Genetic Assessment and Counseling
Genetic counseling is the communication of information and advice about inherited conditions and a person seeking such advice is called a consultand.

This process includes history and pedigree construction, examination, diagnosis, counseling and follow-up.
Common Indications for Referral

- Previous child with multiple congenital anomalies, mental retardation or an isolated birth defect
- Family history of a hereditary condition, such as diabetes, fragile X syndrome
- Prenatal diagnosis for advanced maternal age or other indication
- Consanguinity
- Teratogen exposure, such as to alcohol, chemicals
- Repeated pregnancy loss or infertility
- Newly diagnosed abnormality or genetic condition
- Before undertaking genetic testing and after receiving results, particularly when testing for susceptibility to late-onset disorders, such as cancer or neurological disease
- As follow-up for a positive newborn test, as with PKU, or a heterozygote screening test
Genetic Counselors

Certified Genetic Counselors

Number of Genetic Counselors Certified by Year

Data from ABGC

** 466 individuals sitting for 2005 examination
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Geographic Distribution of Genetic Counseling Graduate Programs

Full Accreditation  
RNPS  
Programs being considered/planned
The Process of Genetic Counseling

1.1 Clinical examination
1.2 Confirmation of diagnosis

2. History and pedigree construction

3. Counseling

4. Prevention of Recurrence in Families

5. Follow-up
1.1 Clinical examination

- A complete physical examination of the proband is desirable.

1.2 Confirmation of diagnosis

- A wide variety of investigations may be required, reflecting the wide spectrum of genetic disease.
- **Chromosomal disorders**: Chromosomal analysis
- **Single-gene disorders**: Pedigree analysis, Clinical examination, Biochemical analysis, DNA analysis
- **Multifactorial disorders**: Clinical examination, Biochemical analysis, DNA analysis, other investigations (functional studies, etc)
- **Mitochondrial disorders**: Pedigree analysis, Clinical examination, DNA analysis
- **Somatic cell genetic disorders**: Histopathology, Chromosomal analysis, DNA analysis
The Process of Genetic Counseling

1.1 Clinical examination
1.2 Confirmation of diagnosis

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4. Prevention of Recurrence in Families

5. Follow-up
2. History and pedigree construction

- Normal male
- Normal female
- X-linked carrier
- Carrier
- Proband
- Dead
- Mating
- Consanguineous mating
- Affected male
- Affected female
- No offspring
- Abortion or stillborn
- Fraternal twins
- Identical twins
- Sex unspecific
Pedigree
The Process of Genetic Counseling

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Single-gene disorders
Chromosome disorders
Multifactorial disorders
Somatic cell genetic disorders
Mitochondrial disorders
Autosomal dominant inheritance, AD
Autosomal recessive inheritance, AR
X-linked dominant inheritance, XD
X-linked recessive inheritance, XR
Y-linked inheritance
Autosomal dominant inheritance, AD

Types:

- complete dominance
- incomplete dominance
- irregular dominance
- codominance
- delayed dominance
*penetrance*— in a population, the proportion of individuals possessing a disease-causing genotype who express the disease phenotype.

*expressivity*— the variation of severity of the disease. It refers to the extent of expression of the disease phenotype.

**Pleiotropy**— *Multiple phenotypic effects of a single gene or gene pair.*
Autosomal recessive inheritance, AR

aa: affected

consanguinity

heterogeneity
X—linked dominant inheritance, XD
X—linked recessive inheritance, XR

X inactivation
Recurrence Risk of Single Gene Diseases

Risk estimation when genotypes are known

Risk estimation when alternative genotypes are possible:
Bayesian analysis
3. Counseling

- Single-gene disorders
- Chromosome disorders
- Multifactorial disorders
- Somatic cell genetic disorders
- Mitochondrial disorders
Morphological Types of Human Chromosomes

Ideogram, Karyotype & Banding

Functions of chromosomes and related structures

Chromosomal Polymorphism

Sex Chromosomes
Chromosome Abnormalities

——An abnormality of chromosome number or structure.

Numerical Chromosome Abnormalities
Structural Chromosome Abnormalities
Chromosome diseases—syndromes due to the chromosomal abnormalities.

**Symptoms:**
- Congenital mental retardation
- Growth or development retardation
- Multiple malformation
- ...

**Spontaneous abortion or habitual abortion**

Abnormal chromosome is inherited or caused by mutation?
3. Counseling

Single-gene disorders
Chromosome disorders
Multifactorial disorders
Somatic cell genetic disorders
Mitochondrial disorders
Genetic factor
- Minor gene
- Codominance
- Additive effect

Environmental factor
Liability of polygenic disorder is determined by genetic and environmental factors simultaneously;

Susceptibility is determined by the genetic basis of a certain polygenic disorder;

Threshold model is a useful tool for our research on polygenetic disorders.

