LECTURE 7: GENETICS

The vast majority of cases of Alzheimer's disease are sporadic, meaning that they are not genetically inherited although some genes may act as risk factors. On the other hand, around 0.1% of the cases are familial forms of autosomal dominant (not sex-linked) inheritance, which usually have an onset before age 65.This form of the disease is known as Early onset familial Alzheimer's disease.

Most of autosomal dominant familial AD can be attributed to mutations in one of three genes: amyloid precursor protein (APP) and presenilins 1 and 2.[74] Most mutations in the APP and presenilin genes increase the production of a small protein called Aβ42, which is the main component of senile plaques.Some of the mutations merely alter the ratio between Aβ42 and the other major forms—e.g., Aβ40—without increasing Aβ42 levels.This suggests that presenilin mutations can cause disease even if they lower the total amount of Aβ produced and may point to other roles of presenilin or a role for alterations in the function of APP and/or its fragments other than Aβ.

Most cases of Alzheimer's disease do not exhibit autosomal-dominant inheritance and are termed sporadic AD. Nevertheless genetic differences may act as risk factors. The best known genetic risk factor is the inheritance of the ε4 allele of the apolipoprotein E (APOE).Between 40 and 80% of people with AD possess at least one apoE4 allele.The APOEε4 allele increases the risk of the disease by three times in heterozygotes and by 15 times in homozygotes.However, it must be noted that this "genetic" effect is not necessarily purely genetic. For example, certain Nigerian populations have no relationship between presence or dose of APOEε4 and incidence or age-of-onset for Alzheimer's disease.Geneticists agree that numerous other genes also act as risk factors or have protective effects that influence the development of late onset Alzheimer's disease,[74] but results such as the Nigerian studies and the incomplete penetrance for all genetic risk factors associated with sporadic Alzheimers indicate a strong role for environmental effects. Over 400 genes have been tested for association with late-onset sporadic AD,[74] most with null results.

Diagnosis

PET scan of the brain of a person with AD showing a loss of function in the temporal lobe

Alzheimer's disease is usually diagnosed clinically from the patient history, collateral history from relatives, and clinical observations, based on the presence of characteristic neurological and neuropsychological features and the absence of alternative conditions.Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and with single photon emission computed tomography (SPECT) or positron emission tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia.[83] Moreover, it may predict conversion from prodromal stages (mild cognitive impairment) to Alzheimer's disease.

Assessment of intellectual functioning including memory testing can further characterise the state of the disease.Medical organisations have created diagnostic criteria to ease and standardise the diagnostic process for practicing physicians. The diagnosis can be confirmed with very high accuracy post-mortem when brain material is available and can be examined histologically.

Criteria

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA, now known as the Alzheimer's Association) established the most commonly used NINCDS-ADRDA Alzheimer's Criteria for diagnosis in 1984,extensively updated in 2007.These criteria require that the presence of cognitive impairment, and a suspected dementia syndrome, be confirmed by neuropsychological testing for a clinical diagnosis of possible or probable AD. A histopathologic confirmation including a microscopic examination of brain tissue is required for a definitive diagnosis. Good statistical reliability and validity have been shown between the diagnostic criteria and definitive histopathological confirmation.Eight cognitive domains are most commonly impaired in AD—memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving and functional abilities. These domains are equivalent to the NINCDS-ADRDA Alzheimer's Criteria as listed in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) published by the American Psychiatric Association.

Techniques

Neuropsychological screening tests can help in the diagnosis of AD. In the tests, people are instructed to copy drawings similar to the one shown in the picture, remember words, read, and subtract serial numbers.

Neuropsychological tests such as the mini-mental state examination (MMSE), are widely used to evaluate the cognitive impairments needed for diagnosis. More comprehensive test arrays are necessary for high reliability of results, particularly in the earliest stages of the disease.Neurological examination in early AD will usually provide normal results, except for obvious cognitive impairment, which may not differ from that resulting from other diseases processes, including other causes of dementia.

Further neurological examinations are crucial in the differential diagnosis of AD and other diseases.Interviews with family members are also utilised in the assessment of the disease. Caregivers can supply important information on the daily living abilities, as well as on the decrease, over time, of the person's mental function.A caregiver's viewpoint is particularly important, since a person with AD is commonly unaware of his own deficits. Many times, families also have difficulties in the detection of initial dementia symptoms and may not communicate accurate information to a physician.

Another recent objective marker of the disease is the analysis of cerebrospinal fluid for amyloid beta or tau proteins,both total tau protein and phosphorylated tau_{181P} protein concentrations.Searching for these proteins using a spinal tap can predict the onset of Alzheimer's with a sensitivity of between 94% and 100%.When used in conjunction with existing neuroimaging techniques, doctors can identify people with significant memory loss who are already developing the disease.Spinal fluid tests are commercially available, unlike the latest neuroimaging technology.Alzheimer's was diagnosed in one-third of the people who did not have any symptoms in a 2010 study, meaning that disease progression occurs well before symptoms occur.

Supplemental testing provides extra information on some features of the disease or is used to rule out other diagnoses. Blood tests can identify other causes for dementia than ADcauses

which may, in rare cases, be reversible.It is common to perform thyroid function tests, assess B12, rule out syphilis, rule out metabolic problems (including tests for kidney function, electrolyte levels and for diabetes), assess levels of heavy metals (e.g. lead, mercury) and anaemia. (See differential diagnosis for Dementia). (It is also necessary to rule out delirium).

Psychological tests for depression are employed, since depression can either be concurrent with AD (see Depression of Alzheimer disease), an early sign of cognitive impairment, or even the cause.

