Basic Genetics 101 and Rare Disorders

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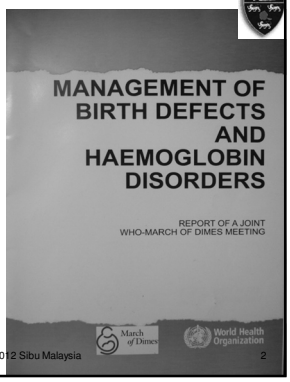
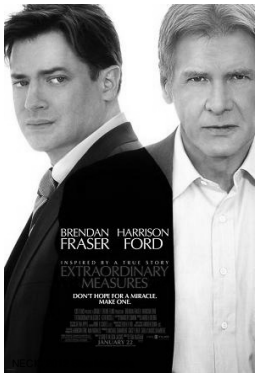
A layman's guide to genetics and rare conditions



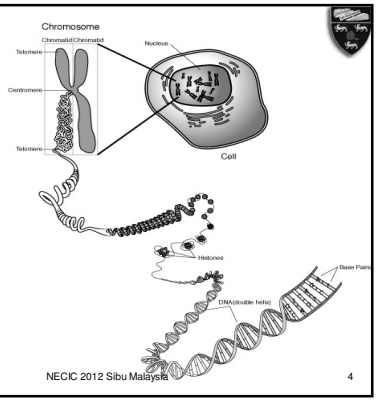
Extraordinary Measures

- Rare disorders: "Double whammy"
- Learning disabilities
- Life-threatening, medical conditions
- Chronic diseases
- Genetic guilt; shame and blame



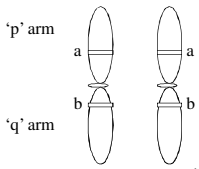
Cell biology 101

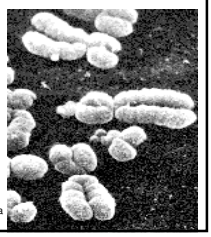
- Estimated 25,000 genes in the human genome
- Two unrelated persons share 99.9% DNA sequences
- Over 14,000 single gene disorders recognised; over 8,000 gene loci identified.

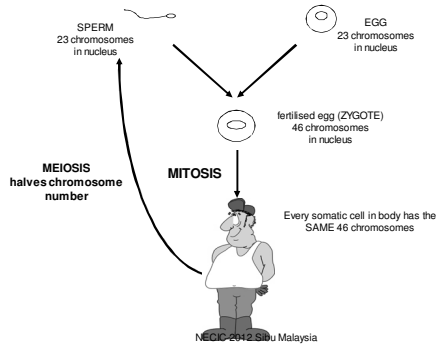


More about chromosomes

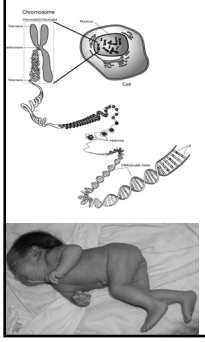
- pairs of chromosome = homologous
  - same length
  - same sequence of genes as each other
- 2 types : 22 pairs of autosomes - do not determine sex; sex chromosomes -determine sex of individual

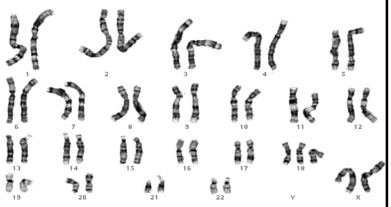






2. chromosomes are then arranged according to number and structure





47,XX,+18

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Cell biology 101

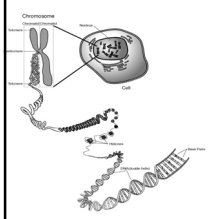


Figure 1: Dogma of DNA to RNA to protein

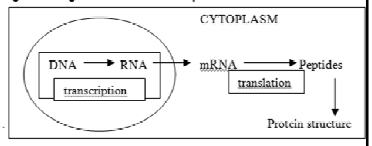
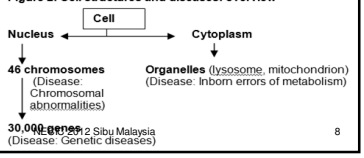


Figure 2: Cell structures and diseases: overview



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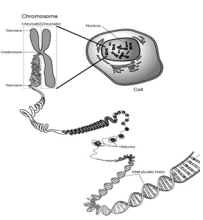
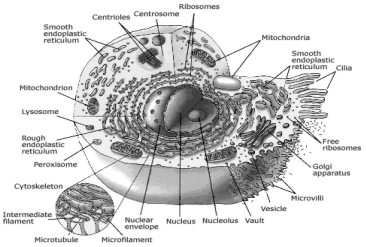
Inherited metabolic disorders





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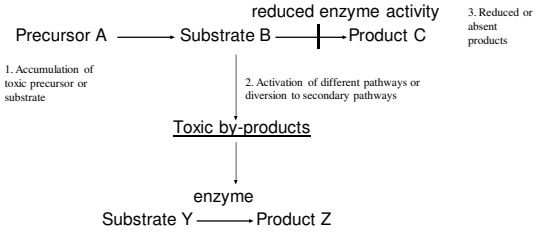
Inherited metabolic disorders



Pathogenesis of IMD: Faults in enzyme function may lead to deficiencies in product formation, accumulation of normal substrates to toxic levels and diversion of normal substrates through abnormal pathways.