Heritability is the fraction of the phenotypic variance due to genetic effects.

Estimating Recurrence Risk
3. Counseling

Single-gene disorders
Chromosome disorders
Multifactorial disorders
Somatic cell genetic disorders
Mitochondrial disorders
Some mammalian genes function differently depending upon whether they come from the mother or the father. Expression of one gene copy is silenced dependent upon its parental origin (mother or father), i.e., it is marked or imprinted.

*Imprinted genes violate the usual rule of mendelian inheritance that both alleles in a heterozygote are equally expressed.*

Imprinting can have a substantial effect on human genetic disease.
HYDATIDIFORM MOLE
An enucleate egg is fertilized by a haploid sperm (which then duplicates its chromosomes), or the egg is fertilized by 2 sperm. Ninety percent are 46,XX, and 10% are 46,XY. All chromosomes are of paternal origin. A complete mole contains no or little fetal tissue and hyperplastic extra embryonic growth.

OVARIAN DERMOID CYSTS
Can result from spontaneous ovarian oocyte activation with duplication of the maternal genome.

HUMAN TRIPLOID ABORTUSES
Phenotypically different depending on parental origin of extra genome
Parent of Origin effects

Mouse experiments (%Surani et al 1984: McGrath et al 1984%)

Diploid uniparental androgenetic (Pg) embryos
Reduced Fetal Growth
Enhanced extra-embryonic growth

Diploid uniparental parthenogenetic (Pg) embryos
Enhanced Fetal Growth
Poor extra-embryonic growth

CONCLUSION
Completion of embryogenesis requires both the maternal and paternal genomes.
Genomic Imprinting

- With female imprinting only the imprinted gene (or genes) on the paternal chromosome is expressed.

- With male imprinting only the imprinted gene (or genes) on the maternal chromosome is expressed.
Genomic Imprinting

[Genetic diagram with symbols indicating imprinting]
Genomic Imprinting

Autosomal dominant with female imprinting
Imprint establishment and propagation

Imprint must be erasable in germline when transmitted through opposite sex

Imprint must be maintained in somatic cell division
Imprinted genes

The mechanisms that mark and regulate imprinted genes are not well understood - methylation.

Imprinted genes rarely found in isolation – about 80% in physically linked clusters

Co-ordinated regulation of these genes in chromosomal domains

Analogous **Imprinting Control Centres** (ICs or ICCs) exist required for regional control of imprinted expression or imprinting
Imprinted Genes in the Mouse

Red: Maternal allele.
Blue: Paternal allele.
Prader-Willi & Angelman Syndromes

- Both of these genetic disorders are caused by deletion of a region of chromosome 15.
- However, the syndromes differ:
  - **Prader-Willi Syndrome** - obesity, mental retardation, short stature. (abbreviated PWS)
  - **Angelman Syndrome** - uncontrollable laughter, jerky movements, and other motor and mental symptoms. (abbreviated AS)
- Syndrome that develops depends upon the parent that provided the mutant chromosome.
  - This is a common phenomenon for - imprinted genes tend to be found in clusters.
PWS
Mouse model

AS
Mouse model

2012/4/6
Prader-Willi & Angelman Syndromes

- **Prader-Willi Syndrome** - develops when the abnormal copy of chromosome 15 is inherited from the father.
- **Angelman Syndrome** - develops when the abnormal copy of chromosome 15 is inherited from the mother.
- The differences reflect the fact that some loci are IMPRINTED.
  - For imprinted loci, only the allele inherited from one parent is expressed.
  - The PWS/AS region contains both maternally and paternally imprinted genes.
Pathogenic mechanisms in PWS and AS

PWS

AS

PWS+ AS-

PWS- AS+

Imprinting centre
PWS

- \(20\%\) UPD

- \(75\%\) deletion

- \(5\%\) imprinting error

PWS+ AS-
PWS- AS+
PWS+ AS-
PWS- AS+
AS

P15

M15

PWS AS

PWS+ AS-

PWS- AS+

~5%

Imprinting error

~75%

deletion

3%

UPD

~5%

2012/4/6
The Process of Genetic Counseling

1.1 Clinical examination
1.2 Confirmation of diagnosis

2. History and pedigree construction

3. Counseling

4. Prevention of Recurrence in Families

5. Follow-up
I. Prenatal screening/testing
II. Newborn screening
III. Carrier and other adult testing
I. Prenatal screening/testing

