Genetic Counseling

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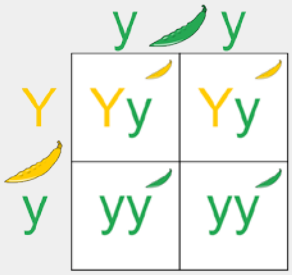
Introduction

- 30 years ago, genetic counseling consisted mainly of applying the Mendelian laws
- Mendelian laws (Laws of Inheritance)
  - Segregation: chromosome pairs are separated into individual gametes (eggs or sperm) to transmit genetic information to offspring
  - Dominance: a dominant allele masks the effects of a recessive allele.
  - Independent assortment: alleles on different chromosomes are distributed randomly to individual gametes

Mendelian Genetics

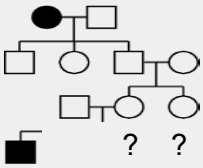


Changes in Genetic Counseling

- Patients with varying diseases and syndromes are referred for evaluation and counseling
- Genetic counseling requires a team of experts
  - Laboratory
  - Medical
  - Surgical

Who is it for?

- A person wanting to know if a genetic disease will reappear in close relatives of someone with the disease
- A person thinking about marriage who may be concerned about a history of a disease in the family
- A person who may want to know the risk for future children or children's children



The Genetic Counselor

- Need a good understanding of genetic principles, a wide knowledge of scientific literature on diseases of possible genetic origin, sympathy, tact and good sense
- Can sometimes be the family physician

The Genetic Counselor

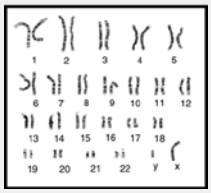
- The role is to estimate *P* (the probability of recurrence) and to assist in deciding the appropriate action
- Should present the genetic facts and options should be non-directive
- Final decision must be left to the family

Genetic Evaluation of the Patient

- Involves a series of questions:
  - Does the patient have a disease of non-genetic origin?
  - Does the patient have a disease of genetic cause?
  - Does the patient have symptoms that suggest a syndrome?
  - Is an examination of chromosomes indicated?
  - Can genetic basis to a problem be found in the family history?

Karyotyping

- A test that examines chromosomes
- Can help identify genetic problems
- Can be performed on any tissue including:
  - Amniotic fluid
  - Blood
  - Bone marrow
  - Placenta



The Most Important Question

- Have problems similar to the present one occurred in other family members?
- Difficulties: A family may not recognize what constitutes a "similar problem"

The Counseling Interview

- The first interview:
  - Collects information
  - Gets to know patient(s)
- Explains the nature of the disorder and the short term prognosis
- Provides emotional support

The Counseling Interview

- 5 Steps:
  - Taking the family history
  - Establishing the recurrence risk
  - Interpreting the recurrence risk
  - Taking action
  - Following up

Taking the Family History

- Make a pedigree
- Communicate with family doctors and hospitals
- Examine medical records and confirm diagnoses of possible relevant diseases
- May want to test certain family members
- Moving beyond cousins or grandparents is not useful

Establishing the Recurrence Risk

- Must place the disease in one of four categories:
  - Major mutant genes
  - Chromosomal aberrations
  - Major environmental agents
  - Multifactorial
- Recurrence risk can be calculated from Mendelian laws with Bayesian modification or another appropriate empirical estimate

Interpreting the Recurrence Risk

- Saying that the risk is a probability introduces uncertainty
- People tend to see probability in binary form:
  - "It will either happen or it won't"
- Must convert probability into a decision
- Counselor can point out important factors:
  - Severity of the disease in relation to the risk of recurrence
  - Impact of the disease on the rest of the family
  - Social and moral pressure they may experience

Taking Action

- The decision reached may require definitive action

The Follow-up

- Able to reinforce the patient's understanding of the information already given
- Can correct any misinformation given

Genetic Screening

- Screening programs are available:
  - Involves prospective counseling rather than retrospective
- Refers to the application of tests to groups of individuals for the purpose of detecting the carriers of deleterious genes or chromosome rearrangements
- Goals:
  - Identify individuals with a genetic disease so they may receive treatment to prevent or eliminate the effects of the mutant phenotype
  - Identify individuals or couples at increased risk for having offspring with genetic disorders