Imaging

When available as a diagnostic tool, single photon emission computed tomography (SPECT) and positron emission tomography (PET) neuroimaging are used to confirm a diagnosis of Alzheimer's in conjunction with evaluations involving mental status examination.In a person already having dementia, SPECT appears to be superior in differentiating Alzheimer's disease from other possible causes, compared with the usual attempts employing mental testing and medical history analysis. Advances have led to the proposal of new diagnostic criteria.

A new technique known as PiB PET has been developed for directly and clearly imaging beta-amyloid deposits in vivo using a tracer that binds selectively to the A-beta deposits.[104] The PiB-PET compound uses carbon-11 PET scanning. Recent studies suggest that PiB-PET is 86% accurate in predicting which people with mild cognitive impairment will develop Alzheimer's disease within two years, and 92% accurate in ruling out the likelihood of developing Alzheimer's.

A similar PET scanning radiopharmaceutical compound called (E)-4-(2-(6-(2-(2-(2-(2-(^{18}F-fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-N-methyl benzenamine, or ^{18}F AV-45, or florbetapir-fluorine-18, or simply florbetapir, contains the longer-lasting radionuclide fluorine-18, has recently been created, and tested as a possible diagnostic tool in Alzheimer's disease.Florbetapir, like PiB, binds to beta-amyloid, but due to its use of fluorine-18 has a half-life of 110 minutes, in contrast to PiB's radioactive half life of 20 minutes. Wong *et al.* found that the longer life allowed the tracer to accumulate significantly more in the brains of people with AD, particularly in the regions known to be associated with beta-amyloid deposits.

One review predicted that amyloid imaging is likely to be used in conjunction with other markers rather than as an alternative.

Volumetric MRI can detect changes in the size of brain regions. Measuring those regions that atrophy during the progress of Alzheimer's disease is showing promise as a diagnostic indicator. It may prove less expensive than other imaging methods currently under study.

Non-Imaging biomarkers

Recent studies have shown that people with AD had decreased glutamate (Glu) as well as decreased Glu/creatine (Cr), Glu/myo-inositol (mI), Glu/N-acetylaspartate (NAA), and NAA/Cr ratios compared to normal people. Both decreased NAA/Cr and decreased hippocampal glutamate may be an early indicator of AD.

Early research in mouse models may have identified markers for AD. The applicability of these markers is unknown.

A small human study in 2011 found that monitoring blood dehydroepiandrosterone (DHEA) variations in response to an oxidative stress could be a useful proxy test: the subjects with MCI did not have a DHEA variation, while the healthy controls did.

Prevention

Intellectual activities such as playing chess or regular social interaction have been linked to a reduced risk of AD in epidemiological studies, although no causal relationship has been found.

At present, there is no definitive evidence to support that any particular measure is effective in preventing AD.Global studies of measures to prevent or delay the onset of AD have often produced inconsistent results. However, epidemiological studies have proposed relationships between certain modifiable factors, such as diet, cardiovascular risk, pharmaceutical products, or intellectual activities among others, and a population's likelihood of developing AD. Only further research, including clinical trials, will reveal whether these factors can help to prevent AD.

Although cardiovascular risk factors, such as hypercholesterolaemia, hypertension, diabetes, and smoking, are associated with a higher risk of onset and course of AD,statins, which are cholesterol lowering drugs, have not been effective in preventing or improving the course of the disease.The components of a Mediterranean diet, which include fruit and vegetables, bread, wheat and other cereals, olive oil, fish, and red wine, may all individually or together reduce the risk and course of Alzheimer's disease.Its beneficial cardiovascular effect has been proposed as the mechanism of action.There is limited evidence that light to moderate use of alcohol, particularly red wine, is associated with lower risk of AD.

Reviews on the use of vitamins have not found enough evidence of efficacy to recommend vitamin C, E,or folic acid with or without vitamin B_{12}, as preventive or treatment agents in AD. Additionally vitamin E is associated with important health risks. Trials examining folic acid (B9) and other B vitamins failed to show any significant association with cognitive decline. Docosahexaenoic acid, an Omega 3 fatty acid, has not been found to slow decline.

Long-term usage of non-steroidal anti-inflammatory drug (NSAIDs) is associated with a reduced likelihood of developing AD. Human postmortem studies, in animal models, or in vitro investigations also support the notion that NSAIDs can reduce inflammation related to amyloid plaques. However trials investigating their use as palliative treatment have failed to show positive results while no prevention trial has been completed. Curcumin from the curry spice turmeric has shown some effectiveness in preventing brain damage in mouse models due to its anti-inflammatory properties. Hormone replacement therapy, although previously used, is no longer thought to prevent dementia and in some cases may even be related to it.There is inconsistent and unconvincing evidence that ginkgo has any positive effect on cognitive impairment and dementia,and a recent study concludes that it has no effect in reducing the rate of AD incidence. A 21-year study found that coffee drinkers of 3–5 cups per day at midlife had a 65% reduction in risk of dementia in late-life.

People who engage in intellectual activities such as reading, playing board games, completing crossword puzzles, playing musical instruments, or regular social interaction show a reduced risk for Alzheimer's disease.[136] This is compatible with the cognitive reserve theory, which states that some life experiences result in more efficient neural functioning providing the individual a cognitive reserve that delays the onset of dementia manifestations. Education delays the onset of AD syndrome, but is not related to earlier death after diagnosis.Learning a second language even later in life seems to delay getting Alzheimer disease. Physical activity is also associated with a reduced risk of AD.

Two studies have shown that medical marijuana may be effective in inhibiting the progress of AD. The active ingredient in marijuana, THC, may prevent the formation of deposits in the brain associated with Alzheimer's disease. THC was found to inhibit acetylcholinesterase more effectively than commercially marketed drugs. A recent review of the clinical research has found no evidence that cannabinoids are effective in the improvement of disturbed behaviour or in the treatment of other symptoms of AD or dementia.