1. ultrasound
2. maternal serum alpha-fetoprotein or multiple marker screening
3. amniocentesis
4. chorionic villus sampling (cvs)
5. Gene diagnosis
Gene diagnosis

Methods of diagnosing a genetic disease:

1) Direct diagnosis: detect disease-causing mutation
2) Indirect diagnosis: tracking the disease gene by linkage analysis
1. Human genome

2. Gene expression and regulation

Nuclear Genome

- Human Gene
- DNA sequences
- Organization

Mitochondrial Genome
DNA Sequences

Genome complexity can be decided by renaturation kinetics

- unique sequences (single copy DNA)

- moderately repetitive sequences

- highly repetitive sequences
Gene families
Gene cluster
Pseudogenes

Regulation of Gene Expression
Gene Mutation

- Definition
- Major Types
- Mutation Detection

DNA Polymorphism

- Definition and characteristics
- Major types
  - RFLP
  - STR
  - SNP
- Applications
DNA Mutation

- Point mutations
  - Coding region
    - silent mutation
    - missense mutation
    - nonsense mutation
    - stop codon mutation
  - Exon/intron boundary
  - 5’UTR
  - Flanking sequence

- Rearrangements
  - Deletion or insertion
  - codon deletion or insertion
  - Frameshift mutation
  - Fusion gene
  - Dynamic mutation or trinucleotide expansion
DNA Polymorphism

Polymorphism: in a population the occurrence of two or more genetically determined alternative variations at such frequency that the rarest has a frequency of at least 1%.

Levels of polymorphism:

- Phenotype polymorphism (Single eye lid and double eye lids)
- Protein polymorphism (ABO blood type or immunoglobulin)
- Chromosomal polymorphism (minor variant in chromosomal structure)

DNA polymorphism
Methods used in human gene mapping

- In Situ Hybridization
- Somatic Cell Hybridization
- Chromosomal abnormalities
- Dosage effect analysis
- Linkage analysis
13.3 Mapping strategies

For known genes

In Situ Hybridization

Specific chromosome

YES

Linkage

Fine mapping

NO

Somatic cell hybrid mapping

YES

Linkage analysis

NO
For disease genes

Collect families

Chromosomal analysis

YES

Candidate chromosome

linkage

Fine mapping

NO

Candidate genes

Genome scanning

Candidate region

Mutation detection

For disease genes

Collect families

Chromosomal analysis

YES

Candidate chromosome

linkage

Fine mapping

NO

Candidate genes

Genome scanning

Candidate region

Mutation detection
II. Newborn Screening
1. purpose: to find newborns who will benefit from early diagnosis and treatment
2. historically, the criteria for inclusion in a newborn screening program:
   preventable damage
   appropriate test needed to recognize disorder
III. Carrier screening

for reproductive decisions
family history: Tay Sachs, cystic fibrosis, sickle cell disease, phenylketonuria
population screening in ethnic groups
Tay Sachs (犹太人群中的黑蒙性痴呆)
sickle cell disease

for late onset disorders
Huntington disease
breast cancer
The Process of Genetic Counseling

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5. Follow-up
B.D. is referred to the genetic clinic at 16.5 weeks’ gestation because of a positive maternal serum screen (MSS) for Down syndrome; she is 30 years of age, and her MSS result indicates that her risk for having a baby with Down syndrome is now increased to that of a 37-year-old.
B.D. Developmentally delayed
Examing B.D’s blood to rule out a structural chromosome rearrangement and to allow molecular testing for fragile X carrier status.

Results: B.D. is a heterozygote for an expanded fragile X syndrome repeat, and her amniocentesis reveals a male fetus with a normal karyotype and with a CGG repeat length in the normal range.
B.D. ‘s brother has fragile X syndrome and their mother is a carrier.

B.D. ‘s half-sisters?

B.D. ‘s daughter?
Hardy-Weinberg equilibrium: Frequencies of alleles & genotypes in an interbreeding population remain constant from generation to generation.

Factors affect H-W Equilibrium
mutation

Selection \( S = 1 - f \) fitness \( (f) \)

Genetic drift Founder effect

migration

Consanguinity- mating

Coefficient of relationship \( (r) \)

Inbreeding Coefficient \( (F) \)
Nucleic acid extraction
Gel electrophoresis
Nucleic acid hybridization
Polymerase chain reaction