Psych 3102
Lecture 3

Mendelian Genetics

Gregor Mendel

- 1822 – 1884 , paper read 1865-66
- Augustinian monk

- genotype alleles present at a locus

  can we identify this?
- phenotype expressed trait/characteristic

  can we identify this?

  - result of genotype and environment

phenotype may not reflect genotype

single gene traits dichotomous phenotypes

polygenic traits normally distributed phenotypes

complex phenotypes – result of many genes and environmental factors

Keys to Mendel's success

1. Good scientific method

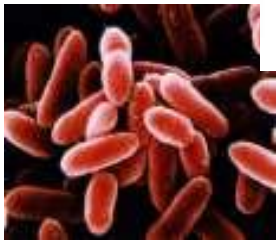
2. Good choice of organism

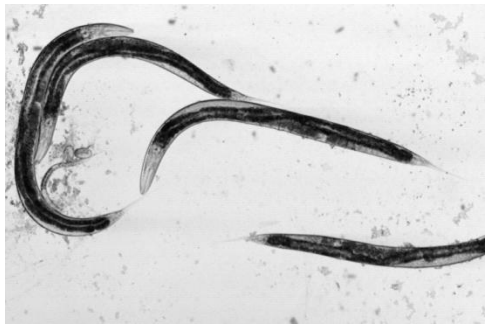
- pea plants
- Drosophila
- bacteria, molds
- Caenorhabiditis elegans