Some studies have shown an increased risk of developing AD with environmental factors such the intake of metals, particularly aluminium, or exposure to solvents. The quality of some of these studies has been criticised,and other studies have concluded that there is no relationship between these environmental factors and the development of AD.

While some studies suggest that extremely low frequency electromagnetic fields may increase the risk for Alzheimer's disease, reviewers found that further epidemiological and laboratory investigations of this hypothesis are needed. Smoking is a significant AD risk factor.Systemic markers of the innate immune system are risk factors for late-onset AD.

Management

There is no cure for Alzheimer's disease; available treatments offer relatively small symptomatic benefit but remain palliative in nature. Current treatments can be divided into pharmaceutical, psychosocial and caregiving.

Pharmaceutical

Five medications are currently approved by regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to treat the cognitive manifestations of AD: four are acetylcholinesterase inhibitors (Tacrine, Rivastigmine, Galantamine and Donepezil) and the other (memantine) is an NMDA receptor antagonist. No drug has an indication for delaying or halting the progression of the disease.

Reduction in the activity of the cholinergic neurons is a well-known feature of Alzheimer's disease.Acetylcholinesterase inhibitors are employed to reduce the rate at which acetylcholine (ACh) is broken down, thereby increasing the concentration of ACh in the brain and combating the loss of ACh caused by the death of cholinergic neurons.Cholinesterase inhibitors approved for the management of AD symptoms are donepezil (brand name *Aricept*), galantamine (*Razadyne*), and rivastigmine (branded as *Exelon* and *Exelon Patch*). There is evidence for the efficacy of these medications in mild to moderate Alzheimer's disease, and some evidence for their use in the advanced stage. Only donepezil is approved for treatment of advanced AD dementia. The use of these drugs in mild cognitive impairment has not shown any effect in a delay of the onset of AD. The most common side effects are nausea and

vomiting, both of which are linked to cholinergic excess. These side effects arise in approximately 10–20% of users and are mild to moderate in severity. Less common secondary effects include muscle cramps, decreased heart rate (bradycardia), decreased appetite and weight, and increased gastric acid production.

Glutamate is a useful excitatory neurotransmitter of the nervous system, although excessive amounts in the brain can lead to cell death through a process called excitotoxicity which consists of the overstimulation of glutamate receptors. Excitotoxicity occurs not only in Alzheimer's disease, but also in other neurological diseases such as Parkinson's disease and multiple sclerosis.Memantine (brand names *Akatinol*, *Axura*, *Ebixa*/*Abixa*, *Memox* and *Namenda*), is a noncompetitiveNMDA receptor antagonist first used as an anti-influenza agent. It acts on the glutamatergic system by blocking NMDA receptors and inhibiting their overstimulation by glutamate. Memantine has been shown to be moderately efficacious in the treatment of moderate to severe Alzheimer's disease. Its effects in the initial stages of AD are unknown. Reported adverse events with memantine are infrequent and mild, including hallucinations, confusion, dizziness, headache and fatigue. The combination of memantine and donepezil has been shown to be "of statistically significant but clinically marginal effectiveness".

Antipsychotic drugs are modestly useful in reducing aggression and psychosis in Alzheimer's disease with behavioural problems, but are associated with serious adverse effects, such as cerebrovascular events, movement difficulties or cognitive decline, that do not permit their routine use.When used in the long-term, they have been shown to associate with increased mortality.

People with Alzheimer’s disease who have taken Huperzine A may have improved general cognitive function, global clinical status, functional performance and reduced behavioural disturbance compared to people taking placebos, according to a Cochrane Review, however, the poor methodological quality of the small trials, including problems with blinding and randomisation, led reviewers to conclude "There is currently insufficient evidence of the effects of Huperzine A for Alzheimer's disease (AD)."

Psychosocial intervention

A specifically designed room for sensory integration therapy, also called snoezelen; an emotion-oriented psychosocial intervention for people with dementia

Psychosocial interventions are used as an adjunct to pharmaceutical treatment and can be classified within behaviour-, emotion-, cognition- or stimulation-oriented approaches. Research on efficacy is unavailable and rarely specific to AD, focusing instead on dementia in general.

Behavioural interventions attempt to identify and reduce the antecedents and consequences of problem behaviours. This approach has not shown success in improving overall functioning, but can help to reduce some specific problem behaviours, such as incontinence. There is a lack of high quality data on the effectiveness of these techniques in other behaviour problems such as wandering.

Emotion-oriented interventions include reminiscence therapy, validation therapy, supportive psychotherapy, sensory integration, also called snoezelen, and simulated presence therapy.

Supportive psychotherapy has received little or no formal scientific study, but some clinicians find it useful in helping mildly impaired people adjust to their illness. Reminiscence therapy (RT) involves the discussion of past experiences individually or in group, many times with the aid of photographs, household items, music and sound recordings, or other familiar items from the past. Although there are few quality studies on the effectiveness of RT, it may be beneficial for cognition and mood. Simulated presence therapy (SPT) is based on attachment theories and involves playing a recording with voices of the closest relatives of the person with Alzheimer's disease. There is partial evidence indicating that SPT may reduce challenging behaviours. Finally, validation therapy is based on acceptance of the reality and personal truth of another's experience, while sensory integration is based on exercises aimed to stimulate senses. There is little evidence to support the usefulness of these therapies.

The aim of cognition-oriented treatments, which include reality orientation and cognitive retraining, is the reduction of cognitive deficits. Reality orientation consists in the presentation of information about time, place or person in order to ease the understanding of the person about its surroundings and his or her place in them. On the other hand cognitive retraining tries to improve impaired capacities by exercitation of mental abilities. Both have shown some efficacy improving cognitive capacities, although in some studies these effects were transient and negative effects, such as frustration, have also been reported.