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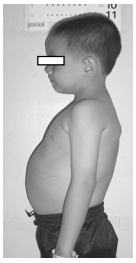
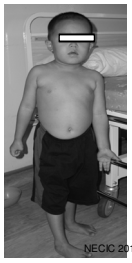
Glycogen storage disease in two siblings

- Index case: 10-year-old boy wakes to feed 2-3 times at night, short stature, learning problems, progressive abdominal distension
- Younger sibling (8 years old) similar problem





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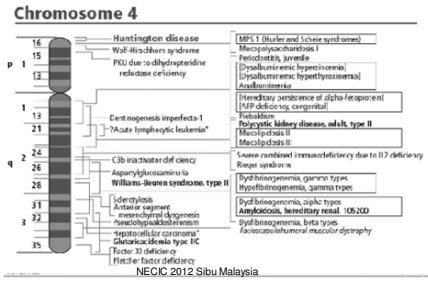
Chromosome and gene



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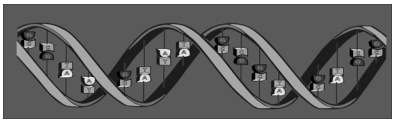
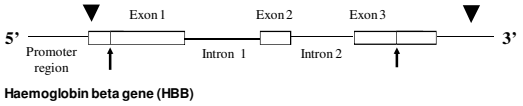
DNA

- 2 linked strands twist to form a DOUBLE HELIX



- complementary base pairing
  - ⋆ reading the gene
  - ⋆ accurate replication of DNA/chromosomes for new cells
- sequence of AT & GC pairs
  - ⋆ all important in determining gene product structure & function

Simplified diagram of a gene

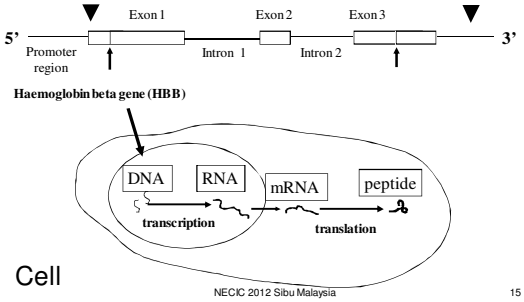


Haemoglobin beta gene (HBB)

- A gene is the DNA sequence (of bases) that contains all the information necessary to make a specific peptide or RNA molecule

Exons: contain sequences coding for specific polypeptide *(**ex**pressing regi**ons**)*
Introns:found between exons *(**int**ervening regi**ons**)*, may be involved in regulation
Structural element of a gene includes both exons and introns

Simplified diagram of a gene



Mutations

- Alterations to DNA sequences are called mutations
- Mutations contribute to natural variation between individuals. It may 'pathological' – mutations at the chromosomes resulting in chromosomal abnormalities or at the DNA level, within genes and between genes.
- Mutations may be detrimental depending upon their nature and their position.
- There are about $5x10^6$ differences between individuals (~1%) The variation in DNA sequence or single nucleotide polymorphisms (SNPs) is a major determinant of susceptibility or resistance to disease, response to drugs and anthropological trait via interaction with environmental factors.

Base-substitutions: missense mutation

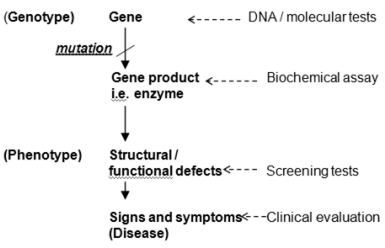
UUC	UCA	CCU	GUU	GAU
Phe	Ser	Pro	Val	Asp
⇓				
UUC	UCA	CCU	GUU	GAA
Phe	Ser	Pro	Val	**Glu**

Analogy: the big cat bit the fat man

⇓

the big cat bit the fit man

Figure 3: Genotype and phenotype correlation

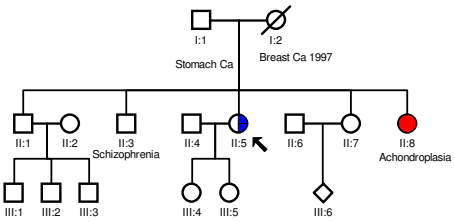


Osteogenesis imperfecta (brittle bone disease)