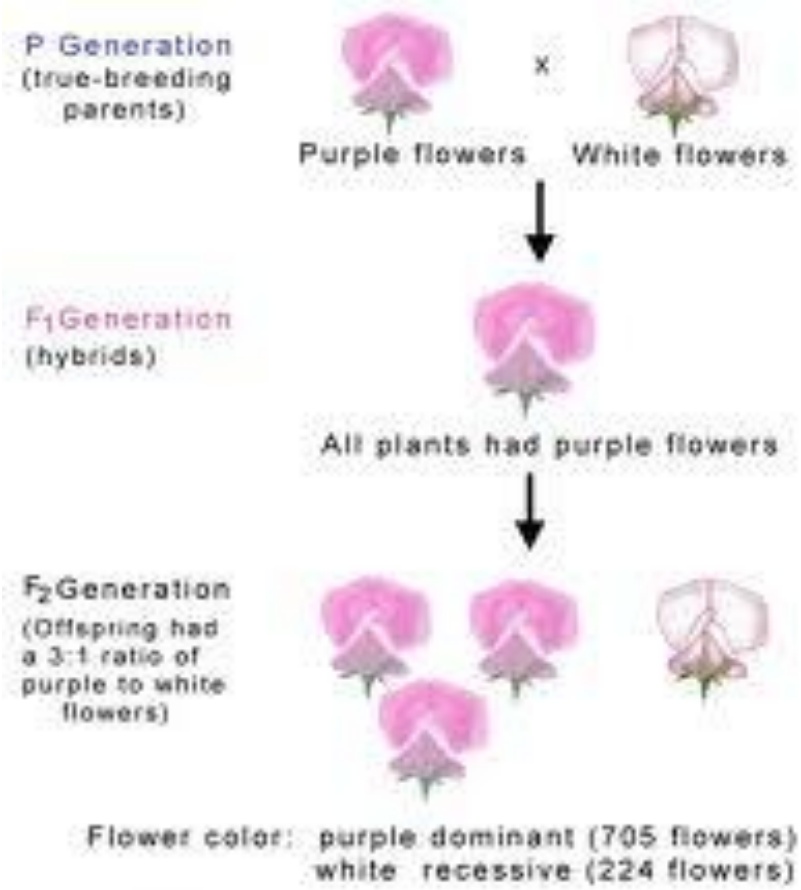
self-fertilization

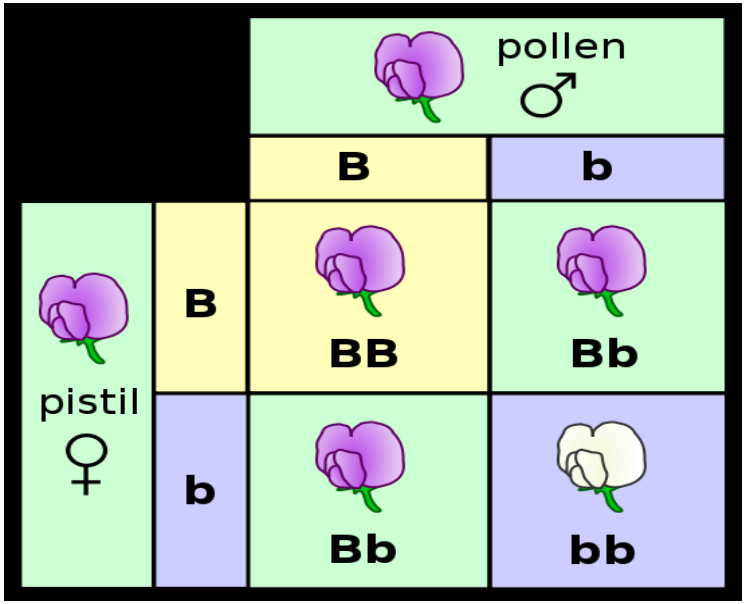
cross-fertilization

cloning






P Generation
(true-breeding parents)
Purple flowers
x
White flowers
F1 Generation
(hybrids)
All plants had purple flowers
F2 Generation
(Offspring had a 3:1 ratio of purple to white flowers)
Flower color: purple dominant (705 flowers)
white recessive (224 flowers)


pollen
♂
B
b
pistil
♀
B
BB
Bb
b
Bb
bb

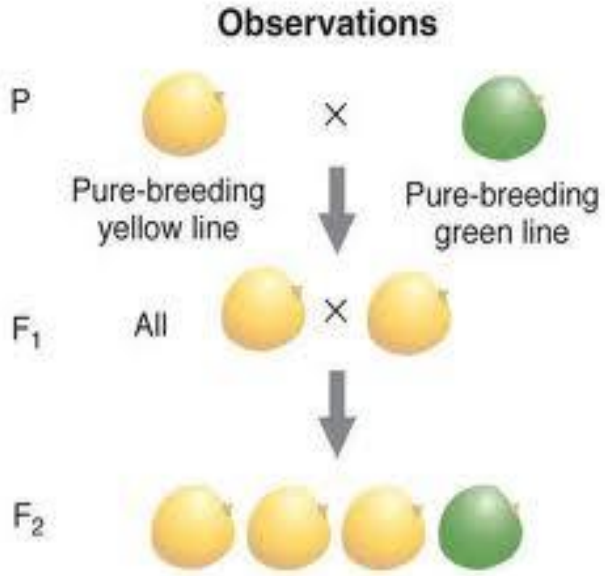

Observations
P
Pure-breeding yellow line
×
Pure-breeding green line
F1
All
×
F2

Table 14.1 The Results of Mendel's F_1 Crosses for Seven Characters in Pea Plants (true breeding: itself × itself)

Character	Dominant Trait	×	Recessive Trait	F_2 Generation Dominant:Recessive	Ratio
Flower color	Purple 	×	White 	705:224	3.15:1
Flower position	Axial 	×	Terminal 	651:207	3.14:1
Seed color	Yellow 	×	Green 	6022:2001	3.01:1
Seed shape	Round 	×	Wrinkled 	5474:1850	2.96:1
Pod shape	Inflated 	×	Constricted 	882:299	2.95:1
Pod color	Green 	×	Yellow 	428:152	2.82:1
Stem length	Tall 	×	Dwarf 	787:277	2.84:1

