Neurogenetics

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² "a branch of genetics dealing with the nervous system and especially with its development"

https://www.merriam-webster.com/medical/neurogenetics

² In relation to human genetics, this would include the genetics of neuro-related disorders and diseases

Outline

² Central nervous system
² Peripheral nervous system
² Neurons and glia
² Disorders of the nervous system with genetic underpinnings
Central nervous system

- Consists of the brain and the spinal cord
- Spinal cord provides connection to the peripheral nervous system
- Composed of gray (soma, dendrites) and white matter (axons)
Peripheral nervous system

- Nervous system excluding the brain and the spinal cord
- Somatic: voluntary control (i.e., through skeletal muscle)
- Autonomic: happens without thinking about it and regulates many body functions (e.g., heart rate, respiratory rate)
- Enteric: controls function of the gastrointestinal tract

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  - Disorders of the nervous system with genetic underpinnings

Neurons

- Consist of a
  - cell body (soma), gray matter
  - a single axon: conducts nerve impulses to other cells or as far as the muscle (motor) dendrites: enlarge the receiving surface and can form dendritic trees, gray matter
- Most are myelinated
  - Type of insulation that increases the speed of nerve impulse
- Two major types
  - projection: signal over long distances
  - interneurons: local transmission for neurons near each other
**Neurons**

- Consist of a cell body (soma), gray matter
  - a single axon: conducts nerve impulses to other cells, white matter
  - dendrite: enlarge the receiving surface and can form dendritic "trees", gray matter
- Most are myelinated
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  - projection: signal over long distances
  - interneurons: local transmission for neurons near each other

**Soma**

- Contains a large nucleus with light staining
  - much of the genome is in use
  - prominent nucleolus
- Many mitochondria
  - high metabolic activity
- Many rough endoplasmic reticulum
  - high level of protein synthesis

**Axon**

- Terminal branches have boutons
  - contact directly to another cell and this site is called a synapse
  - PNS synapses are between boutons and muscle cells
  - CNS synapses are between boutons and nerve cells
- Signaling between the bouton and the next cell occurs via signaling molecules called neurotransmitters
- Presynaptic refers to the bouton side of the synapse
- Postsynaptic refers to the membrane of the cell being contacted
Along the dendritic "tree" there are also dendritic spines. These form contacts with other neurons - sites of synaptic activity.

Dr. Kieran Boyle

Synaptic function and neurotransmitters

Key events of signal transfer
- Action potential reaches bouton and depolarizes it
- Depolarization causes opening of Ca²⁺ channels
- Ca²⁺ enters the terminal and this increase causes neurotransmitter release into the synaptic cleft
- The neurotransmitter binds to receptors in the postsynaptic membrane

Two types of transmitter receptors
- Ionotropic: on ion channels
  - Very fast signaling
  - Na⁺ and Ca²⁺ are excitatory (depolarizes the next cell)
  - Cl⁻ are inhibitory (hyperpolarizes the next cell)
- Metabotropic: coupled indirectly to ion channels
  - Slower and longer lasting

Excitatory synapses are located on the dendrites
Inhibitory synapses are on or near the soma
Types of neurotransmitters

<table>
<thead>
<tr>
<th>Neuron</th>
<th>Cholinergic</th>
<th>Adrenergic</th>
<th>Dopaminergic</th>
<th>Serotonergic</th>
<th>Opioidergic</th>
<th>Endorphinergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axon</td>
<td>Acetylcholine</td>
<td>Norepinephrine</td>
<td>Dopamine</td>
<td>Serotonin</td>
<td>Endorphins</td>
<td>Enkephalins</td>
</tr>
<tr>
<td>Terminals</td>
<td>Neocortex, thalamus</td>
<td>Hypothalamus, medulla, autonomic ganglia</td>
<td>Midbrain, substantia nigra, limbic system</td>
<td>Serotoninergic nuclei, raphe nuclei</td>
<td>Opioidergic neurons</td>
<td>Endorphinergic neurons</td>
</tr>
<tr>
<td>Synapses</td>
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Glia

- Three main types
  - Astrocytes: homeostatic functions, controlling ion concentration and osmotic pressure
  - Oligodendrocytes: produce myelin sheets in the CNS
  - Microglia: nervous system macrophages
    - Uniquely from the mesoderm and invade the nervous system very early
    - Constantly scanning the brain

- Note: in the PNS, the myelin sheath producing cells are Schwann cells

The Central Nervous System: Brodal 2010

16 17 18
Neurogenetic diseases and disorders can occur across the lifetime. 