Stimulation-oriented treatments include art, music and pet therapies, exercise, and any other kind of recreational activities. Stimulation has modest support for improving behaviour, mood, and, to a lesser extent, function. Nevertheless, as important as these effects are, the main support for the use of stimulation therapies is the change in the person's routine.

Caregiving

Since Alzheimer's has no cure and it gradually renders people incapable of tending for their own needs, caregiving essentially is the treatment and must be carefully managed over the course of the disease.

During the early and moderate stages, modifications to the living environment and lifestyle can increase patient safety and reduce caretaker burden.Examples of such modifications are the adherence to simplified routines, the placing of safety locks, the labelling of household items to cue the person with the disease or the use of modified daily life objects. The patient may also become incapable of feeding themselves, so they require food in smaller pieces or pureed.When swallowing difficulties arise, the use of feeding tubes may be required. In such cases, the medical efficacy and ethics of continuing feeding is an important consideration of the caregivers and family members.The use of physical restraints is rarely indicated in any stage of the disease, although there are situations when they are necessary to prevent harm to the person with AD or their caregivers.

As the disease progresses, different medical issues can appear, such as oral and dental disease, pressure ulcers, malnutrition, hygiene problems, or respiratory, skin, or eyeinfections. Careful management can prevent them, while professional treatment is needed when they do arise. During the final stages of the disease, treatment is centred on relieving discomfort until death.

A small recent study in the US concluded that people whose caregivers had a realistic understanding of the prognosis and clinical complications of late dementia were less likely to receive aggressive treatment near the end of life.

NEUROSCIENCE

Feeding tubes

There is strong evidence that feeding tubes do not help people with advanced Alzheimer's dementia gain weight, regain strength or function, prevent aspiration pneumonias, or improve quality of life.

Huntington's disease

Huntington's disease (**HD**) is a neurodegenerativegenetic disorder that affects muscle coordination and leads to cognitive decline and psychiatric problems. It typically becomes noticeable in mid-adult life. HD is the most common genetic cause of abnormal involuntary writhing movements called chorea, and indeed the disease used to be called **Huntington's chorea**.

It is much more common in people of Western European descent than in those of Asian or African ancestry. The disease is caused by an autosomaldominantmutation in either of an individual's two copies of a gene called Huntingtin, which means any child of an affected parent has a 50% risk of inheriting the disease. Physical symptoms of Huntington's disease can begin at any age from infancy to old age, but usually begin between 35 and 44 years of age. Through genetic anticipation, the disease may develop earlier in life in each successive generation. About 6% of cases start before the age of 21 years with an akinetic-rigid syndrome; they progress faster and vary slightly. The variant is classified as **juvenile**, **akinetic-rigid** or **Westphal variant HD**.

The *Huntingtin* gene provides the genetic information for a protein that is also called "huntingtin". Expansion of a CAG triplet repeat stretch within the *Huntingtin* gene results in a different (mutant) form of the protein, which gradually damages cells in the brain, through mechanisms that are not fully understood. The genetic basis of HD was discovered in 1993 by an international collaborative effort spearheaded by the Hereditary Disease Foundation.

Genetic testing can be performed at any stage of development, even before the onset of symptoms. This fact raises several ethical debates: the age at which an individual is considered mature enough to choose testing; whether parents have the right to have their children tested; and managing confidentiality and disclosure of test results. Genetic counseling has developed to inform and aid individuals considering genetic testing and has become a model for other genetically dominant diseases.

Symptoms of the disease can vary between individuals and even among affected members of the same family, but usually progress predictably. The earliest symptoms are often subtle problems with mood or cognition. A general lack of coordination and an unsteady gait often follows. As the disease advances, uncoordinated, jerky body movements become more apparent, along with a decline in mental abilities and behavioral and psychiatric problems. Physical abilities are gradually impeded until coordinated movement becomes very difficult. Mental abilities generally decline into dementia. Complications such as pneumonia, heart disease, and physical injury from falls reduce life expectancy to around twenty years after symptoms begin. There is no cure for HD, and full-time care is required in the later stages of the disease. Existing pharmaceutical and non-drug treatments can relieve many of its symptoms.

Research and support organizations, first founded in the 1960s and increasing in number, work to increase public awareness, to provide support for individuals and their families, and to promote and facilitate research. Many new research discoveries have been made and understanding of the disease is improving. Current research directions include determining the exact mechanism of the disease, improving animal models to expedite research, clinical trials of pharmaceuticals to treat symptoms or slow the progression of the disease, and studying procedures such as stem cell therapy with the goal of repairing damage caused by the disease.

Contents

Signs and symptoms

Symptoms of Huntington's disease commonly become noticeable between the ages of 35 and 44 years, but they can begin at any age from infancy to old age.In the early stages, there are subtle changes in personality, cognition, and physical skills.The physical symptoms are usually the first to be noticed, as cognitive and psychiatric symptoms are generally not severe enough to be recognized on their own at the earlier stages. Almost everyone with Huntington's disease eventually exhibits similar physical symptoms, but the onset, progression and extent of cognitive and psychiatric symptoms vary significantly between individuals.

The most characteristic initial physical symptoms are jerky, random, and uncontrollable movements called chorea.Chorea may be initially exhibited as general restlessness, small unintentionally initiated or uncompleted motions, lack of coordination, or slowed saccadic eye movements.These minor motor abnormalities usually precede more obvious signs of motor dysfunction by at least three years. The clear appearance of symptoms such as rigidity, writhing motions or abnormal posturing appear as the disorder progresses.These are signs that the system in the brain that is responsible for movement has been affected.Psychomotor functions become increasingly impaired, such that any action that requires muscle control is affected. Common consequences are physical instability, abnormal facial expression, and difficulties chewing, swallowing and speaking.Eating difficulties commonly cause weight loss and may lead to malnutrition.Sleep disturbances are also associated symptoms.Juvenile HD differs from these symptoms in that it generally progresses faster and chorea is exhibited briefly, if at all, with rigidity being the dominant symptom. Seizures are also a common symptom of this form of HD.