Vocabulary

- pure (true)- breeding organism

  - for a single gene trait, both alleles are the same

  - homozygous at locus in question

- hybrid organism

  - for a single gene trait, alleles are different at the locus for the trait

  - heterozygous at the locus in question

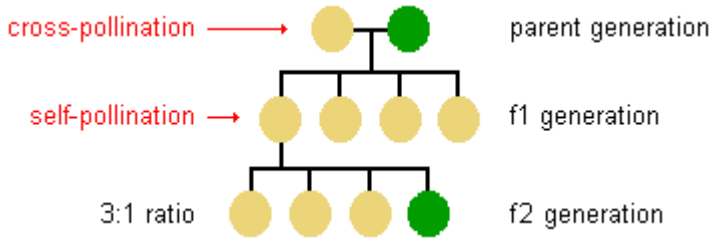
- monohybrid cross

  - follows inheritance of one trait controlled by a single gene

- dihybrid cross

  - follows inheritance of 2 traits each controlled by a different single gene

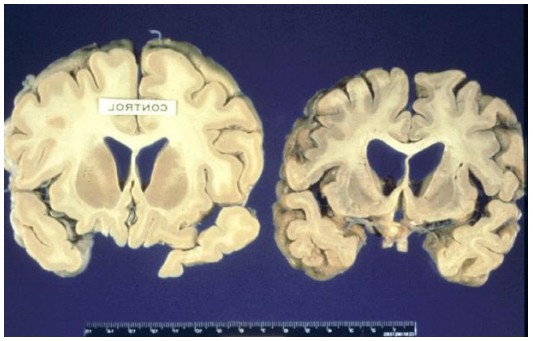
P F_1 F_2



Monohybrid cross

Examples:

Huntington disease (HD)



Phenylketonuria (PKU)

Both are single gene disorders that effect the nervous system

Huntington disease

- Phenotype (characteristics)

personality changes memory loss involuntary spasms
complete loss of motor control and intellectual functioning
late onset (~ 40 years)
lethal within 15-20 years

- Prevalence

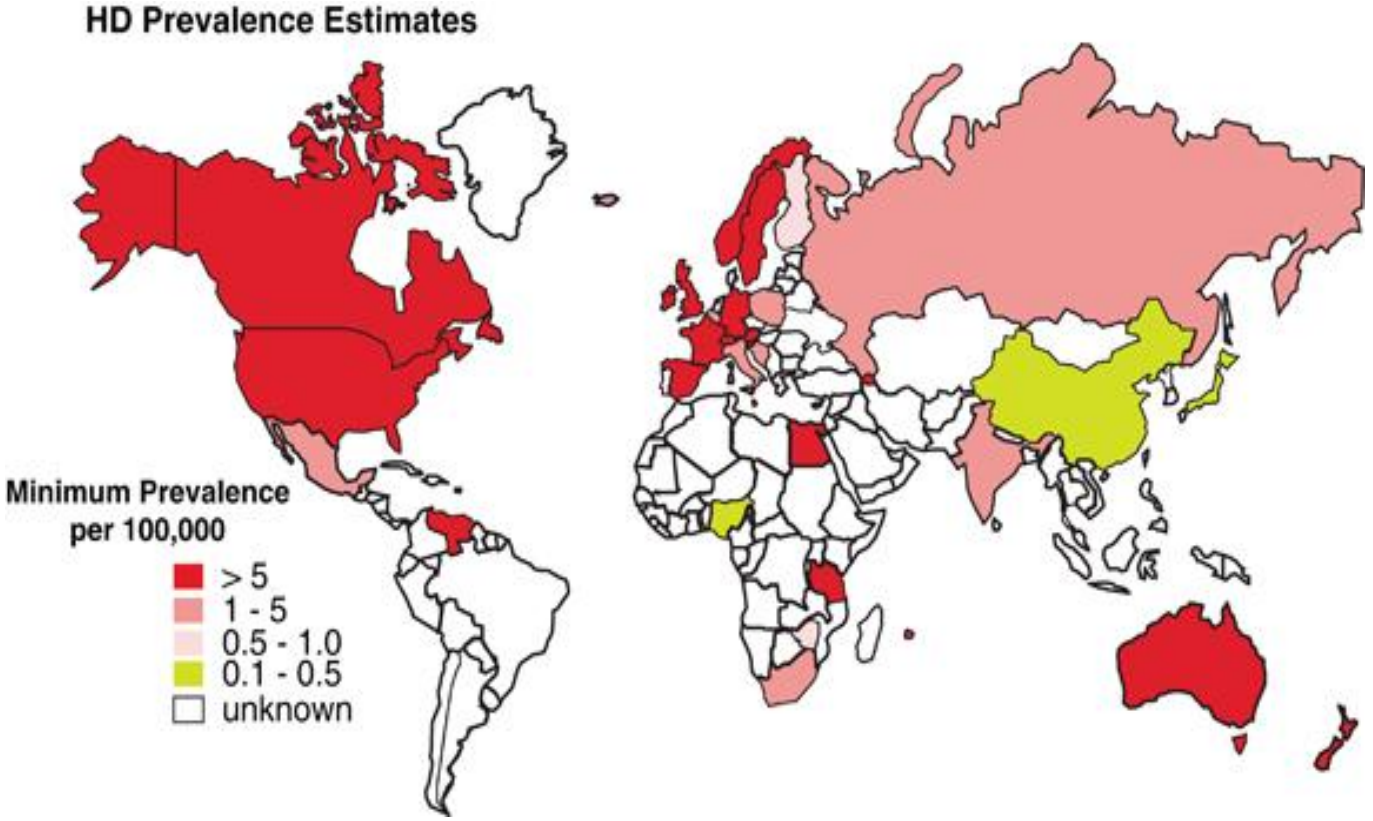
1 in 20,000 live births (very rare)