Family tree

- Can be used to record medical conditions
- Concisely record family relationships
- Can assist in identifying people at risk of a genetic condition

A picture paints a 1000 words

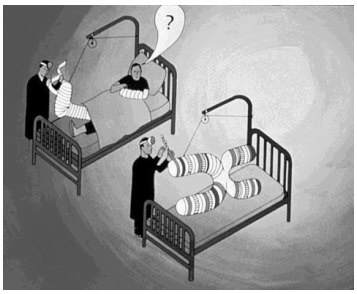


Genetic counselling

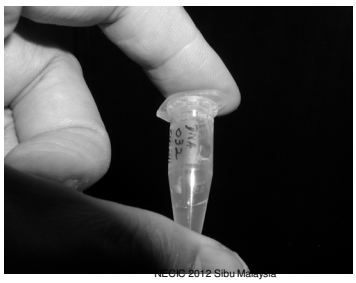
- a process where an individual or family obtains information regarding a real or possible inherited disorder, to make an informed decision about their reproductive options and to assist them in coming to terms with issues they face
  - Collecting a family history
  - Performing a clinical examination
  - Providing genetic information
  - Explaining genes and genetics
  - Discussing genetic testing and prenatal diagnosis
  - Discussing the implications for other family members
  - Providing non-directive counselling and support

Genetic Testing

- Gene tests (also called DNA-based tests) involve direct examination of the DNA molecule itself.
- Other genetic tests include biochemical tests for gene products (enzymes or other proteins) and for microscopic examination of stained or fluorescent chromosomes.

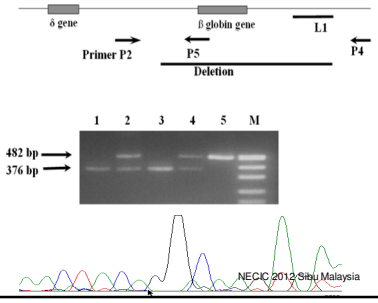


Genomic DNA prepared from white blood cells sample for molecular studies



Genetic testing using PCR (polymerase chain reaction)

- The cells removed from each white blood cells are analyzed using PCR-based DNA amplification



M =marker
5 = normal
2,4 = carrier
1,3 = affected

Deletion in the beta globin gene in the Kadazandusun population in Sabah (Thong et al, Human Mutations 1999)

Management of genetic conditions

Gene ← Transplantation / gene therapy
↓
Protein ← Protein replacement
↓
Symptoms ← Special diet; medications
↓
Disease ← Medical or surgical treatment
↓
Support for family & patient education
↓
The family ← Genetic counselling; screening & genetic testing
Support for family & patient education

Rare Disorders: Myths & Facts

- About 3-5% of babies are born with serious birth defects. Each year, there are about 20,000 Malaysian babies born with birth defects
- Individually rare but collectively common
- Some of these can be recognised at birth, while some are diagnosed later in life
- Some are due to genetic changes, while others are due to both genetic and environmental factors
- These conditions cause medical and social problems and may recur again in some families

Rare Disorders:

Problems:

Low scientific knowledge (false perception about rare disorders - 'not important' enough)

⇩

Absence of cure and treatment that could improve quality of life

⇩

Low knowledge amongst health professionals & public

⇩

Negative social consequences

What are Rare Disorders?

- Prevalence of less than 1 in 4000 people (for registration with Malaysian Rare Disorders Society)
- Some conditions: prevalence range from 1 in 10,000 to 1 in 100,000
- Examples:
  - O*steogenesis imperfecta* (brittle bone disease),
  - *Duchenne muscular dystrophy* (DMD),
  - *Prader-Willi* syndrome,
  - *Fragile-X* syndrome,
  - Mucopolysaccharidosis
  - Chromosomal abnormalities
  - Inborn errors of metabolism
  - Syndromes and many others.

Duchenne muscular dystrophy

Many challenges…

- Limited educational resources on rare disorders for patients and family members especially in different languages
- Lack of public support groups for patients with rare disorders
- Limited professionals trained in early intervention programmes and services
- Lack of awareness and understanding among medical professionals, organisations and community on the needs of individuals with rare disorders

Prader-Willi syndrome

More challenges…

- Limited funds to support treatment or to purchase special orphan drugs
- Limited genetic testing available locally
  - too costly to send overseas
  - insufficient laboratories and technologists
- Limited local research data on rare disorders

Achondroplasia

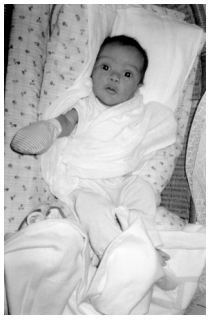
Day to day challenges…

- Specific diagnosis
  - Rare unique syndromes – parents feeling alone in facing challenges
  - Breaks for parents – respite care for caregivers
- Coping with loss of child, grief and bereavement
- Dealing with feelings of guilt, shame and blame
- No specific diagnosis:
  - dealing with uncertainties
  - management based on needs
  - family planning issues

