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Chapter 16

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 16

Basic sciences Genetics

• primary amenorrhoea • associated absent uterus and streak ovaries • cystic hygroma (often diagnosed prenatally) • high-arched palate • short fourth metacarpal • multiple pigmented naevi • keloid scars • lymphoedema in neonates (especially feet) • Horseshoe kidney is strongly associated with Turner’s syndrome often initially presents with stone disease, pelviureteric junction (PUJ) obstruction, trauma, infections and tumors. In a pediatric patient with multiple urinary tract infections or renal stones, imaging must be performed to rule out this congenital anomaly. Which anatomical structures is responsible for horseshoe kidney anomaly during normal embryological development? Inferior mesenteric artery occurs when the isthmus of the kidney becomes trapped behind the inferior mesenteric artery as the kidneys ascend during embryonic life. Associated conditions
• autoimmune diseases: autoimmune thyroiditis (hypothyroidism (much more common in Turner’s)) and Crohn's disease • Hypertension is quite common in Turner syndrome (10%) and is typically idiopathic - essential. In a small proportion causes can include: coarctation of the aorta and renal dysfunction due to horsehoe kidney. • metabolic abnormalities (dyslipidaemia and glucose intolerance) • recurrent otitis media. • Diabetes mellites Although the incidence of diabetes mellitus is increased in patients with Turner syndrome, it is thought to be driven by insulin resistance and is very responsive to weight loss. Diagnosis • karyotype →identification of 45X0 . Prognosis • What condition is responsible for most of the excess mortality associated with Turner syndrome? Thoracic aortic aneurysm rupture

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Marfan's syndrome Overview • autosomal dominant connective tissue disorder. • caused by a defect in the fibrillin-1 gene on chromosome 15 Mutation of FBN1 that encodes Fibrillin-1. Marfan's syndrome is caused by a mutation in a protein called fibrillin-1

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• affects around 1 in 3,000 people. • may occur as a spontaneous mutation, (1/3rd of cases), and this occurs more commonly to offspring of older males. Features • Skeletal tall stature with arm

span to height ratio > 1.05 high-arched palate arachnodactyly pectus excavatum pes planus scoliosis of > 20 degrees crowded teeth. Dural ectasia: ballooning of the dural sac at the lumbosacral level Dural ectasia affects around 60% of patients with Marfan's syndrome. It may cause lower back pain associated with neurological problems such as bladder and bowel dysfunction. ligamentous/joint laxity resulting in multiple joint dislocations, hypermobile joints • Heart: Dilation of the aortic sinuses (seen in 90%) which may lead to aortic aneurysm, aortic dissection, aortic regurgitation, mitral valve prolapse (75%). • Lungs: repeated pneumothoraxes • Eyes: Upwards lens dislocation (superotemporal ectopia lentis) seen in 50% of patients Retinal detachment Blue sclera, myopia, early glaucoma, and early cataracts. Diagnosis • Unfortunately, DNA testing for fibrillin gene mutations, whilst helpful, cannot exclude a diagnosis of Marfan because a number of mutations exist (at least 130). • Hence diagnosis is made on the major and minor features associated with the syndrome. Prognosis & treatment : • The life expectancy of patients used to be around 40-50 years. • With the advent of regular echocardiography monitoring and beta-blocker/ACE-inhibitor therapy this has improved significantly over recent years. Treatment with β-blockers reduces the rate of aortic dilatation and the risk of rupture • Aortic dissection and other cardiovascular problems remain the leading cause of death however. • Pregnancy is associated with increased risk of aortic rupture. A mutation of which gene is most closely associated with Marfan's syndrome? FBN-1 mutation FBN-1 gene mutation →Defect in fibrillin →Marfan's