- Inheritance pattern

males and females affected
affected person always has one affected parent
half of children from an affected parent are typically affected

Mode of inheritance autosomal dominant

- gene is on an autosome, allele for the disorder always expresses itself when present - it is dominant



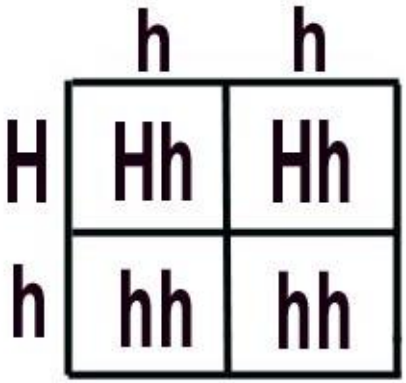
Worldwide estimates of the prevalence of HD. Overall, the prevalence of HD is much higher in European populations than in East Asia. Average minimum prevalence on the basis of several studies are shown (references in Supplementary Table 1). Note that prevalence studies occurring before the discovery of the HD gene in 1993 could underestimate the true prevalence of HD by as much as 14–24%.[17, 45] In particular, many of the studies in Africa have small sample sizes and the HD diagnosis has not confirmed by molecular testing. As HD phenocopy disorders are relatively common in Africa,[46] these studies could have significantly overestimated the HD prevalence in these regions. Currently, the Maracaibo region of Venezuela has the highest reported worldwide prevalence of HD (700 per 1 00 000).[39] Venezuela was colonized by the Spanish in the 16th century, and the origins of HD in Venezuela can be traced back to Europe.[38] Also see Harper,[4] Conneally[47] and Al Jader *et al*[2] for earlier reviews on the worldwide prevalence of HD.

- Let H = allele for HD – the dominant allele
  h = normal allele – the recessive allele

Cross between an affected person and an unaffected person:

P Hh x hh
affected normal

F_1 Punnet square:



1:1 ratio normal:affected
50% affected
0.5 probability of being affected

Affected person always dies, allele would be expected to get selected out of human population. Why is it still present?

late onset

new mutation

Phenylketonuria

Phenotype (characteristics)

mental retardation (post-natal brain damage)

affected person cannot metabolize phenylalanine

Prevalence

1 in 10,000 live births

Inheritance pattern

affected person can have 2 normal parents, males and females equally affected

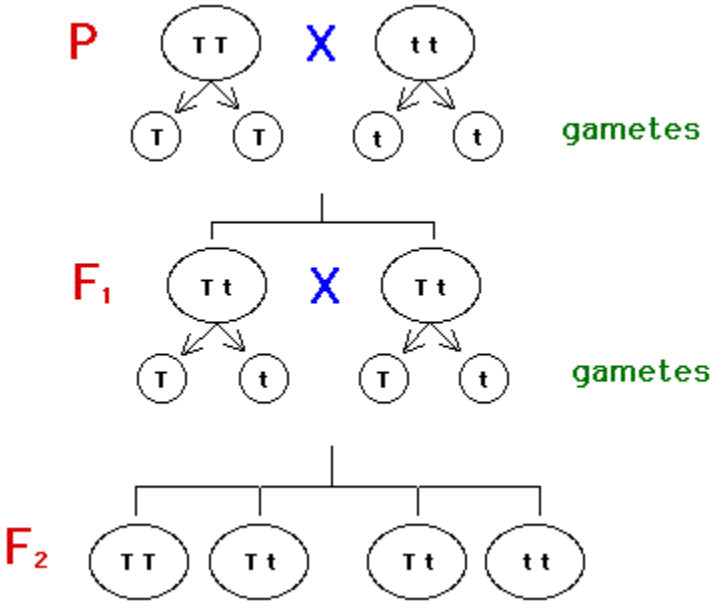
1 in 4 children from normal but heterozygous parents are typically affected

autosomal recessive

both alleles at the locus have to be for the disorder – typical for recessive allele

gene for PKU is on an autosome

If T = normal allele (dominant)
t = PKU allele (recessive)



Outcome when one parent is homozygous normal and the other is a normal carrier?

no possibility of PKU child

Outcome when one parent is affected and one is a carrier?

