Introduction to Medical Genetics

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- **Medical Genetics**, a specialty of **medicine** dealing with the **diagnosis** and **management** of **hereditary disorders**.
- It is the application of **genetics** to **medical care**.
- It **diagnose**, **manage**, and **counsel** individuals with **genetic disorders**.
- **Genetic Medicine** is also used for **Medical Genetics.**

Scope of Medical Genetics

- **Medical genetics** is comprised of many areas, including
  - clinical practice of physicians,
  - genetic counselors, and nutritionists,
  - clinical diagnostic laboratory activities,
- Pathologic conditions of medical genetics include
  - **birth defects and dysmorphology, mental retardation, autism, metabolic** and **mitochondrial disorders, skeletal dysplasia, connective tissue disorders, cancer genetics, teratogens**, and **prenatal diagnosis.**
- **Medical genetics** overlaps with other **Medical Specialties** such as
  - **neurologic, endocrine, cardiovascular, pulmonary , ophthalmologic, renal, psychiatric.**

Subspecialties of Medical Genetics

- Individual fields in **Medical Genetics** are **hybrids** between **Clinical Care** and **Research**.
- Recent advances in science and technology (e.g. the **Human Genome Project**) have enabled an great understanding of **Genetic Disorders**.
- These include:
  - **Clinical Genetics**
  - **Metabolic Genetics**
  - **Cytogenetics**
  - **Molecular Genetics**
  - **Mitochondrial Genetics**

Clinical genetics

- **Clinical genetics** is the practice of **clinical medicine** with particular attention to **hereditary disorders**.
- **Referrals** are made to **genetics clinics** for a variety of reasons, including **birth defects,developmental delay, autism, epilepsy, short stature,** etc.
- Examples of genetic syndromes are **chromosomal rearrangements, Down syndrome, DiGeorge syndrome Fragile X syndrome, Marfan syndrome, Neurofibromatosis, Turner**

Genetic counseling

- **Genetic counseling** is the process through which a **genetic counselor** provides information about **genetic conditions**.
- It involves **diagnostic testing**, and risks in other family members, within the framework of **nondirective counseling**.

Metabolic/biochemical genetics

- **Metabolic (or biochemical) genetics** involves the **diagnosis** and **management** of **inborn errors of metabolism**
- In this case patients have **enzymatic deficiencies** that **perturb biochemical pathways** involved in **metabolism of carbohydrates, amino acids**, and **lipids.**
- Examples of metabolic disorders include **galactosemia, glycogen storage disease, lysosomal storage disorders, metabolic acidosis, peroxisomal disorders, phenylketonuria,** and **urea cycle disorders**

Cytogenetics

- **Cytogenetics** is the study of **chromosomes** and **chromosome abnormalities.**
- While cytogenetics uses **microscopy** to analyze chromosomes and new molecular technologies such as **array comparative genomic hybridization** .
- Examples of chromosome abnormalities include **aneuploidy, chromosomal rearrangements,** and **genomic deletion/duplication disorders**.

Molecular genetics

- **Molecular genetics** involves laboratory testing for **DNA mutations** that underlie many **single gene disorders.**
- **Examples:achondroplasia, cystic fibrosis, Duchenne muscular dystrophy, hereditary breast cancer, Huntington disease, Marfan syndrome, Noonan syndrome,** and **Rett syndrome**.
- Molecular tests are used in the **diagnosis of syndromes** involving **epigenetic abnormalities**, such as **Angelman syndrome, Beckwith-Wiedemann syndrome, Prader-willi syndrome,** and **uniparental disomy.**

Mitochondrial genetics

- **Mitochondrial genetics** concerns the **diagnosis** and **management** of **mitochondrial disorders**
- This results in **biochemical abnormalities** due to **deficient energy production**.
- Overlap exists between **medical genetic diagnostic laboratories** and **molecular pathology.**

Historical Development of Medical Genetics

- **Gregor Mendel** resulted in **Mendelian (single-gene) inheritance**
- Studies on a number of important disorders such as **albinism, brachydactyly** (short fingers and toes), and **hemophilia**.
- Mathematical approaches were also devised and applied to human genetics. **Population genetics** .
- **Victor McKusick** (1921-2008), **Medical genetics**
- Medical genetics saw an increasingly rapid rise in the second half of the 20th century and continues in the 21st century.

Practice of Medical Genetics

- The clinical setting in which patients are evaluated determines the scope of practice, diagnostic, and therapeutic interventions.
- Specialty genetics clinics focusing on management of **inborn errors of metabolism, skeletal dysplasia, or lysosomal storage diseases**.
- risks to the pregnancy, **teratogen exposure**, family history of a genetic disease), test results (abnormal maternal serum screen, abnormal ultrasound), and/or options for
- **prenatal diagnosis (typically amniocentesis or chorionic villus sampling**).
- Multidisciplinary specialty clinics that include a clinical geneticist or genetic counselor (cancer genetics, cardiovascular genetics, craniofacial or cleft lip/palate, hearing loss clinics, muscular dystrophy/neurodegenerative disorder clinics).