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Homocystinuria Overview • Autosomal recessive disease • Caused by deficiency of cystathionine beta synthase results in an accumulation of homocysteine cystathionine beta synthase is responsible for converting homocysteine to cystathionine. Cystathionine is later converted to cysteine, so, patients who have this enzyme deficiency need to supplement their diets with exogenous cysteine. Levels of homocysteine and methionine accumulate Types • Homocystinuria type 1 →a defect in cystathionine synthetase is responsible. • Homocystinuria type 2 →defects in methylene tetrahydrofolate reductase However, individuals with this condition rarely survive the neonatal period or, if they survive longer than this, they often have more severe mental retardation. Features • fine, fair hair • musculoskeletal: may be similar to Marfan's - arachnodactyly etc • neurological: learning difficulties, mild to moderate mental handicap ,seizures • ocular: downwards (inferonasal) dislocation of lens The sudden visual deterioration could either be due to a thrombotic episode or to the lens dislocation associated with this condition. • increased risk of arterial and venous thromboembolism (atherosclerosis, thrombosis, MI) the most common cause of death. • malar flush, • livedo reticularis Diagnosis • made by the cyanide-nitroprusside test, which is also positive in cystinuria addition of sodium nitroprusside to urine → urine changes color to an intense red • Guthrie test is used for screening the neonates for the presence of homocystinuria. Treatment • Dietary modification aim to: reduce intake of methionine and increase intake of cysteine. • vitamin B6 (pyridoxine) supplements 50% of patients respond to large doses of pyridoxine (vitamin B6) • Folate and vitamin B12 supplements facilitate the conversion of homocysteine to methionine. homocysteine levels (homocysteinemia) are more commonly tested

in diagnosis of Vitamin B12 Deficiency. Marfanoid skeletal abnormalities (tall and thin, elongated limbs, arachnodactyly) + mental retardation Homocystinuria

Homocystinuria VS Marfan's homocystinuria Marfan's syndrome inheritance autosomal recessive autosomal dominant lens dislocation downward lens dislocation upward lens dislocation aortic incompetence heart rarely affected aortic incompetence may occur intellectual development mental retardation (nearly 50%) normal seen due to the venous thrombosis in the small vessels of the skin livedo reticularis osteoporosis, recurrent thromboembolism; characteristic laboratory features: other principle features plasma methionine and homocystine levels are elevated, homocystine is excreted in the urine, plasma cystine levels are reduced, positive urine cyanide-nitroprusside test; response to treatment with pyridoxine

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Fragile X syndrome Overview • Fragile X syndrome is a disorder affecting the methylation and expression of the fragile X mental retardation 1 gene. • genetic inheritance X-linked dominant with variable penetration • Patients affected by fragile X syndrome usually have over 200 CGG trinucleotide repeats. Features • moderate to severe mental retardation • prognathism • face: (long face, prominent forehead, large jaw (prognathism) and large ears • macro-orchidism In post pubertal males, abnormally large testes are a distinctive feature. • speech delays • double-jointedness • autistic symptoms, • occasional self-mutilation. • Otitis media, strabismus, and dental problems may be present • hyperextensible joints • hypotonia, • heart problems, including mitral valve prolapse. Management • Treatment focused on preventing common medical problems such as gastroesophageal reflux, sinusitis, and otitis media,+ • speech, occupational, and physical therapy. Notes & Notes for MRCP
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NO flat feet, herniae, scoliosis; there is a 50% reduction in life expectancy

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Trinucleotide repeat disorders Definition • Trinucleotide repeat disorders are genetic conditions caused by an abnormal number of repeats (expansions) of a repetitive sequence of three nucleotides. • These expansions are unstable and may enlarge which may lead to an earlier age of onset in successive generations - a phenomenon known as anticipation. In most cases, an increase in the severity of symptoms is also noted • Friedreich's ataxia is unusual in not demonstrating anticipation Examples (note dominance of neurological disorders): • Fragile X (CGG) • Huntington's (CAG) • myotonic dystrophy (CTG) CTG repeats in the DMPK gene • Friedreich's ataxia* (GAA) (*Friedreich's ataxia is unusual in not demonstrating anticipation) • spinocerebellar ataxia • spinobulbar muscular atrophy • Kennedy disease, also known as 'X-linked bulbospinal neuronopathy' • dentatorubral pallidoluysian atrophy

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Genetic anticipation • Definition: The 'classic' definition of anticipation is earlier onset in successive generations. However, in most cases, an increase in the severity of symptoms is also noted. If both options (earlier onset and sever symptoms) are presented, then the earlier onset should be chosen • Example: A man aged 33 presents with features of Huntington’s disease (depression, weight loss and choreiform movements). He informs you that his father had similar symptoms aged 50, his grandfather aged 75 and both deteriorated in terms of mobility and mental state, and eventually died. • Occur in: Huntington’s disease Myotonic dystrophy
 Fragile X syndrome Anticipation: successive generations present with symptoms at an earlier age Trinucleotide repeat disorders mnemonic: Try (trinucleotide) hunting for my fried eggs (X). Anticipation in trinucleotide repeat disorders = earlier onset in successive generations