50% affected

Why is PKU more common in consanguineous marriages?

If PKU is in the family, blood relations are more likely to carry the allele for PKU than non-blood relations.

1 in 50 people in the general population are carriers of the PKU allele.

Mendel's Laws of Heredity

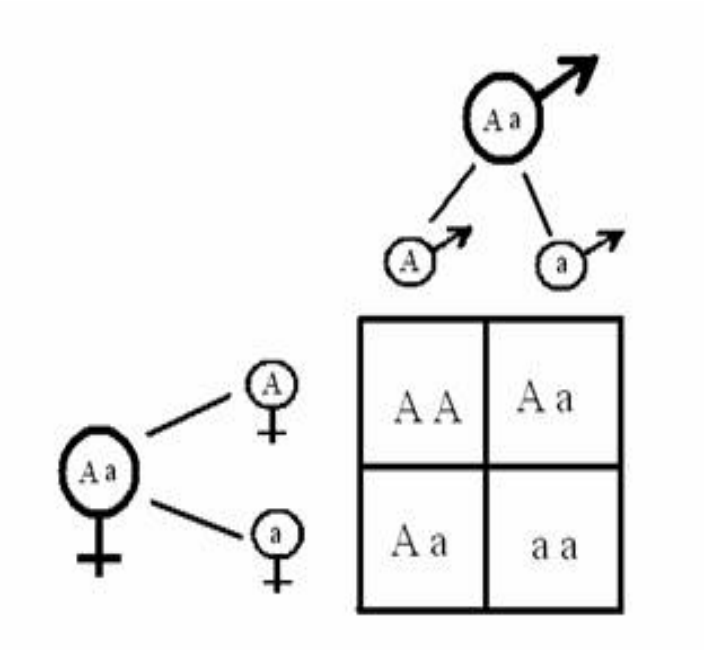
1. LAW OF SEGREGATION (MENDEL'S FIRST LAW)