Mass Screening

- Factors include:
  - Disease frequency
  - Disease severity
  - Availability and effectiveness of treatment
  - Cost of tests
  - Accuracy of diagnostic tests
  - Benefits

Mass Screening

- Disease frequency:
  - If the condition is rare, the effort of mass screening may not be justified. If the condition is common, it may be better the treat everyone than to screen
- Disease severity:
  - The greater the burden the greater the pay-off per case
- Availability and effectiveness of treatment:
  - Availability of treatment is a strong argument for detecting diseases early and absence of treatment is an argument against screening to identify affected individuals

Mass Screening

- Cost of tests:
  - Time consuming or expensive tests are difficult to justify for mass screening programs
- Accuracy of diagnostic tests:
  - Specificity should be high (no false positives) and sensitivity should be high (no false negatives)
- Benefits:
  - Tests should be accurate, simple, inexpensive and benefits should justify cost

What You Can Learn From Genetic Testing

- A diagnosis if an individual is displaying symptoms
- Determine if an individual is a carrier
- Prenatal testing (unborn child)
- Screen newborns for abnormalities
- Determine if you have a disease before you display symptoms (Huntington's)

Genetic Testing

These tests look for changes in structure of key proteins coded for by specific genes or alterations in a persons genes
- Abnormal results may mean the individual has a genetic disorder

- **Types of genetics tests include:**
  - **Gene tests**
    - Individual genes of short lengths of DNA or RNA are tested
  - **Chromosomal tests**
    - Whole chromosomes or long stretches of DNA are tested
  - **Biochemical tests**
    - Protein levels or enzyme activities are tested

Gene Tests

- Looks for signs of a disease or disorder in the DNA or RNA taken from a persons blood, other bodily fluids or tissues
  - Looks for large changes
  - May also detect genes with too many copies, genes which are turned off or are entirely lost
  - Examines an individuals DNA in a variety of ways

Types of Gene Tests

Probes
- Short string of DNA with complementary sequence to the sequence of the altered gene
- Have fluorescent tags attached to them
- Probe looks for compliment, if present it attaches to it
- Indicating the presence of an alteration

DNA or RNA sequencing
- Looks at the individual on a base by base perspective
- Can compare their sequence to that of a 'normal' individual

Chromosomal Tests

Chromosomes: large DNA containing structures in the nucleus of a cell

- Tests look at features of a persons chromosomes; structure, number and arrangement
- Looks for changes i.e. deletions switches

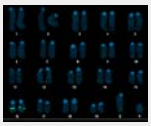
Karyotype

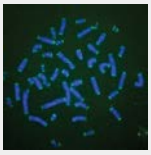
- Picture of an individuals chromosomes, arranged largest to smallest
- Can identify changes in number and large changes in structure
- For instance can identify trisomy 21 (extra copy of chromosome 21)

FISH

FISH analysis (fluorescent in situ hybridization)

- Identifies certain regions on chromosomes by using DNA probes
- FISH analysis can find small missing pieces or those having extra copies of and individual piece
- Small changes which may be missed by karyotypes





Biochemical Tests

- Looks at amount or activity of key proteins
- Abnormal activity here ay cause problems
- Often used in newborn screening
- E.g. PKU testing

Why Get A Genetic Test?

- **Diagnostic testing:** Confirm signs or symptoms of a suggested disease. (E.g physically suggests trisomy 21, can confirm with karyotype)
- **Predictive testing:** Show who has higher chance of getting a disease before symptoms. (I.e. cancer BRCA 1&2)
- **Presymptomatic:** Test who in family is at risk if the disease is already known to be present in a family
  - Done for those not yet showing the disease E.g. Huntington's
  - Graves disease , can preventatively remove the thyroid
- **Preconception/Carrier testing:** Tell individuals if they carry a gene they may pass on to their offspring
  - Done for many recessive disorders
  - E.g. Cystic fibrosis or Tay-sahcs

Why Get A Genetic Test?