- e.g., epilepsy
- e.g., Alzheimer

Neurogenetic diseases and disorders are of different types:

- Migration defect
- Loss of myelin
- Reduced or absent neurons
- Peripheral neuropathy
- Channelopathy
- Neurotransmitter and/or neurotransmitter receptor dysregulation

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Miller-Dieker Syndrome

Case report

Incomplete migration of neurons to the cerebral cortex during development

Causes lissencephaly (absence of gyri; smooth brain)

17p13.3 hemizygous deletion
Contiguous gene syndrome
>50 genes in region
PAFAH1B1 (LIS1) is associated with lissencephaly
Other genes may be related to the other phenotypes
80% of patients have de novo deletion
20% inherit a deletion from a parent with balanced translocation

FISH testing
Miller-Dieker Syndrome:
- Common
  - Brain dysgenesis
  - Hypotonia
  - Failure to thrive
  - Facial dysmorphism
- In some cases
  - Heart malformations
  - Omphaloceles
  - Spasticity
  - Seizures

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Multiple Sclerosis:
- Chronic inflammation
- Activation of microglia
- Progressive loss of oligodendrocytes
- Demyelination of neurons
- Axon degradation
Multiple Sclerosis: genetics
- Multifactorial
- Common variants with the highest signal in HLA (major histocompatibility complex in humans)
- Genes in HLA are critical for immune and inflammation activity

\[\text{Andlauer et al. 2016, Neurological Disorders}\]
\[\text{Undlien et al. 2001, Trends in Genetics}\]

Multiple Sclerosis: phenotype
- Monocular vision loss
- Diplopia
- Urinary incontinence
- Spasticity
- Depression
- Cognitive dysfunction
- Weakness
- Sensory loss
- Women more often affected than men
- Increased CSF immunoglobulin levels
- Oligoclonal bands in CSF
- Myelin basic protein in CSF

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Alzheimer Disease: Neuronal Features

- β-amyloid plaques = contains Aβ, derived from amyloid protein precursor (APP)
- Neurofibrillary tangles = contain paired helical filaments (abnormal tau)
- Cortical atrophy
- Amyloid deposits in cerebral arteries
- Loss of neurons in basal nucleus
- Problems with acetylcholine and acetylcholine receptors

Alzheimer Disease: Genetics

- Familial and usually earlier onset
- Linkage and genome-wide association studies

L.W. was an elderly woman with dementia. Eight years before her death, she and her family noticed a deficit in her short-term memory. Initially, they ascribed this to the forgetfulness of "old age," but her cognitive decline continued, however, and progressively interfered with her ability to drive, shop, and look after herself. L.W. did not have findings suggestive of thyroid disease, vitamin deficiency, brain tumor, drug intoxication, chronic infection, depression, or stroke; magnetic resonance imaging of her brain showed diffuse cortical atrophy. L.W.'s brother, father, and two other paternal relatives had died of dementia in their 70s. A neurologist explained to L.W. and her family that normal aging is not associated with dramatic declines in memory or judgment and that declining cognition with behavioral disturbance and impaired daily functioning suggested a clinical diagnosis of familial dementia, possibly Alzheimer disease. The suspicion of Alzheimer disease was supported by her apolipoprotein E genotype c4/c4. L.W.'s condition deteriorated rapidly during the next year, and she died of malnutrition at 82 years of age. Her autopsy confirmed the diagnosis of Alzheimer disease.
Alzheimer Disease:

- Affects 1-2% of the population
- Higher risk to females
- Chronic, progressive loss of cognitive function
- Recent memory
- Abstract reasoning
- Concentration
- Language
- Visual perception
- Visual-spatial function

- Rigidity
- Mutism
- Incontinence

Other associated phenotypes:
- Agitation
- Social withdrawal
- Neuropsychiatric
- Myoclonus
- Parkinsonian features

Neurogenetic disease and disorders are of different types:

- Migration defect
- Loss of myelin
- Reduced or absent neurons (in peripheral nervous system)
- Peripheral neuropathy
- Channelopathy
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Hirschsprung Disease: Case report

S.L. and Y.L. were referred to the genetics clinic to discuss their risk of having another child with Hirschsprung disease; their daughter had been born with long-segment Hirschsprung disease and was doing well after surgical removal of the aganglionic segment of colon. On examination and by history, the daughter did not have signs or symptoms of other disease. The mother knew of an uncle and a brother who had died at infancy of bowel obstruction. The genetic counselor explained that in contrast to short-segment Hirschsprung disease, long-segment disease usually segregates as an autosomal dominant trait with incomplete penetrance and is often caused by mutations in the RET (rearranged during transfection) gene, which encodes a cell surface tyrosine kinase receptor. Subsequent testing showed that the affected daughter and the mother were heterozygous for a mutation in RET.
Hirschsprung Disease: General Features

- Affects the enteric nervous system
- Absence of parasympathetic ganglion cells in the intestine
- Can be long-segment or short-segment aganglionosis
- Enteric neurons are not present causing the gut to not function appropriately (failure to pass stool)

