

1. Mendelian Genetics

Mendelian Genetics

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2. Definition of Medical Genetics

Definition of Medical Genetics

- Application of genetic principles to the practice of medicine
- Dx and Rx of genetic diseases
- Study of inheritance of diseases in families
- Mapping of disease genes to chromosomes
- Molecular genetics and pathogenesis
- Genetic counseling
- Genetic therapy

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3. Main Course Objectives

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- Learn how to take an appropriate family history and recognize the most likely patterns of inheritance for various clinical problems
- Learn how a disease gene is localized and the potential benefits of molecular and cytogenetic diagnosis and therapy
- Recognize which patients might benefit from genetic counseling

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4. Pisum Experiments

Pisum Experiments

- Crossed varieties differing in shape and color of seeds
- Round shape prevailed over angular = “dominating”
- Angular shape had temporarily receded = “recessive”
- Demonstrated segregation of traits in hybrid progeny (F₂, F₃=1:2:1)=3:1

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5.

Mendel's Laws

How do Mendel's laws relate to single gene disorders and the practice of medicine?

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6.

Autosomal Dominant Inheritance

Autosomal Dominant Inheritance

- Only one copy necessary for expression
- Transmission is vertical
- Equal number affected males and females
- Male to male transmission
- Unaffected individuals have unaffected children
- Disorder may arise as a new mutation

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7. Example of AD Inheritance: Achondroplasia

Example of AD Inheritance: Achondroplasia

- Most common form of short-limbed dwarfism (1 per 10,000 live births)
- Over 80% of cases are new mutations
- Gene was localized to 4p16 in 1994
- Causative gene is FGFR3
- Molecularly homogeneous
- All affected individuals have a substitution for glycine at aa #380 of protein

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8. Clinical Characteristics of Autosomal Dominant Disorders

Clinical Characteristics of Autosomal Dominant Disorders

- Variable expressivity
- Penetrance (the proportion of people who carry the gene who present with any of the known phenotypic effects of the gene)
- Variation in the age of onset
- New mutations with advanced paternal age (“hot spots” in the genome)

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9. Autosomal Recessive Inheritance

Autosomal Recessive Inheritance

- Two copies needed for expression
- Both parents are carriers, generally clinically normal
- Family history may be negative or prior children may have been affected
- Equal number affected males and females
- Consanguinity may be present
- Little clinical variability

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10. X-Linked Recessive Disorders

X-Linked Recessive Disorders

- Hemizygous males affected
- Heterozygous females unaffected
- Incidence is much higher in males than females
- No male to male transmission
- Carrier females may show variable expression due to lyonization

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11. X-Linked Recessive Disorders in Females

X-Linked Recessive Disorders in Females

- Cells with normal X are inactivated in disproportionate numbers
- Affected female has 45,X karyotype or X chromosome with deletion of normal gene, and inactivation of normal X
- Affected female has an affected father and a carrier mother (rare)
- Disorder is genetically heterogenous (really AR)

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12. X-Linked Dominant Inheritance

X-Linked Dominant Inheritance

- Disorders generally seen in females
- Lethal in males
- Affected individuals have a 50% chance of having an affected child
- X-linked dominant disorders are less common than X-linked recessive disorders

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13.

Case 1- S.E.

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- 25 yo pregnant Puerto Rican woman seen at 19 weeks of gestation
- Referred for “familial Parkinson disease”

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14.

S.E.’s Medical History

S.E.’s Medical History

- Developed tremor in her right hand at age 19
- By age 22, involved both hands and legs
- Started taking her mother’s Sinemet (levodopa)
- Had significant improvement on medication but developed dyskinesias ~1 hour after Sinemet
- Movement specialist in PR changed her to Mirapex
- Without medicine, has rigidity and difficulty walking
- Evaluated initially to r/o Wilson’s disease
- MRI normal

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15. Parkinson Disease, Familial, Type 1; Park 1

Parkinson Disease, Familial, Type 1; Park 1

- Autosomal dominant condition
- Mean age of onset=46 yrs,
- Rapid progression~10 years from presentation until death
- Responds to levodopa
- Caused by mutation in alpha-synuclein gene, located on 4q21

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16. Juvenile Parkinson Disease, Park 2

Juvenile Parkinson Disease, Park 2

- Autosomal recessive condition
- Characterized by rigidity, bradykinesia, and tremor at rest with onset between 20 and 40 years
- Slowly progressive
- Levodopa-induced dyskinesia occurs frequently
- Caused by mutations within *Park 2* gene, located on 6q25-27
- 90% of disease-causing mutations can be identified through sequencing of 12 exons

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17. Victor McKusick, M.D.(1921-present)

Victor McKusick, M.D. (1921-present)

- Tufts Undergraduate- never received degree
- William Osler Professor and Chairman of Medicine at Johns Hopkins 1973-1985
- Established Catalog of Mendelian Inheritance in Man
- Initially X-linked, then recessive in Amish
- Now online
- “Morbidity anatomy of the human genome”

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18. Helpful Web Sites for Mendelian Genetics

Helpful Web Sites for Mendelian Genetics

- OMIM
<http://www3.ncbi.nlm.nih.gov/omim>
- Gene Tests
<http://www.genetests.org/servlet/access>
- www.mendel-museum.org
- www.ashg.org
- www.acmg.net

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