CASE 1

Short case number: 3_16_1
Category: Children and Young People
Discipline: Paediatrics_Medicine
Setting: Hospital outpatients
Topic: The Child with dysmorphic features [SDC]

Case

You are an intern doing a paediatrics rotation, Mrs Juanita Mascord-Perez presents with her 4 month old son, Marco. The referral letter from her GP comments on his facial appearance in particular his eyes seem to slant outward, are widely spaced and he has low set ears.
Marco has otherwise been well and his mother is very concerned that her GP believes there is something wrong with him. He is her first child.
On general observation of Marco there is no immediately recognisable syndrome.

Questions

1. What are the key features of history that you would explore with Marco's mother?
2. Outline the systematic approach to the physical examination that you would complete.
3. If Marco had an uncommon syndrome that was not immediately recognisable what resources would you utilise to make the diagnosis?
4. What causes genetic mutations? Summarise the types of genetic mutations, providing a clinical example for each type.
5. Outline the inheritance pattern in an autosomal recessive condition, an autosomal dominant condition, an X-linked recessive disorder and a polygenic disorder.
6. What is meant by the following genetic terms: malformation, disruption and deformation?
7. In a table summarise the cause of birth defects.
8. Define the term teratogen and describe the effects of teratogens.
9. Marco is diagnosed with Noonan Syndrome; his parents are concerned regarding future pregnancies. List the indications for formal genetic counselling, briefly outline what Mr & Mrs Mascord-Perez will be told about future pregnancies.

Suggested reading:

- Hotham, N., Poplawski, N., Barnett, C. & Delatycki, M (2012). Inherited Metabolic Problems. In South, M & Isaacs, D. (Eds) Practical Paediatrics (pp 276 – 317) Edinburgh, Churchill Livingston.

Useful references

- http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=noonan Judith E Allanson, MD Department of Genetics Children's Hospital of Eastern Ontario : October 7, 2008.
- http://emedicine.medscape.com/article/947504-overview Author: Jennifer Ibrahim, MD, Fellow, Department of Paediatrics, Division of Genetics, Children's Hospital of New Jersey and Mount Sinai School of Medicine
  Co-author(s): Margaret McGovern, MD, PhD, Vice Chair, Professor, Department of Human Genetics, Mount Sinai School of Medicine Dec 12, 2007.

ANSWERS

1. **What are the key features of history that you would explore with Marco's mother?**

   A detailed medical history is important. Special points to note include:

   - antenatal history:
     - teratogens, such as drugs, viruses, maternal diabetes, maternal hyperthermia
     - foetal movements - a neuromuscular disorder may cause reduced foetal movements, resulting in arthrogryposis (multiple fixed deformities of joints)
     - prenatal screening and diagnostic tests
   - perinatal history, weight, length and head circumference and Apgar scores at birth
   - growth and development, behaviour, sleep patterns
   - family history; draw a family tree noting the following:
     - miscarriages, stillbirths and deaths of siblings
     - information about other family members with the same features.

2. **Outline the systematic approach to the physical examination that you would complete.**

   Observe the child before undressing or disturbing her/him. On the other hand, the examination is not complete until the child has been fully undressed. Especially note:

   - behaviour and alertness
   - body size and proportions, relative head size, asymmetry, chest shape and spinal curvature
   - height, weight, head circumference, arm span, upper and lower body segments
   - always plot measurements on standard normal charts. Charts are available for many different body parts, e.g. hand measurements, foot and ear length. Special charts are available for certain disorders, e.g. Down syndrome, and various bone dysplasias, e.g. achondroplasia
   - facial features:
     - shape of the head and face
     - spacing of the eyes (hyper- or hypotelorism, i.e. wide or closely spaced); slant of the palpebral fissures (up or down)
     - shape and size of the nose and mouth
     - structure and position of the ears
   - proportions of the limbs, muscle bulk and tone, joint contractures and mobility
   - structure of hands and feet (shape, length, number of digits, dermal ridges, nails)
   - skin pigmentary or vascular markings
   - external genitalia
   - any birth defects (e.g. cleft palate)?
   - auscultate the chest for any cardiac murmurs
   - palpate the abdomen for organomegaly.