Image from Thompson & Thompson Genetics in Medicine, 2007

Hirschsprung Disease: Genetics

- Can be autosomal dominant, autosomal recessive or multifactorial with at least one major gene (RET)
- Multiple genes are known including RET, EDNRB, EDN3, GDNF, and NRTN
- Identified using linkage, association, and whole-exome sequencing studies

Alves et al. 2013, Developmental Biology

Hirschsprung Disease: Phenotype

- More common in males
- Failure to pass stool
- Dilation of the proximal bowel
- Increased intraluminal pressure
- Decreased blood flow
- Deterioration of the mucosal barrier
- Bacterial invasion
- Enterocolitis

Often occurs with other syndromes
- Down syndrome
- Waardenburg syndrome
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Charcot-Marie-Tooth Case report

During the past five years, a 17-year-old patient had exhibited progressive difficulty in his hands, wrists, and feet, which started leading to a total loss of sensation. His family history revealed similar symptoms. On examination, it was clear that subtle changes in the size and distribution of sensory nerves and motor nerves indicated a potential nerve disorder. The patient’s symptoms also showed a decrease in the size of the peripheral nerves, indicating a possible nerve disorder. The patient was referred to a neurologist, who diagnosed the patient with Charcot-Marie-Tooth disease (CMT). CMT is a genetic disorder characterized by a gradual weakening of the muscles and nerves, leading to progressive weakness and changes in sensation.

Charcot-Marie-Tooth: Natural features

- Paucity of myelin
- Segmental demyelination
- Axonal degeneration
- Muscle denervation
Charcot-Marie-Tooth: Genetics

- Mutations in PMP22 that lead to overexpression of the gene
- Duplication
- Activating point mutation
- Region is flanked by 98% identical repeated DNA sequences
- Causes an inability to form or maintain compact myelin

Image from Thompson & Thompson Genetics in Medicine, 2007

Charcot-Marie-Tooth: Phenotype

- Variability in severity, onset and progression
- Starts with slow, progressive weakness and atrophy of distal leg muscles
- Leads to gait abnormalities, foot deformities, and loss of balance
- Late in the disease weak hand muscles can occur
- Other findings can include:
  - Decreased or absent reflexes
  - Upper extremity ataxia
  - Scoliosis

Image from Thompson & Thompson Genetics in Medicine, 2007

Neurogenetic disease and disorders are of different types

- Migration defect
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Some forms of epilepsy are due to mutation in ion channels. Disruption or failure of channels to function properly causes improper neuronal signaling. Different effects can include neuronal hyperexcitability. Defects in fast inactivation gating, allowing for non-inactivating current during membrane depolarization.

Mutations in many channel genes are associated with epilepsy including:
- Na+ channels (SCN1A, SCN1B, SCN2A)
- K+ channels (KCNQ2, KCNQ3)
- Ca2+ channels (CACNA1A, CACNB4)
- Cl- channels (CLCN2)

Seizures

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Huntington Disease
Case report

M.P., a 45-year-old man, presented initially with declining memory and concentration. As his intellectual function deteriorated during the ensuing year, he developed involuntary movements of his fingers and toes as well as facial grimacing and pouting. He was aware of his condition and became depressed. He had been previously healthy and did not have a history of any similarly affected relatives; his parents had died in their 40s in an automobile accident. M.P. had one healthy daughter. After an extensive evaluation, the neurologist diagnosed M.P.’s condition as Huntington disease. The diagnosis of Huntington disease was confirmed by a DNA analysis showing 43 CAG repeats in one of his HD alleles (normal, <36). Subsequent preemergent testing of M.P.’s daughter showed that she had also inherited the mutant HD allele (Fig. C122). Both received intensive counseling.

Huntington’s Disease:
neuronal features
- Atrophy of the caudate nucleus
- Neuronal inclusions with aggregates of polyglutamine

Huntington’s Disease:
genetics
- Triplet repeat expansion
  - Expansion of a polyglutamine-encoding CAG repeat sequence in exon 1 (HTT)
  - 97% inherit from an affected parent
  - 3% is from a de novo expansion

Image from https://www.youtube.com/watch?v=_NnOOwywMx8&t=171

Images from “Genetics” by Benjamin A. Pierce
Huntington’s Disease:

- Progressive motor, cognitive, and psychiatric abnormalities
- Chorea
- Language is also affected
- Social disinhibition
- Aggression
- Outbursts
- Apathy
- Increased appetite
- Personality changes
- Affective psychosis
- Schizophrenia
- Severe motor impairment
- Weight loss
- Sleep disturbance
- Mutism
- Incontinence

Neurogenetics in the age of large-scale genomics

Can get > 2 Mbp reads, ~95% accuracy

Can get > 50 kbp reads and > 99.999% accuracy

Usually get 150 bp reads and > 99.999% accuracy

Neurogenetics in the age of large biobanks

https://www.biobank.org.uk
https://biobanksverige.se/english/research/getting-started/biobank-sweden
https://www.decode.com