Chromosome studies

- Chromosome studies are used in the general genetics clinic to determine a cause for developmental delay/mental retardation, birth defects, dysmorphic features, and/or autism.
- Chromosome analysis is also performed in the prenatal setting to determine whether a fetus is affected with aneuploidy or other chromosome rearrangements. F
- **Array comparative genomic hybridization** is a new molecular technique that involves hybridization of an individual DNA sample to a glass slide or microarray chip containing molecular probes

Basic metabolic studies

- Biochemical studies are performed to screen for imbalances of metabolites in the bodily fluid, usually the blood (plasma/serum) or urine, but also in cerebrospinal fluid (CSF).
- Specific tests of enzyme function (either in leukocytes, skin fibroblasts, liver, or muscle) are also employed under certain circumstances.
- screen for treatable conditions such as **galactosemia** and **phenylketonuria** (PKU).
- Patients suspected to have a metabolic condition might undergo the following tests:
- Quantitative amino acid analysis is performed using the **ninhydrin reaction**, followed by **liquid chromatography** to measure the **amount of amino acid in the** in the evaluation of disorders of amino acid metabolism such as urea cycle disorders, **maple syrup urine disease,**
- Measurement of amino acids in urine can be useful in the diagnosis of **cystinuria** or renal **Fanconi syndrome** as can be seen in **cystinosis.**
- The **acylcarnitine** combination profile detects compounds such as organic acids and fatty acids conjugated to **carnitine**.

Molecular studies

- **DNA sequencing** is used to directly analyze the genomic DNA sequence of a particular gene.
- **DNA methylation** analysis is used to diagnose certain genetic disorders that are caused by disruptions of **epigenetic** mechanisms such as **genomic imprinting** and **uniparental disomy.**
- **Southern blotting is** an early technique basic on detection of fragments of DNA separated by size through **gel electrophoresis** and detected using radiolabeled probes.
- This test was routinely used to detect deletions or duplications in conditions such as **Duchenne muscular dystrophy** but is being replaced by high-resolution array **comparative genomic hybridization** techniques.
- **Short tandem repeats** are unique markers that can be used to determine **haplotypes** and are used in identity testing for maternal cell contamination.

Diagnostic evaluation

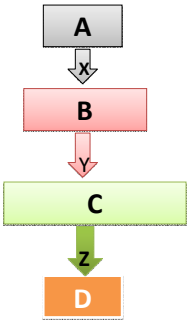
- Each patient will undergo a diagnostic evaluation tailored to their own particular presenting signs and symptoms.
- The geneticist will establish a differential diagnosis and recommend appropriate testing.
- These tests might evaluate for **chromosomal** disorders, **inborn errors of metabolism**, or **single gene disorders**.

Treatments of Genetic Disorders

- Each cell contains the hereditary
- there is no treatment currently available.
- Therefore, there is currently no "cure" for genetic disorders.
- However, genetic syndromes can be managed
- In some cases, particularly **inborn errors of metabolism**, the **mechanism of disease is well understood**
- Offers **dietary** and **medical management** to prevent or reduce the long-term complications.
- infusion therapy is used to replace the missing enzyme.
- Current research seeking to use **gene therapy** or other new medications to treat specific genetic disorders.

Management of Metabolic disorders

- metabolic disorders arise from **enzyme deficiencies** that disrupt normal **metabolic pathways**
- Example in the **hypothetical example:**



Diet

- **Dietary restriction** and **supplementation**
- e.g. **galactosemia**, **phenylketonuria**, **ma ple syrup urine disease**, **organic acidurias** and **urea cycle disorders.**
- Difficulties arise

Medication

- enhancement of residual enzyme activity
- inhibition of other enzymes in the biochemical pathway to prevent buildup of a toxic compound,
- or diversion of a toxic compound to another form that can be excreted.
- E.g use of high doses of **pyridoxine (vitamin B6)** in some patients with **homocystinuria** to boost the activity of the residual **cystathione synthase enzyme**,
- administration of **biotin** to restore activity of several enzymes affected by deficiency of **biotinidase,**
- treatment with **NTBC in Tyrosinemia** to inhibit the production of **succinylacetone** which causes liver toxicity, and the use of **sodium benzoate** to decrease **ammonia** build-up in **urea cycle disorders**.

Enzyme Replacement Therapy

- Certain **lysosomal storage diseases** are treated with infusions of a **recombinant enzyme** which can reduce the accumulation of the compounds in various tissues. Examples include **Gaucher disease, Fabry disease, Mucopolysaccharidoses** and **Glyco gen storage disease type II.**
- Such treatments are limited by the ability of the enzyme to reach the affected areas, and can sometimes be associated with **allergic reactions.**