Reported prevalences of behavioral and psychiatric symptoms in Huntington's disease	
Irritability	38–73%
Apathy	34–76%
Anxiety	34–61%
Depressed mood	33–69%
Obsessive and compulsive	10–52%
Psychotic	3–11%

Cognitive abilities are impaired progressively.Especially affected are executive functions which include planning, cognitive flexibility, abstract thinking, rule acquisition, initiating appropriate actions and inhibiting inappropriate actions.As the disease progresses, memory deficits tend to appear. Reported impairments range from short-term memory deficits to long-

term memory difficulties, including deficits in episodic (memory of one's life), procedural (memory of the body of how to perform an activity) and working memory.Cognitive problems tend to worsen over time, ultimately leading to dementia. This pattern of deficits has been called a subcortical dementia syndrome to distinguish it from the typical effects of cortical dementias e.g. Alzheimer's disease.

Reported neuropsychiatric manifestations are anxiety, depression, a reduced display of emotions (blunted affect), egocentrism, aggression, and compulsive behavior, the latter of which can cause or worsen addictions, including alcoholism, gambling, and hypersexuality.Difficulties in recognizing other people's negative expressions have also been observed.The prevalence of these symptoms is highly variable between studies, with estimated rates for lifetime prevalence of psychiatric disorders between 33% and 76%.For many sufferers and their families, these symptoms are among the most distressing aspects of the disease, often affecting daily functioning and constituting reason for institutionalization.Suicidal thoughts and suicide attempts are more common than in the general population.

Mutant Huntingtin is expressed throughout the body and associated with abnormalities in peripheral tissues that are directly caused by such expression outside the brain. These abnormalities include muscle atrophy, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis and testicular atrophy.

Genetics

All humans have two copies of the Huntingtin gene (*HTT*), which codes for the proteinHuntingtin (Htt). The gene is also called *HD* and *IT15*, which stands for 'interesting transcript 15'. Part of this gene is a repeated section called a trinucleotide repeat, which varies in length between individuals and may change length between generations. When the length of this repeated section reaches a certain threshold, it produces an altered form of the protein, called mutant Huntingtin protein (mHtt). The differing functions of these proteins are the cause of pathological changes which in turn cause the disease symptoms. The Huntington's disease mutation is genetically dominant and almost fully penetrant: mutation of either of a person's *HTT* genes causes the disease. It is not inherited according to sex, but the length of the repeated section of the gene, and hence its severity, can be influenced by the sex of the affected parent.

Genetic mutation

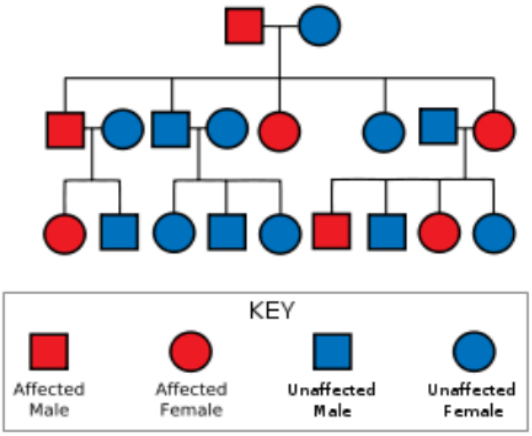
HD is one of several trinucleotide repeat disorders which are caused by the length of a repeated section of a gene exceeding a normal range.The *HTT* gene is located on the short arm of chromosome $4^{[13]}$ at 4p16.3. *HTT* contains a sequence of three DNA bases—cytosine-adenine-guanine (CAG)—repeated multiple times (i.e. ... CAGCAGCAG ...), known as a trinucleotide repeat.CAG is the genetic code for the amino acidglutamine, so a series of them results in the production of a chain of glutamine known as a polyglutamine tract (or polyQ tract), and the repeated part of the gene, the *PolyQ region*.

Classification of the trinucleotide repeat, and resulting disease status, depends on the number of CAG repeats

Repeat count	Classification	Disease status
<28	Normal	Unaffected
28–35	Intermediate	Unaffected
36–40	Reduced Penetrance	+/- Affected
>40	Full Penetrance	Affected

Generally, people have fewer than 36 repeated glutamines in the polyQ region which results in production of the cytoplasmic protein Huntingtin. However, a sequence of 36 or more glutamines results in the production of a protein which has different characteristics.This altered form, called mHtt (mutant Htt), increases the decay rate of certain types of neurons. Regions of the brain have differing amounts and reliance on these type of neurons, and are affected accordingly.Generally, the number of CAG repeats is related to how much this process is affected, and accounts for about 60% of the variation of the age of the onset of symptoms. The remaining variation is attributed to environment and other genes that modify the mechanism of HD.36–40 repeats result in a reduced-penetrance form of the disease, with a much later onset and slower progression of symptoms. In some cases the onset may be so late that symptoms are never noticed.With very large repeat counts, HD has full penetrance and can occur under the age of 20, when it is then referred to as juvenile HD, akinetic-rigid, or Westphal variant HD. This accounts for about 7% of HD carriers.

Inheritance



Huntington's disease is inherited in an autosomal dominant fashion. The probability of each offspring inheriting an affected gene is 50%. Inheritance is independent of gender, and the phenotype does not skip generations.