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Polygenic diseases • Definition: genetic disorder that is caused by the combined action of more than one gene. Because such disorders depend on the presence of several genes, they are not inherited as simply as are single-gene diseases. • Examples: hypertension, coronary heart disease, diabetes Amyotrophic lateral sclerosis (ALS)

Lysosomal storage diseases Definition • Lysosomal storage diseases are a group of inherited metabolic disorders caused by a deficiency of specific enzymes. This causes an accumulation of abnormal substances that are usually degraded within lysosomes, resulting in cell damage and death. Risk factors • Ashkenazi ethnicity • Male sex Fabry's disease is X-linked, but heterozygous females typically (>75%) do have symptoms, although less severe, more variable in expression, and at a later age of onset. Key features • Hyperacusis →Characteristic of Tay-Sachs disease. • Optic atrophy or retinitis pigmentosa are seen in juvenile form of Tay-Sachs disease. • hx of renal failure →Found in adult Fabry's disease. • Hepatosplenomegaly →common in Gaucher's disease • onset in adulthood (Fabry's, Gaucher's type 1, Pompe's) Diagnosis • Enzyme assay (1st investigations to order)

Gaucher's disease Gaucher • Glucocerebrosidase deficiency • Glucocerebroside accumulation Features involve multiple systems: Blood (pancytopaenia , anaemia, recurrent infections,) bones, hepatosplenomegaly, lung (cough) →think of Gaucher's disease

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Pathophysiology • Autosomal recessive mutation in the glucocerebrosidase (GBA) gene located on chromosome 1 → Deficiency of β-glucocerebrosidase → accumulation of glucocerebroside (sphingolipid found in cell membranes that can accumulate in the lysosome of macrophages) in the brain, liver, spleen, and bone marrow (i.e., Gaucher cells). Epidemiology • Gaucher's disease is the most common lysosomal storage diseases. • About one in 100 people in the United States are

carriers of the most common type of Gaucher disease (type I). • The carrier rate among Ashkenazi Jews is 8.9% while the birth incidence is one in 450. Consequences • Parkinson's disease is more common in Gaucher's disease patients (the most commonly known genetic risk factor for Parkinson's) • Cancer risk may be increased, particularly myeloma. Types • GD type I (Chronic non-neuropathic; adult Gaucher disease) Most common form Associated with a normal lifespan • GD type II (Acute neuropathic; infantile Gaucher disease) typically begins within 6 months of birth Symptoms include progressive brain damage, spasticity and seizures. carries the worst prognosis, affected children usually die by age two. • GD type III (Subacute neuropathic; juvenile Gaucher disease) can begin at any time in childhood or even in adulthood characterized by slowly progressive, but milder neurologic symptoms compared to type II. Patients often live into their early teen years and adulthood Features • Hepatosplenomegaly (massive splenomegaly) • Bone pathology (bone crises, osteoporosis, aseptic necrosis) the chief complaint is of bone pain in an adult. • Blood abnormalities: anemia, thrombocytopenia • diffuse infiltrative pulmonary disease • Growth delays • Yellowish-brown skin and scleral pigmentation (Characteristic yellow or yellow-brown papules (pingueculae) develop at the sclerocorneal junctions). Diagnosis • Enzyme analysis (Enzyme studies of blood leucocytes) → Reduced glucocerebrosidase activity in leukocytes or fibroblasts • Accumulation of glucocerebroside in leukocytes or fibroblasts • Gaucher cell: lipid-rich macrophages with an enlarged cytoplasm with inclusions that resemble crumpled tissue paper on microscopy

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Treatment • Recombinant glucocerebrosidase. The slide shows yellow papules (pingueculae) in the cornea; these are characteristic of Gaucher disease. Common exam questions • Features of anaemia, recurrent pneumonia, bone pain and hepatosplenomegaly. Which of the following is the most likely diagnosis? Gaucher’s disease • Features of anaemia, recurrent pneumonia, bone pain and hepatosplenomegaly .Which of the following is the most likely enzyme deficiency found in this patient? Glucocerebrosidase

