the disease and affect the whole cognitive system
- Language affected later than other cognitive functions
- Behavioural disturbances include; social disinhibition, aggression, outbursts, apathy, sexual deviation and increase appetite
- Psychiatric manifestations include; personality changes, affective psychosis and schizophrenia
- Behavioural disturbances decrease as the disease advances

Physical:

- Shown at the end stages of HD
- Develop such sever motor impairments that they are completely dependent on others
- Weight loss
- Sleep disturbances
- Incontinence
- Mutism

Advanced patients have difficulty swallowing, and typically die of pneumonia, cardiorespiratory failure, subdural haematoma after head trauma or suicide.

Management

Currently, no curative treatments are available for HD. Instead, therapy focuses on supportive care as well as pharmacological management of behavioural and neurological problems

- Drugs can suppress symptoms of involuntary movements, depression and mood swings.
- Speech therapy can help to improve upon speech and swallowing problems
- High calorie intake will help to maintain weight and improve symptoms.
- Constant nursing care is needed in the later stage of the disease and support for carers Is important too.
- In Vitro Fertilisation (IVF), for future children so egg, sperm or embryo can be screened make sure the gene is not present.

Research

Transplant of Embryonic Stem Cells (ESG) appear in some cases to repair and rejuvenate the damaged area.

Researchers in the University of Leeds have noted that a naturally occurring protein in the body is causing some of the disruption in the brains of HD patients. Its effects may be modified and controlled by using drugs that are currently being used to help cancer patients.

Also it has been shown in mice models that the drug Memantine, which is approved to treat Alzheimer's disease, successfully treated Huntington's disease; by preserving normal synaptic electrical activity and suppressing excessive extrasynaptic electrical activity.

Unfortunately, It is likely to be years before these developments will result in an effective treatment.

Ethics

There are several ethical issues arising from Huntington's disease. This spread from genetic testing, embryonic stem cells, abortion if prenatal diagnoses shows molecular features of Huntington's, IVF and euthanasia/suicide.

A large problem with Huntington's is the late on-set of the disease. This brings about further issues.

- The first being whether a patient wishes to be tested and possibly finding out they will die early or not. Due to the 50/50 chance of inheriting the disease many people do not wish to find out if they have Huntington's or not and would rather live unsure, as knowing will change their life forever.
- The second is that by the time people develop the disease they may have already had children and therefore may have already past on the disease.

It is possible for sperm eggs to be screened and selected against the gene, so any found with the gene my be discarded. If a foetus is found to be carrying the disease the mother may opt to abort it, which has the obvious ethical issues. Stem cells used in possible treatments also carry ethical issues.

Many people if they know they have disease commit suicide before the disease takes hold, or in the early stages, which some people view as wrong. Other people may wish to end their lives with help when the disease has taken hold (euthanasia) which also causes large ethical debates.

Links

http://www.who.int/genomics/public/geneticdiseases/en/index2.html

http://nervous-system.emedtv.com/huntinton’s-disease/huntington’s-disease-statistics-p2.html

http://www.bbc.co.uk/health/physical-health/condtions/huntingtons1.shtml

http://www.sciencedaily.comn/releases/2009/11/09/091115134134.html

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Pritchard, Dorian J. – Korf, Bruce R “Medical Genetics at a Glance” 2nd edition, Blackwell publishing, 2007 ISBN: 1405148462