Huntington's disease has autosomal dominant inheritance, meaning that an affected individual typically inherits one copy of the gene with an expanded trinucleotide repeat (the mutant allele) from an affected parent.Since penetrance of the mutation is very high, those who have a mutated copy of the gene will have the disease. In this type of inheritance pattern, each offspring of an affected individual has a 50% risk of inheriting the mutant allele and therefore being affected with the disorder (see figure). This probability is sex-independent.

Trinucleotide CAG repeats over 28 are unstable during replication and this instability increases with the number of repeats present. This usually leads to new expansions as

generations pass (dynamic mutations) instead of reproducing an exact copy of the trinucleotide repeat.This causes the number of repeats to change in successive generations, such that an unaffected parent with an "intermediate" number of repeats (28–35), or "reduced penetrance" (36–40), may pass on a copy of the gene with an increase in the number of repeats that produces fully penetrant HD. Such increases in the number of repeats (and hence earlier age of onset and severity of disease) in successive generations is known as genetic anticipation. Instability is greater in spermatogenesis than oogenesis; maternally inherited alleles are usually of a similar repeat length, whereas paternally inherited ones have a higher chance of increasing in length. It is rare for Huntington's disease to be caused by a new mutation, where neither parent has over 36 CAG repeats.

In the rare situations where both parents have an expanded HD gene, the risk increases to 75%, and when either parent has two expanded copies, the risk is 100% (all children will be affected). Individuals with both genes affected are rare. For some time HD was thought to be the only disease for which possession of a second mutated gene did not affect symptoms and progression,but it has since been found that it can affect the phenotype and the rate of progression.

Mechanism

The Htt protein interacts with over 100 other proteins, and appears to have multiple biological functions.The behavior of mutant huntingtin protein is not completely understood, but it is toxic to certain types of cells, particularly in the brain. Early damage is most evident in the striatum, but as the disease progresses, other areas of the brain are also more conspicuously affected. Early symptoms are attributable to functions of the striatum and its cortical connections - namely control over movement, mood and higher cognitive function.

Htt function

Htt is expressed in all mammalian cells. The highest concentrations are found in the brain and testes, with moderate amounts in the liver, heart, and lungs.The function of Htt in humans is unclear. It interacts with proteins which are involved in transcription, cell signaling and intracellular transporting.In animals genetically modified to exhibit HD, several functions of Htt have been found.In these animals, Htt is important for embryonic development, as its absence is related to embryonic death. It also acts as an anti-apoptotic agent preventing programmed cell death and controls the production of brain-derived neurotrophic factor, a protein which protects neurons and regulates their creation during neurogenesis. Htt also facilitates vesicular transport and synaptic transmission and controls neuronal gene transcription.If the expression of Htt is increased and more Htt produced, brain cell survival is improved and the effects of mHtt are reduced, whereas when the expression of Htt is reduced, the resulting characteristics are more typical of the presence of mHtt.In humans the disruption of the normal gene does not cause the disease.It is thought that the disease is not caused by inadequate production of Htt, but by a gain of toxic function of mHtt.

Cellular changes due to mHtt

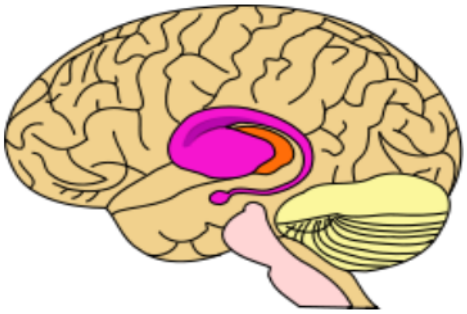
There are multiple cellular changes through which the toxic function of mHtt may manifest and produce the HD pathology.During the biological process of posttranslational modification of mHtt, cleavage of the protein can leave behind shorter fragments constituted of parts of the polyglutamine expansion.The polar nature of glutamine causes interactions

with other proteins when it is overabundant in Htt proteins. Thus, the mHtt molecule strands will form hydrogen bonds with one another, forming a protein aggregate rather than folding into functional proteins.Over time, the aggregates accumulate, ultimately interfering with neuron function because these fragments can then misfold and coalesce, in a process called protein aggregation, to form inclusion bodies within cells.Neuronal inclusions run indirect interference. The excess protein aggregates clump together at axons and dendrites in neurons which mechanically stops the transmission of neurotransmitters because vesicles (filled with neurotransmitters) can no longer move through the cytoskeleton. Ultimately, over time, less and less neurotransmitters are available for release in signaling other neurons as the neuronal inclusions grow.Inclusion bodies have been found in both the cell nucleus and cytoplasm.Inclusion bodies in cells of the brain are one of the earliest pathological changes, and some experiments have found that they can be toxic for the cell, but other experiments have shown that they may form as part of the body's defense mechanism and help protect cells.

Several pathways by which mHtt may cause cell death have been identified. These include: effects on chaperone proteins, which help fold proteins and remove misfolded ones; interactions with caspases, which play a role in the process of removing cells; the toxic effects of glutamine on nerve cells; impairment of energy production within cells; and effects on the expression of genes. The cytotoxic effects of mHtt are strongly enhanced by interactions with a protein called *Rhes*, which is expressed mainly in the striatum. Rhes was found to induce sumoylation of mHtt, which causes the protein clumps to disaggregate—studies in cell culture showed that the clumps were much less toxic than the disaggregated form.

An additional theory that explains another way cell function may be disrupted by HD proposes that damage to mitochondria in striatal cells (numerous accounts of mitochondrial metabolism deficiency have been found) and the interactions of the altered huntingtin protein with numerous proteins in neurons leads to an increased vulnerability of glutamine, which, in large amounts, has been found to be an excitotoxin. Excitotoxins may cause damage to numerous cellular structures. Although glutamine is not found in excessively high amounts, it has been postulated that because of the increased vulnerability, even normal amounts glutamine can cause excitotoxins to be expressed.