- 2 alleles for each gene in each person

- alleles separate (segregate) during reproduction

- offspring receive 1 allele from each parent

- In a monohybrid cross, homozygous parents give 3 : 1 ratio of phenotypes in F2

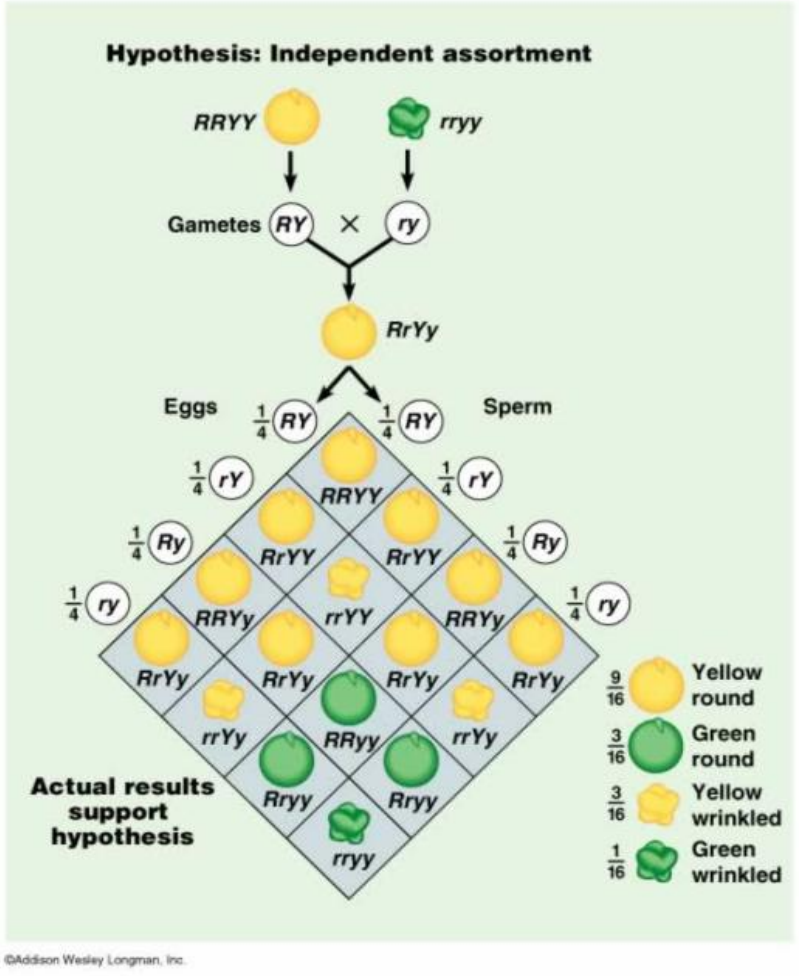


2. LAW OF INDEPENDENT ASSORTMENT (MENDEL'S SECOND LAW)

- alleles for different genes segregate independently

- dihybrid cross, double homozygous parents give 9 : 3 : 3 : 1 ratio of phenotypes in F2

Second law is only true if the genes for the 2 traits are…….. ?



The second law is only true if the genes for the traits are on different chromosomes

- linkage

  - when genes are on the same chromosome they are said to be linked

linkage analysis – used to detect linkage

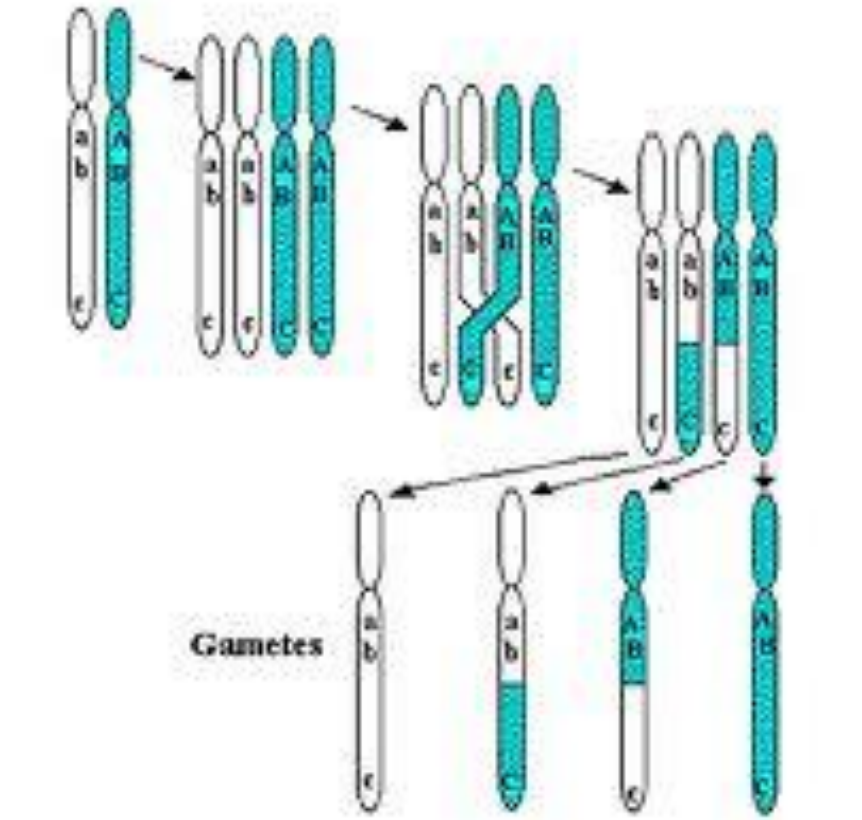
ie whether 2 loci under investigation are on same chromosome

- can be used to locate genes that influence a trait - one of the loci is a marker (ie. is a sequence of known location), use phenotype to identify those with particular trait allele, look for linkage between marker allele and trait

Experimental organisms:

dihybrid cross – used in linkage analysis for two single-gene traits

linked genes gives ratios that differ from the expected 9:3:3:1



Crossing-over and recombination during meiosis

Parental

Recombinant

Huntington gene

- linkage analysis with a large pedigree and markers used to locate gene to chromosome 4p in 1983

- finer mapping using markers near the suspected location pin-pointed the exact position of the gene in 1993

- genetic test now available would you take the test?