- **Prenatal testing:** available during pregnancy for several reasons:
  - Age of mother
  - Family history
  - Ethnic background increasing chance of being a carrier
  - Screen for common disorders such as trisomy 21 or spina bifid
  - Eg. ultrasound, amniocentesis and chorionic villus sampling (CVS)
- **Newborn screening:**
  - Done almost immediately after birth
  - Tests for many disorders and can help reduce the effects of these disorders or combat their symptoms
- **Pharmacogenetic testing:**
  - Examines genes to determine how drugs may be broken down and effect the body
  - Help tailor drug treatments
  - I.e. how are these drugs broken down in the liver will this effect their usefulness ?

Genetic Disorders

Can be divided into three categories:

- Multifactorial inherited disorders
- Chromosome disorders
- Monogenetic disorders

Disorder	Mutation	Chromosome
22q11.2 deletion syndrome	D	22q
Angelman syndrome	DCP	15
Canavan disease		17p
Charcot-Marie-Tooth disease		
Color blindness	P	X
Cri du chat	D	5
Cystic fibrosis	P	7q
Down syndrome	C	21
Duchenne muscular dystrophy	D	Xp
Haemochromatosis	P	6
Haemophilia	P	X
Klinefelter syndrome	C	X
Neurofibromatosis		17q/22q?
Phenylketonuria	P	12q
Polycystic kidney disease	P	16 (PKD1) or 4 (PKD2)
Prader–Willi syndrome	DC	15
Sickle-cell disease	P	11p
Tay–Sachs disease	P	15
Turner syndrome	C	X

Risks of being tested

- Psychological
  - Positive results for a mutation can lead to distress for predispositions and hopelessness for those with no cure
  - Negative results can lead to "survivor guilt" when other family members test positive

Risks of being tested

- Possibility of denied health and life insurance
- Chance of being denied employment due to an increased risk of developing a severe illness

Monogenetic disorders

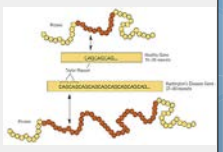
- Caused by a mutation in a single gene
- May be present in one or both chromosomes
- Are relatively rare
- Can be dominant or recessive
- Dominant only required in one chromosome to be affected (50%)
  - Huntington's or Marfan syndrome
- Recessive require presence in both inherited chromosomes (25%)
  - Cystic fibrosis and Tay-sachs

Huntington's Disease

- Inherited neurological disease
- Symptoms:
  - Emotional disturbance
  - Involuntary movements
  - Declined cognitive ability
- Currently affects 30,000 Americans and 75, 000 carry the gene

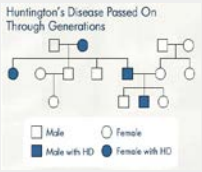
Huntington's Disease

- Disease is produced by a single abnormal gene on chromosome 4
  - Codes for the protein "huntingtin" with no known function
- The normal gene has 11-29 repeats of CAG, abnormal gene has 40-80
- Repeats cause abnormal proteins which clump together and destroy nerve cells
  - Areas for coordinated movement, thought, perception and memory are most affected



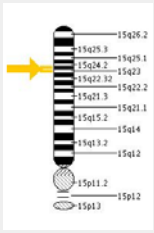
Huntington's Disease

- Is a dominant condition
  - A parent with the disease has a 50% chance of passing it on to their children
- If the gene is present the individual will develop the disease in mid-life
- DNA is analyzed from blood samples to determine number of CAG repeats
- There is no cure



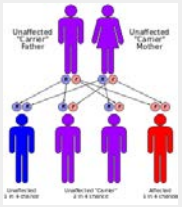
Tay-Sachs

- A rare inherited recessive disorder
- Defective gene on chromosome 15 (which codes for Hex A) specifically 15q23-24
- Body lacks Hexosaminidase A (enzyme)
- Lipid Ganglioside accumulates, leads to the progressive destruction of the nervous system



Chromosome 15

Tay-Sachs



- More prominent among Jewish populations, Cajuns and French Canadians
- Blood sample can be taken to diagnose
- Prenatal CVS or amniocentesis to diagnose in utero
- There is no cure or effective treatment