   A *photograph* (with parental consent) is useful for:

   - comparing later on to see how the face has changed
   - consulting colleagues.

3. If Marco had an uncommon syndrome that was not immediately recognisable what resources would you utilise to make the diagnosis?

- ***Check textbooks of syndromes*** by trying to match the most important dysmorphic features and comparing the photographs with those of the patient
- ***Consultation***:
    - *Paediatricians* will recognize the more common syndromes, e.g. Down syndrome
    - *Clinical geneticists* have experience in identifying many more syndromes. Some have a special interest and expertise in syndrome diagnosis (*dysmorphologists*)
    - it's not easy! A skilled dysmorphologist makes a syndrome diagnosis in a dysmorphic child in only 20% of cases referred from an experienced paediatrician
    - if an overall diagnosis is not made, the recognized problems must still be managed.
- ***Review*** in a few years time may allow a diagnosis to be made, as the features of many syndromes evolve with time and new information or laboratory techniques may be available for specific diagnoses
- ***Computerized databases***
    - several thousand syndromes are published, and many are individually rare
    - computerized databases combine pictures and descriptions of syndromes
    - searches are made using a few key dysmorphic features and a number of possible diagnoses are suggested that can be compared with the patient
    - occasionally, a match will be achieved
    - success is more likely if relatively rare features are used for the search. For example, a common feature such as hypertelorism (wide-spaced eyes) would give a long list of suggested syndromes, whereas imperforate anus would give a more manageable list to consider
    - training and experience are needed to use these databases effectively
- Examples of these databases are:
    - POSSUM (Pictures Of Standard Syndromes and Undiagnosed Malformations), developed by the Genetic Health Services, Victoria, Australia
    - the Winter-Baraitser Dysmorphology Database (previously called the London Dysmorphology Database)
    - REAMS (a Radiological Electronic Atlas of Malformation Syndromes and Skeletal Dysplasias)
    - the Baraitser-Winter Neurogenetic Database (previously called the London Neurogenetics Database)
    - the London Ophthalmic Genetics Database (GENEYE)

4. What causes genetic mutations?

DNA replication consists of accurately copying the 6 billion nucleotides that are spread along the 2 m of DNA within the few microns of space within the nucleus of a cell The penalty for failing to copy DNA accurately is the generation of new genetic errors (or *mutations*), which are transmitted to all of the cell's progeny.

The enzyme *DNA polymerase* is very good at copying DNA accurately, having an error rate of only one wrong nucleotide pair per million processed. This is impressive, but it would amount to thousands of new mutations at every cell division. There is an additional proofreading mechanism that compares the original with the copied strand and corrects any mismatched nucleotides on the new strand. This mechanism reduces the overall mutation rate to approximately one wrong nucleotide per billion processed. As a consequence, the division of any cell results in approximately six new mutations in the DNA sequence.

Despite the frequency of mutations, most of them have no adverse effect on the information encoded in the DNA. Genes account for only 5% of the human genome, and the majority of mutations occur in non-coding DNA and do not affect genes or the proteins they encode. These mutations are usually referred to as *polymorphisms* (meaning 'many forms') because they do not reduce an individual's ability to survive. Polymorphisms are very common. Mutations in genes are much less common than polymorphisms. They may interfere with the function of a gene, compromise the cell's function, and so cause a disorder.

Summarise the types of genetic mutations, providing a clinical example for each type.