- gene product is called huntingtin (htt)
- mutant htt first kills medium spiny neurons in striatum and then cortical neurons

No treatment but: melatonin(MT) found to be protective in models of neurodegeneration – delays onset & mortality in transgenic HD mice also

cells expressing mutant htt lose mitochondrial MT1 receptors

- gene is conserved

  - found in slime mold, sea urchin as well as mammals

- trinucleotide (CAG) repeat mutation (polyglutamine) in first exon of gene
- dominant, leads to loss of function of wild type allele and toxic gain of function of mutant protein (mHtt)
- fewer repeats found in lower organisms
- expressed in developing brain in mammals, regulates neural tube formation, possibly via cell adhesion formation
- mutant protein disrupts many pathways within cell

  eg postsynaptic signaling, regulation of transcription, protein trafficking, vesicle transport

over time – combination of effects leads to progressive nerve degeneration?

glutamate is known to be neurotoxic, normally cleared by astrocytes

relationship to immune system response being investigated

Molecular Psychiatry (2011) 16, 889–902

www.nature.com/mp

FEATURE REVIEW

The role of immunity in Huntington's disease

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Huntington's disease (HD) is a devastating and incurable neurodegenerative disorder characterized by progressive cognitive, psychiatric and motor impairments. Although the disease has been seen as a disorder purely of the brain, there is now emerging evidence that abnormalities outside the central nervous system are commonly seen in HD. Indeed, the mutant huntingtin (mHtt) coded for by the abnormal gene in HD is found in every cell type where its presence has been sought. In particular, there are a number of recent observations in HD patients that mHtt interacts with the immune system with accumulating evidence that changes in the immune system may critically contribute to the pathology of HD. However, the nature of this contribution remains unclear, to the extent that it is not even known whether the immune system has a beneficial or detrimental role in HD patients. In this review, we attempt to bring a novel understanding to the interaction of the immune system to HD pathology, thereby shedding light on its potential pathogenic role. As part of this discussion, we revisit the clinical data on the anti-inflammatory drug trials in HD and propose new experimental approaches to interrogate the role of immunity in this currently incurable disorder.
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Keywords: anti-inflammatory treatment; immune response; inflammation; mutant huntingtin; neurodegenerative diseases

Introduction

Huntington's disease (HD) is an autosomal-dominant inherited neurodegenerative disorder characterized by marked psychiatric, cognitive and motor impairments. The features of the disease are caused by a CAG codon/polyglutamine repeat expansion in the first exon of the huntingtin gene, which leads to the expression of a mutated form of the huntingtin protein (mHtt) in cells of the central nervous system (CNS).

However, the presence of abnormalities is not restricted to the CNS, but found in several other compartments including the neuroendocrine system, skeletal muscles, cardiovascular system, blood, digestive tract, thyroid, skeleton and genital organs[1] (Figure 1). Understanding this systemic nature of HD is important in better developing models of disease pathogenesis to design disease modifying therapies, as currently the condition can only be treated with drugs that offer varying degrees of symptomatic benefits.[2–4]

At the cellular level, the loss of function of the wild-type protein and toxic gain of function of the mHtt both contribute to the disruption of multiple intracellular pathways, including postsynaptic signaling, apoptosis, transcriptional regulation, protein trafficking and vesicular transport (Figure 2). Consequently, mHtt induces a cascade of events involving excitotoxicity, proteasome impairment, mitochondrial dysfunction, oxidative stress, metabolic impairment, calcium homeostasis dysregulation, apoptosis and autophagy.[5] The combination of these intracellular dysfunctions over time causes the progressive neuronal degeneration that characterizes HD.[6]

In this review, we examine the current evidence that the immune system is implicated in the pathogenesis of HD, and that it may be a potential therapeutic target. In particular, we explore the interplay between the peripheral expression of mHtt and the activation of the innate immune response and how this may impact on the disease process.