Tay-Sachs

- Most common in children and is fatal
- Babies are normal until approx. 6 months , development then slows
- At 2 years, seizures in most and diminishing mental function

Three types :

- Classic infantile
- Juvenile
- Late onset

Multifactorial Inheritance Disorders

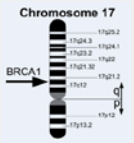
- Caused by a combination of small inherited variations in genes
- May act together with environmental factors
  - Heart disease, diabetes, many cancers
- Can also influence behaviors
  - Contributes to alcoholism, obesity and mental illness

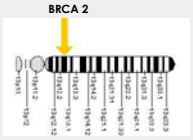
Breast Cancer

- 1 in 9 American women will develop breast cancer
  - 5-27% of breast cancers are hereditary
- 2 identified genes are associated with the disease
  - BRCA 1 on chromosome 17
  - BRCA 2 on chromosome 13

Breast Cancer

- Mutations on these genes lead to a predisposition for breast and ovarian cancer
- Parents with either gene have a 50% chance of passing it on to their children
- Having the gene DOES NOT mean you will develop cancer



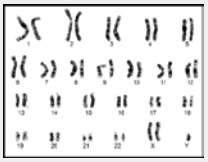


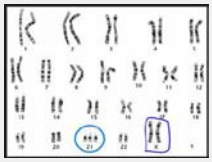
Breast Cancer

- Strong family histories of breast cancer indicates it could be hereditary
- DNA tests can show mutations in BRCA1 and BRCA 2
- Positive results mean the patient has a higher risk of developing cancer
- Mastectomy can be performed as a preventative measure

Chromosome Disorders

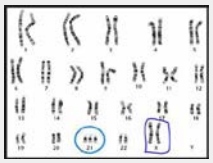
- Caused by excess or deficiency of genes
- Also by structural changes of chromosomes
- Disorders such as Down syndrome, Kleinfelter's & Prader-willi syndrome





Trisomy 21

- Also referred to as Down Syndrome
- Caused by an extra chromosome 21
- Occurs as a result of non-disjunction of chromosomes during meiosis
- One parent gives two of chromosome 21 the other gives one
- Incidence up to 50 fold higher in older mother's
- Occurs in both sexes and in all ethnicities
- Most with the disorder are functional sterile therefore "genetic" but not "inherited or heritable"
- Prenatal diagnosis of amniocentesis, fetal cells from amniotic fluid



Trisomy 21

- Often have common physical features
  - Flattened broad face (bridge of nose)
  - Short neck
  - Small ears
  - Small hands & feet
  - Almond shaped eyes that slant up
  - Epicanthic eye folds

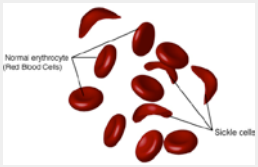
Sheilagh O'Leary

Sickle Cell Anemia

- Caused by hemoglobin S
  - Causes red blood cells to become fragile and crescent shaped
- Inherited from both parents
  - If you get the gene from only one parent you will have the sickle cell trait
- Severe symptoms can include:
  - Fatigue
  - Paleness
  - Rapid heart rate
  - Shortness of breath
  - Painful joints
  - Infections
  - Yellowing of eyes and skin

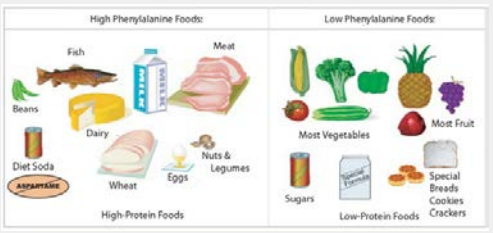
Sickle Cell Anemia

- Testing:
  - Hemoglobin electrophoresis
  - Sickle cell test (blood test)
- Treatment:
  - Folic acid supplements
  - Antibiotics



Phenylketonuria (PKU)

- Missing an enzyme called phenylalanine hydroxylase
- Person is unable to properly break down the amino acid phenylalanine
- Phenylalanine plays a role in production of melanin
- Symptoms:
  - Delayed mental and social skills
  - Hyperactivity
  - Seizures
  - Tremors
- Testing:
  - Blood test (part of newborn screening panel)
- Treatment:
  - A diet extremely low in phenylalanine



Legal, Moral and Ethical Issues

- Our social, ethical and legal development lags behind our technological development

Ethics

- Ethics has been a huge factor in genetics since long before genetic counselling was founded,
- Since its discovery and increase in popularity, the ethical debates in the field have become exponentially more heated and complex

Eugenics

Eugenics: a term describing selective breeding of people with "desired genes" in order to benefit humanity, or to create a "master/superior race".