Table 100-1. Types of mutations that occur during DNA replication

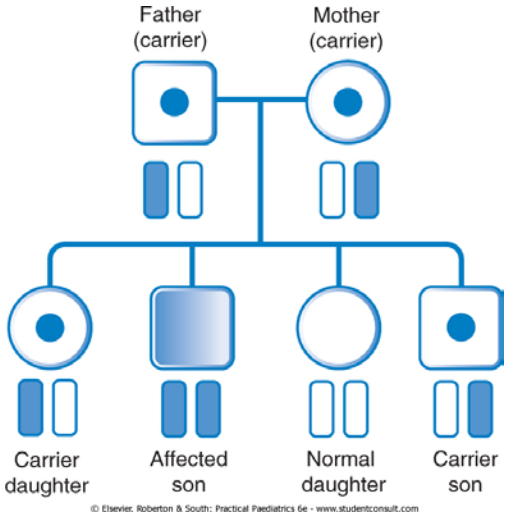
Scale and type of error	Mutation	Description	Examples of diseases due to these mutations*
Structural errors	Deletion of genes	Loss of all or part of a gene, resulting in little or no protein product	Duchenne muscular dystrophy
	Duplication	Duplication of all (or part) of a gene resulting in excess (or deficiency) of the protein product	Charcot-Marie-Tooth disease
	Nonsense/truncation	Mutation involving one or more nucleotides that prevents the cell from generating a complete RNA strand	Hurler syndrome
	Missense	Mutation involving one codon that causes a critical alteration in the protein sequence	Achondroplasia

	Splicing error	Mutation involving the nucleotides which identify the junction between exons and introns resulting in generation of an abnormal RNA strand	Crouzon syndrome
Functional errors of genes	Regulatory mutation	Mutation in the regulatory region of a gene causing inappropriate activation or silencing of gene	Thalassaemia
	Abnormal imprint	Reversal of the normal silencing or activation of specific genes in the maternal or paternal germline	Beckwith-Wiedemann syndrome
	Unstable triplet repeat	Increase in the number of copies of a repeated triplet of nucleotides causing impairment of function of gene or protein	Fragile X syndrome
Structural errors of chromosomes	Monosomy (deletion)	Loss of whole (or part) of a chromosome	Turner syndrome
	Trisomy (duplication)	Excess of the whole (or part) of a chromosome	Down syndrome
	Triploidy	Presence of an extra copy of each chromosome	Miscarriage
Functional errors of chromosomes	Uniparental disomy	Both copies of all or part of a chromosome inherited from just one parent	Prader-Willi syndrome

* Note that different patients with the same genetic disorder may have different types of mutation in the same gene.

5. Outline the inheritance pattern in an autosomal recessive condition, an autosomal dominant condition, an X-linked recessive disorder and a polygenic disorder.

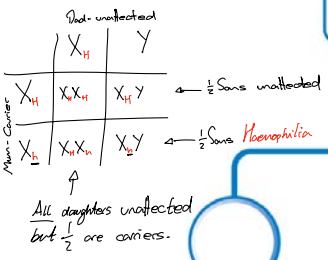
autosomal recessive



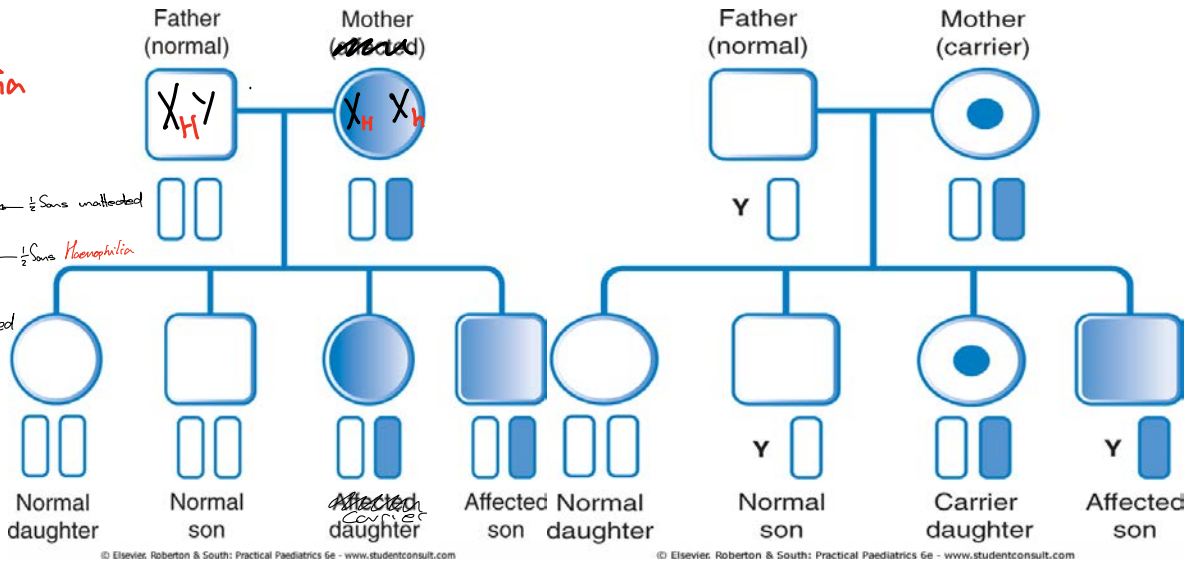
x-linked recessive (e.g. Haemophilia)