Day to day challenges…

- Health maintenence
  - Routine paediatric care e.g. vaccination
  - Monitoring growth and nutrition
  - Ensure development of skills
- Health surveillance
  - Hearing loss
  - Visual impairment
  - Difficulties in ambulating and getting around
  - Dental care
  - Personal hygiene and toilet

Congenital disorder of glycosylation (CDG)



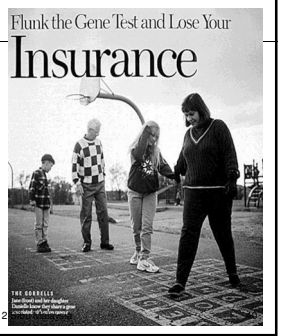
Day to day challenges…

- Sleep problems
- Behavioural challenges
  - Autism & Hyperkinetic disorder
  - Others: depression, aggression
  - Role of psychologist and psychiatrists
- Learning difficulties
  - IQ assessment: accurate?
  - Early intervention programme
  - Occupational therapy
  - Physiotherapy, speech therapy
  - Schooling?

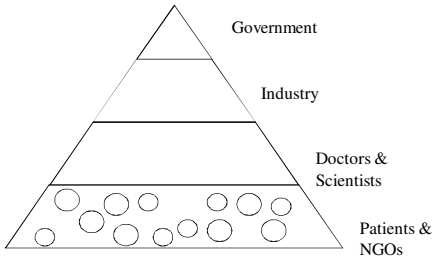
Ectodermal dysplasia

Support for patients and families

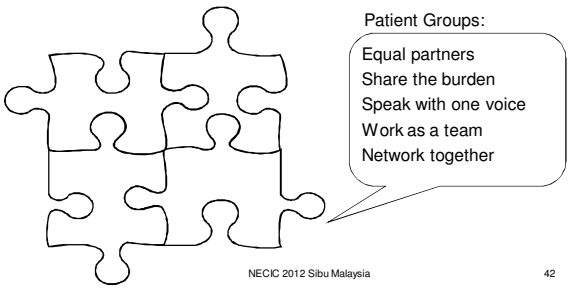
- Stigmatisation and discrimination
- Achieving equitable access to services
- Insurance issues
- Difficulties with early interventional programs
- Ethical, legal, social and religious issues



Patients and their partners in health



Rare Disorders: Putting the Jigsaw Puzzle Together



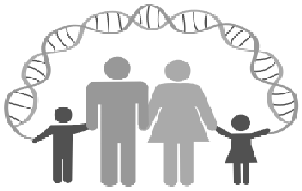
Jabatan Kebajikan Malaysia

- www.jkm.gov.my
- OKU registration
- Kemudahan pengangkutan awam
  - MAS 50% penerbangan domestik
  - KTM 50% bagi semua kelas
  - LRT, KL Monorail 50%
  - Rapid KL – tiada bayaran
  - Transnasional 50%
- Pelepasan cukai sebanyak RM 5000 kepada pembayar cukai yang mempunyai anak OKU yang berusia dibawah 18 tahun
- Pelepasan cukai sehingga RM 5000 bagi membeli alat-alat khas untuk kegunaan sendiri,anak atau ibubapa OKU.
- Pengecualian Bayaran dokumen perjalanan

Rare Disorders: The Way Forward

Early childhood intervention programs
Transdisciplinary and multidisciplinary
Family-centred

Provisions for genetic services
Training of genetic counsellors and support staff
Getting stakeholders together to speak with one voice



MALAYSIAN RARE DISORDERS SOCIETY
(Registration No. : 0064-07-WKL)

Malaysian Rare Disorders Society

Create a network among individuals and families with rare disorders.

Create a network among MRDS members with organisations, agencies and professionals involved in treating, educating and conducting research on rare disorders.

Serve as a contact and resource centre on rare disorders.

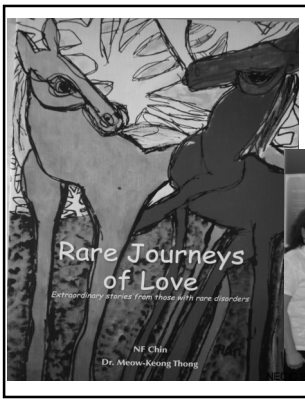
Promote the awareness on rare disorders among the Malaysian community.

Support and assist individuals and families affected with rare disorders in terms of welfare, treatment, rehabilitation, education and socials needs.

Collaborate with agencies and organisations that diagnose, research and treat rare disorders to increase the quality of life for the individuals and families affected.

Raise funds to support the activities and objectives of MRDS.

E-maill MRDS: info@mrds.org.my



www.mrds.org.my

Thank you

Visit www.apchg2012.org

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