- Done by encouraging people with beneficial qualities to breed, while discouraging those with genetic deficiencies to not give birth, and ever sterilizing these people.

Confidentiality

- Another ethical issue with genetics
- Since genes contain information about which potential diseases you may acquire over life, people argue about how confidential this information should be.
- For example, what if a person can not get life insurance based on the companies knowing it is probable that they will get cancer sometime in their future?
- This also adds psychological stress on the person being tested, as they now would know that cancer may very well be in their future.

Ethics & Pregnancy

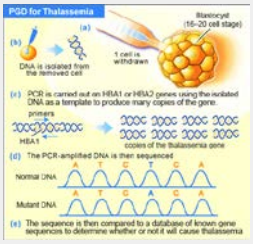
- Since the birth of genetic screening, people can now screen the genetics of their pregnancies to determine if the fetus will be born with any genetic disorders or diseases
- The parents can then decide whether or not to consider abortion based on the results, which leads to a magnitude of not only ethical debates, but also stress and psychological duress on the parents

Ethics & Family

- What should happen when one family member wants to be tested and others don't?
  - For example, if a mother does not want to be tested for Huntington's but her child tests positive she would then know without her consent that she possesses the mutation

PGD

- PGD stands for Pre-implantation Genetic Diagnosis
- Used in many places around the world, yet is banned in others
- Can be used to determine certain genetic qualities of fertilized embryo
- These qualities can range from lifesaving, to cosmetic



PGD

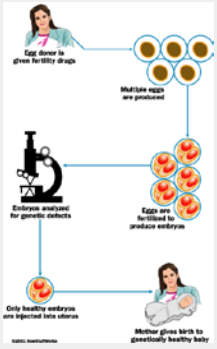
- For example, some parents can be recessive for a gene that causes miscarriage in the fetus if the fetus is homozygous for the same gene
- Another example could be parents who desire a female daughter over a male
- In many places PGD is banned unless it is used to determine harmful/ fatal genes in the fetus.

PGD

- The process of PGD begins with the collection of eggs from the potential mother, who is sometimes provided drugs which produce egg production.
- This is done because the more eggs there are, the more probable it is that one of the embryos will contain the desired genes.
- The egg is fertilized with the potential father's sperm, and incubated for 48 hours.

PGD

- After this period, the blastula's (around 8 cells) membrane is denatured (sometimes using acid) and a single cell (blastomere) is extracted
- If the blastomere contains the normal or desired genes, then so will the blastula it was extracted from.
- The blastomeres are then screened, and the ones with the correct genes are noted (can sometimes be a very low percentage).
- Finally the blastula that the correct blastomeres came from are implanted back into the mother, and the pregnancy is continued from there.



PGD

- This process is debated frequently, as people argue whether it is ethical or not to breed only babies with selected genes
- Although PGD can not completely design a "perfect" baby that would possess all desired genes, some people argue that this is the first step in a direction towards eugenics.

Donor Babies

- Another ethical issue with PGD involves the issue of donor babies
- This is when parents that have a child with a genetic disorder, which could be fixed with a donation (i.e. blood transfusions) from a person with the same blood type who does not have the disorder, decide to use PGD to have a child that fits these qualifications, in order to save their other child
- This is highly debated, and has been done in the past

Donor Babies

- One reason people are against this, is because they believe that is not ethical to play god this way. They also debate that it is unfair to the "donor baby" because they will spend their entire life knowing that their only reason for existing is to save their older sibling.
- It is important to note that these donor babies still go on to live full lives
- This is another issue that would add immense psychological stress to the parent, as they would have to debate whether or not they could raise another child, and also whether or not they agree with the process itself.

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