Macroscopic changes due to mHtt



Area of the brain most damaged in early Huntington's disease – striatum (shown in purple)

HD affects the whole brain, but certain areas are more vulnerable than others. The most prominent early effects are in a part of the basal ganglia called the neostriatum, which is

composed of the caudate nucleus and putamen.Other areas affected include the substantianigra, layers 3, 5 and 6 of the cerebral cortex, the hippocampus, purkinje cells in the cerebellum, lateral tuberal nuclei of the hypothalamus and parts of the thalamus.These areas are affected according to their structure and the types of neurons they contain, reducing in size as they lose cells.Striatal spiny neurons are the most vulnerable, particularly ones with projections towards the external globuspallidus, with interneurons and spiny cells projecting to the internal pallidum being less affected.HD also causes an abnormal increase in astrocytes and activation of the brain's immune cells, microglia.

The basal ganglia—the part of the brain most prominently affected in early HD—play a key role in movement and behavior control. Their functions are not fully understood, but current theories propose that they are part of the cognitive executive systemand the motor circuit. The basal ganglia ordinarily inhibit a large number of circuits that generate specific movements. To initiate a particular movement, the cerebral cortex sends a signal to the basal ganglia that causes the inhibition to be released. Damage to the basal ganglia can cause the release or reinstatement of the inhibitions to be erratic and uncontrolled, which results in an awkward start to motion or motions to be unintentionally initiated, or a motion to be halted before, or beyond, its intended completion. The accumulating damage to this area causes the characteristic erratic movements associated with HD.

Transcriptional dysregulation

CREB-binding protein (CBP), a transcription factor, is essential for cell function because as a coactivator at a significant number of promoters, it activates the transcription of genes for survival pathways. Furthermore, the amino acids that form CBP include a strip 18 glutamines. Thus, the glutamines on CBP interact directly with the increased numbers of glutamine on the Htt chain and CBP gets pulled away from its typical location next to the nucleus.[34] Specifically, CRB contains aacetyltransferase domain that, in an experiment performed by Steffan and colleagues, showed that a Htt exon 1 with 51 glutamines binded to this domain in CBP.Autopsied brains of those who had Huntington's disease also have been found to have incredibly reduced amounts of CBP.Plus, when CBP is overexpressed, polyglutamine-induced death diminished, further demonstrating that CBP plays an important role in Huntington's disease and neurons in general.

Diagnosis

Medical diagnosis of the onset of HD can be made following the appearance of physical symptoms specific to the disease.[1] Genetic testing can be used to confirm a physical diagnosis if there is no family history of HD. Even before the onset of symptoms, genetic testing can confirm if an individual or embryo carries an expanded copy of the trinucleotide repeat in the *HTT* gene that causes the disease. Genetic counseling is available to provide advice and guidance throughout the testing procedure, and on the implications of a confirmed diagnosis. These implications include the impact on an individual's psychology, career, family planning decisions, relatives and relationships. Despite the availability of pre-symptomatic testing, only 5% of those at risk of inheriting HD choose to do so.

Clinical

Coronal section from a MRbrain scan of a patient with HD showing atrophy of the heads of the caudate nuclei, enlargement of the frontal horns of the lateral ventricles (hydrocephalus *ex vacuo*), and generalized cortical atrophy.

A physical examination, sometimes combined with a psychological examination, can determine whether the onset of the disease has begun. Excessive unintentional movements of any part of the body are often the reason for seeking medical consultation. If these are abrupt and have random timing and distribution, they suggest a diagnosis of HD. Cognitive or psychiatric symptoms are rarely the first diagnosed; they are usually only recognized in hindsight or when they develop further. How far the disease has progressed can be measured using the *unified Huntington's disease rating scale* which provides an overall rating system based on motor, behavioral, cognitive, and functional assessments. Medical imaging, such as computerized tomography (CT) and magnetic resonance imaging (MRI), only shows visible cerebral atrophy in the advanced stages of the disease. Functional neuroimaging techniques such as fMRI and PET can show changes in brain activity before the onset of physical symptoms but are experimental tools, and not used clinically.

Genetic

Because HD follows an autosomal dominant pattern of inheritance, there is a strong motivation for individuals who are at risk of inheriting it to seek a diagnosis. The genetic test for HD consists of a blood test which counts the numbers of CAG repeats in each of the *HTT* alleles. A positive result is not considered a diagnosis, since it may be obtained decades before the symptoms begin. However, a negative test means that the individual does not carry the expanded copy of the gene and will not develop HD.

A pre-symptomatic test is a life-changing event and a very personal decision. The main reason given for choosing testing for HD is to aid in career and family decisions. Over 95% of individuals at risk of inheriting HD do not proceed with testing, mostly because there is no treatment. A key issue is the anxiety an individual experiences about not knowing whether they will eventually develop HD, compared to the impact of a positive result. Irrespective of the result, stress levels have been found to be lower two years after being tested, but the risk of suicide is increased after a positive test result.Individuals found to have not inherited the disorder may experience survivor guilt with regard to family members who are affected.[12] Other factors taken into account when considering testing include the possibility of discrimination and the implications of a positive result, which usually means a parent has an affected gene and that the individual's siblings will be at risk of inheriting it. Genetic counseling in HD can provide information, advice and support for initial decision-making, and then, if chosen, throughout all stages of the testing process. Counseling and guidelines on the use of genetic testing for HD have become models for other genetic disorders, such as autosomal dominant cerebellar ataxias. Presymptomatic testing for HD has also influenced testing for other illnesses with genetic variants such as polycystic kidney disease, familial Alzheimer's disease and breast cancer.