H = Normal

h = haemophilia



autosomal dominant:



A polygenic disorder is due the interaction of a number of different genes

Many common genetic disorders cannot be attributed to a mutation in a single gene but are due to the interaction of a number of genes. Examples of such *polygenic* disorders include common congenital malformations, such as cleft lip, and disorders of later life, such as asthma, diabetes and schizophrenia. These conditions result from the interaction of a number of genes, each of which has some mutation or polymorphism that increases the risk of the condition. Any one of these mutations or polymorphisms is unlikely to cause the disorder on its own.

Even if a foetus has inherited a number of mutations that place it at increased risk of a birth defect, non-genetic factors, such as maternal nutrition or chance, may ultimately determine whether the malformation occurs. A disorder due to the interaction of multiple genes and non-genetic factors is called a *multifactorial* disorder. An example is spina bifida in which a nutritional deficiency of the vitamin folate and variations in genes responsible for folate metabolism are associated with an increased risk of this major malformation.

Polygenic and multifactorial disorders typically affect between 0.1% and 1% of the population. The recurrence risk among close relatives is usually 10-20 times higher. Few of the genes responsible for polygenic disorders have been identified, and this remains a major objective in genetic research.

6. What is meant by the following genetic terms: malformation, disruption and deformation?

Structural birth defects may be classified on the basis of the mechanism by which they arise:

- *Malformations* arise during the initial formation of the embryo and foetus as a result of genetic and/or environmental factors during organogenesis (2-8 weeks postconception). Malformations may include failure of formation, incomplete formation or abnormal configuration. Examples include spina bifida, cleft palate and hypospadias
- *Disruptions* result from a destructive process that alters structures after formation. Examples include early amnion rupture causing amputation defects of digits, or an abdominal wall defect
- *Deformations* result from moulding of a part by mechanical forces, usually acting over a prolonged period. Examples include talipes, congenital hip dislocations and plagiocephaly associated with oligohydramnios.

7. In a table summarise the cause of birth defects.

Causes of birth defects

Mechanism	Example	Cause
Whole chromosome missing or duplicated	Down syndrome Turner syndrome	Trisomy 21 Monosomy X
Part of chromosome deleted or duplicated	Cri du chat syndrome Cat eye syndrome	Deletion 5p Duplication 22q
Submicroscopic deletion or duplication of chromosome material	Williams syndrome Velocardiofacial syndrome Charcot-Marie-Tooth disease 1A	Deletion 7q Deletion 22q Duplication 17p

Mutation in single gene	Smith-Lemli-Opitz syndrome Holt-Oram syndrome Apert-Crouzon-Pfeiffer syndrome	7-dehydrocholesterol reductase TBX5 Fibroblast growth factor receptor 2
Consequence of normal imprinting	Prader-Willi syndrome	Maternal uniparental disomy or paternal deletion for 15q12
Imprinting errors	Beckwith-Wiedemann syndrome Angelman syndrome	Multiple mechanisms resulting in overexpression of IGF2 Mutations in UBE3A gene
Multifactorial/polygenic: one or more genes and environmental factors	Isolated heart malformations, neural tube defects and facial clefts	Complex interactions between genes and environmental factors not yet defined
Non-genetic vascular and other 'accidents during development'	Poland anomaly Oculoauriculovertebral dysplasia	Subclavian artery ischaemia Stapedial artery ischaemia
Uterine environment	Talipes, hip dysplasia, plagiocephaly	Oligohydramnios, twins, bicornuate uterus
Maternal environment	Mental retardation Caudal regression	Maternal phenylketonuria Maternal diabetes mellitus
Wider environment	Foetal rubella syndrome Foetal alcohol syndrome Microcephaly Limb deficiency	Rubella infection in pregnancy Maternal alcohol ingestion High-dose X-irradiation Thalidomide