Inflammation and immunity in HD

Astrocytes and microglia are two types of cells that are remarkably reactive to local environmental changes. They are thus key players in the brain inflammatory response. Under normal conditions, astrocytes are involved in structural, metabolic and synaptic functions,[7] while the microglia are the major intrinsic immunocompetent cells of the central nervous system[8] actively monitoring the parenchymal environment.[9]

Early descriptions of some of the major pathological features of HD[10] interestingly reported important

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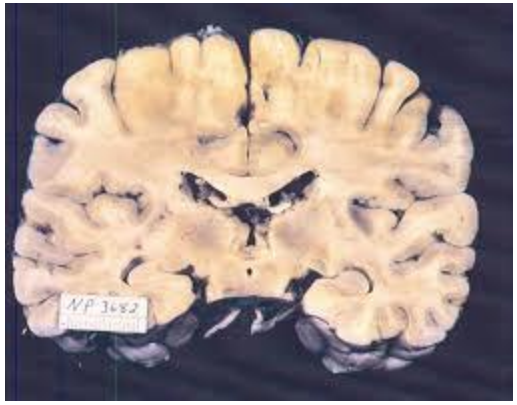
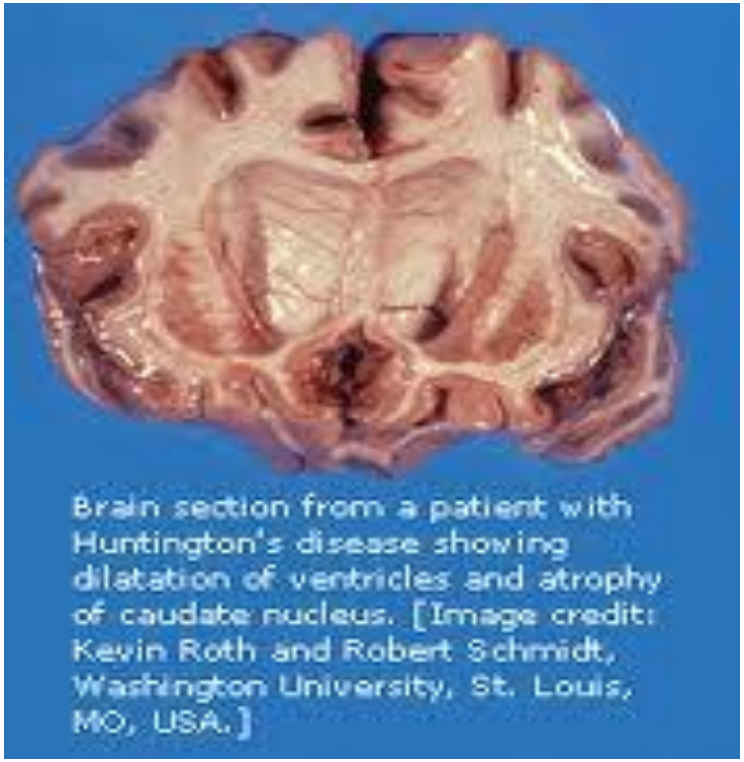


Normal brain section



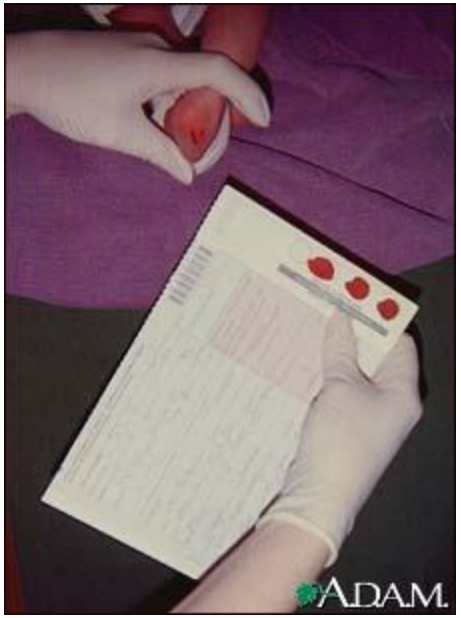
Brain section from a patient with Huntington's disease showing dilatation of ventricles and atrophy of caudate nucleus. [Image credit: Kevin Roth and Robert Schmidt, Washington University, St. Louis, MO, USA.]

PKU

- located to chromosome 12 using its product, 1984

amino acid sequence -> codon sequence on mRNA -> DNA sequence

- blood test used to detect PKU at birth



- strict diet prevents brain damage
- many different point mutations (>400)
  - makes DNA testing difficult
- carriers can be identified by an enzyme assay

Incidence of PKU around the world

Country	Incidence of PKU
China	1 in 18,000
Finland	<1 in 100,000
Ireland	1 in 4,500
Japan	1 in 120,000
Korea	1 in 41,000
Norway	1 in 13,000
Turkey	1 in 2,600
United States	1 in 15,000