Preimplantation genetic diagnosis

Embryos produced using in vitro fertilization may be genetically tested for HD using preimplantation genetic diagnosis. This technique, where one or two cells are extracted from a typically 4 to 8 cell embryo and then tested for the genetic abnormality, can then be used to ensure embryos affected with HD genes are not implanted, and therefore any offspring will

not inherit the disease. Some forms of preimplantation genetic diagnosis — non-disclosure or exclusion testing — allow at-risk people to have HD-free offspring *without* revealing their own parental genotype, giving no information about whether they themselves are destined to develop HD. In exclusion testing, the embryos' DNA is compared with that of the parents and grandparents to avoid inheritance of the chromosomal region containing the HD gene from the affected grandparent. In non-disclosure testing, the embryo is tested in the usual way but the result is withheld from the would-be parents.

Prenatal testing

It is also possible to obtain a prenatal diagnosis for an embryo or fetus in the womb, using fetal genetic material acquired through chorionic villus sampling. This, too, can be paired with exclusion testing to avoid disclosure of parental genotype. Prenatal testing is performed on the understanding that if the fetus is found to carry an expanded *HTT* gene (or, in exclusion testing, found to be at 'high risk'), the pregnancy will be terminated.

Differential diagnosis

About 99% of HD diagnoses based on the typical symptoms and a family history of the disease are confirmed by genetic testing to have the expanded trinucleotide repeat that causes HD. Most of the remaining are called HD-like disorders. Most of these other disorders are collectively labelled HD-like (HDL). The cause of most HDL diseases is unknown, but those with known causes are due to mutations in the prion protein gene (HDL1), the junctophilin 3 gene (HDL2), a recessively inherited *HTT* gene (HDL3—only found in one family and poorly understood), and the gene encoding the TATA box-binding protein (HDL4/SCA17). Other autosomal dominant diseases that can be misdiagnosed as HD are dentatorubral-pallidoluysian atrophy and neuroferritinopathy. There are also autosomal recessive disorders that resemble sporadic cases of HD. Main examples are chorea acanthocytosis, pantothenate kinase-associated neurodegeneration and X-linkedMcLeod syndrome.

Management

There is no cure for HD, but there are treatments available to reduce the severity of some of its symptoms. For many of these treatments, comprehensive clinical trials to confirm their effectiveness in treating symptoms of HD specifically are incomplete. As the disease progresses and a person's ability to tend to his own needs reduces, carefully managed multidisciplinarycaregiving becomes increasingly necessary. Although there have been relatively few studies of exercises and therapies that help rehabilitate cognitive symptoms of HD, there is some evidence for the usefulness of physical therapy, occupational therapy, and speech therapy.

Tetrabenazine was approved in 2008 for treatment of chorea in Huntington's disease in the US. Other drugs that help to reduce chorea include neuroleptics and benzodiazepines. Compounds such as amantadine or remacemide are still under investigation but have shown preliminary positive results. Hypokinesia and rigidity, especially in juvenile cases, can be treated with antiparkinsonian drugs, and myoclonic hyperkinesia can be treated with valproic acid.

Psychiatric symptoms can be treated with medications similar to those used in the general population. Selective serotonin reuptake inhibitors and mirtazapine have been recommended

for depression, while atypical antipsychotic drugs are recommended for psychosis and behavioral problems. Specialist neuropsychiatric input is recommended as patients may require long-term treatment with multiple medications in combination.

Weight loss and eating difficulties due to dysphagia and other muscle discoordination are common, making nutrition management increasingly important as the disease advances. Thickening agents can be added to liquids as thicker fluids are easier and safer to swallow.Reminding the patient to eat slowly and to take smaller pieces of food into the mouth may also be of use to prevent choking. If eating becomes too hazardous or uncomfortable, the option of using a percutaneous endoscopic gastrostomy is available. This is a feeding tube, permanently attached through the abdomen into the stomach, which reduces the risk of aspirating food and provides better nutritional management. Assessment and management by speech and language therapists with experience in Huntington's disease is recommended.

Patients with Huntington's disease may see a physical therapist for non-invasive and non-medication ways of managing the physical symptoms of HD. Physical therapists may implement fall risk assessment and prevention, as well as strengthening, stretching, and cardiovascular exercises. Consensus guidelines on physiotherapy in Huntington's disease have been produced by the European HD Network.

The families of individuals, who have inherited or are at risk of inheriting HD, have generations of experience of HD which may be outdated and lack knowledge of recent breakthroughs and improvements in genetic testing, family planning choices, care management, and other considerations. Genetic counseling benefits these individuals by updating their knowledge, dispelling any myths they may have and helping them consider their future options and plans.

Prognosis

The length of the trinucleotide repeat accounts for 60% of the variation in the age of onset and the rate of progression of symptoms. A longer repeat results in an earlier age of onset and a faster progression of symptoms. For example, individuals with a trinucleotide repeat greater than sixty repeats often develop the disease before twenty years of age, and those with less than forty repeats may not develop noticeable symptoms. The remaining variation is due to environmental factors and other genes that influence the mechanism of the disease.

Life expectancy in HD is generally around 20 years following the onset of visible symptoms.Most of the complications that are life-threatening result from muscle coordination issues, or to a lesser extent from behavioral changes resulting from the decline in cognitive function. The largest risk is pneumonia, which is the cause of death of one-third of those with HD. As the ability to synchronize movements deteriorates, difficulty clearing the lungs and an increased risk of aspirating food or drink both increase the risk of contracting pneumonia. The second greatest risk is heart disease, which causes almost a quarter of fatalities of those with HD. Suicide is the next greatest cause of fatalities, with 7.3% of those with HD taking their own lives and up to 27% attempting to do so. It is unclear to what extent suicidal thoughts are influenced by psychiatric symptoms, as they may be considered to be a response of an individual to retain a sense of control of their life or to avoid the later stages of the disease. Other associated risks include choking, physical injury from falls, and malnutrition.