8. Define the term teratogen and describe the effects of teratogens.

A teratogen is an environmental agent that can cause abnormalities of form or function in an exposed embryo or foetus. It is estimated that between 1% and 3% of birth defects may be related to teratogenic exposure.
A teratogen may cause its effect by a number of different pathophysiological mechanisms, including:

Mechanisms of teratogens

1. cell death
2. alteration of cell division and tissue growth, including cell migration
3. interference with cellular differentiation.

Examples of the different ways in which teratogens may have their effects are seen with alcohol and sodium valproate, which are believed to cause dysmorphic facial features with underdevelopment of the mid-face and philtrum due to cell death in these areas, whereas syndactyly can result from failure of programmed death of cells between the digits.

9. Marco is diagnosed with Noonan Syndrome; his parents are concerned regarding future pregnancies. List the indications for formal genetic counselling,

Indications for formal genetic counselling

Anybody who suspects that there might be an increased risk of a genetic condition or producing a child with a genetic condition or birth defect may wish to receive formal genetic counselling. This includes:

- individuals who themselves have a genetic disorder
- couples who have had a stillbirth
- couples who have had a child with a birth defect
- couples who have had a child with intellectual disability
- family history of any of the above
- family history of known genetic disorders, such as Huntington disease, muscular dystrophy
- multiple miscarriages
- exposure to radiation or drugs during pregnancy
- advanced maternal age
- consanguinity
- chromosome anomalies, including translocations and inversions
- cancers, particularly where there are multiple affected family members and/or where there is a very young age at disease onset.

10. Briefly outline what Mr & Mrs Mascord-Perez will be told about future pregnancies.* note references

Noonan syndrome occurs in either a sporadic or autosomal dominant fashion. Many affected individuals have *de novo* mutations; however, an affected parent is recognized in 30%-75% of families.

A parent may have mild clinical picture that can be recognised by careful examination.

The risk of a subsequent child having Noonan syndrome depends on the genetic status of the parents. NS is inherited in an autosomal dominant manner. Therefore, If a parent is affected, the risk is 50%.
When the parents are unaffected, the risk for a subsequent pregnancy appears to be low (<1%) This is higher than the general population because of the possibility of germ line mosaicism in one or other parent (i.e. a mix of affected and unaffected germ cells).

Disease causing genes (*PTPN11, SOS1, RAF1,* and *KRAS*) have been identified and can be tested for by molecular genetic testing both in the child to confirm diagnosis and if found, in parents who may have no obvious clinical features.
Not all patients have a mutation in one of the (so far) 4 known genes, of which PTPN11 mutations are the most common, present in about 50%.

Note that Genetic testing to find the causative mutation in a patient is expensive (about 1000$ per gene) only done in overseas labs right now, no Medicare rebate. Could add up to about $4,000 Australian to do all genes known so far, only done in overseas labs right now, no Medicare rebate. Testing is sometimes done if it will alter management or family planning. Prenatal genetic testing is possible for further reassurance in a future pregnancy IF the causative mutation has been established in the affected child.

*References

1. http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=noonan Judith E Allanson, MD Department of Genetics Children's Hospital of Eastern Ontario: October 7, 2008.
2. http://emedicine.medscape.com/article/947504-overview Author: Jennifer Ibrahim, MD**,** Fellow, Department of Paediatrics, Division of Genetics, Children's Hospital of New Jersey and Mount Sinai School of Medicine
   Co-author(s): Margaret McGovern, MD, PhD**,** Vice Chair, Professor, Department of Human Genetics, Mount Sinai School of Medicine Dec 12, 2007.