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Fabry's disease Pathophysiology (a lysosomal storage disorder) • X-linked recessive mutation → α-Galactosidase A deficiency → accumulation of trihexoside ceramide (a glycolipid found in multiple body tissues) in the endothelium of vessels, in the epithelium of many organs, and in smooth muscle cells → disorder affecting many organ systems. Epidemiology • Typical onset is during childhood but may also appear in 60–80-year-old adults • Mainly affects boys Features • Early features Peripheral neuropathy: Periodically occurring dysesthesia in the hands and feet caused by small fiber neuropathy , which manifests as burning pain (Fabry crises) Anhidrosis or hypohidrosis (decreased sweating) Angiokeratomas (warty skin lesions with telangiectasia and hyperkeratinized covering) Corneal clouding Cataract Gaucher disease causes massive splenomegaly

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• Late features Restrictive cardiomyopathy Cerebrovascular lesions (TIA and stroke) Fabry nephropathy, causing progressive renal failure (the first manifestation of renal insufficiency in Fabry disease is proteinuria.) The disorder has three distinct clinical entities:

1. Classical presentation in the male homozygote with early presentation in childhood - angiokeratomas, heart failure, cataracts and renal disease
2. Male homozygotes with atypical presentation in adulthood with proteinuria, acroparaesthesia, angiokeratomas and cardiomegaly
3. Female heterozygotes can present again in adulthood with similar mild symptoms. An X linked recessively inherited condition can exist in female carriers who may exhibit mild to moderate symptoms. This is due to variable expression according to random X inactivation of the affected gene in embryogenesis most common symptoms →peripheral neuropathy, angiokeratomas, and hypohidrosis. Diagnosis • Absent or deficient levels of alpha-galactosidase A in leucocytes, plasma or cultured fibroblasts. • Gene analysis of alpha-galactosidase A (GLA) gene (the gold standard for the diagnosis) • Slit-lamp examination of the cornea → microscopic lipid deposits • Microscopy of the spun urine sediment may demonstrate 'Maltese cross' lipid globules In Fabry disease, tissue accumulation of which is most likely to occur? Trihexosyl ceramide Treatment • Enzyme replacement therapy with α-galactosidase A

Mucopolysaccharidoses (MPS) (Hurler's & Hunter's syndromes) Pathophysiology • Mutations in lysosomal enzymes → impaired breakdown of glycosaminoglycans → Accumulation of glycosaminoglycans, i.e., heparan sulfate (HS) and dermatan sulfate (DS) Features • Occur in both conditions (typically milder in Hunter syndrome): Developmental delay Facial dysmorphism: frontal bossing, elongated skull , flattened nasal bridge, broad nasal tip, thickened gingiva, anteverted nostrils, constant nasal discharge, spaced and protruded eyes. Airway obstruction Hepatosplenomegaly Diagnosis • Increased urinary levels of dermatan sulfate (DS) and heparan sulfate (HS) • Enzyme assay to confirm specific enzyme deficiency (definitive test) Treatment • Enzyme replacement therapy • Bone marrow transplantation

Hurler syndrome (mucopolysaccharidosis type I) Hunter syndrome (mucopolysaccharidosis type II) Inheritance Autosomal recessive X-linked recessive Pathophysiology Deficiency of α-L-iduronidase (enzyme responsible for the hydrolysis of glycosaminoglycans) Features Corneal clouding Inguinal hernia Which feature suggests a diagnosis of Hurler's syndrome rather than Hunter's syndrome? Cloudy cornea. Hunter syndrome presents as Hurler syndrome, but patients with Hunter syndrome have normal vision and aggressive behavior.

Glycogen storage disorders (GSD) Key feature of glycogen storage disorders: • Tay-Sachs commonly has a 'cherry red spot' macula • Pompe disease leads to cardiomyopathies • McArdle's disease leads to rhabdomyolysis after exercise and lactic acidaemia • Von Gierke disease leads to hypoglycaemia and hepatomegaly Pompe trashes the Pump (heart) Glycogen • Glycogen is the storage form of carbohydrate, found predominantly in muscle and liver. • Chains of glucose residues are linked by alpha-1,4 glycosidic bonds, i.e. between the first carbon of one glucose and the fourth carbon of the next. Branches occur about every ten residues, and are formed by alpha-1,6 glycosidic linkages. • Glycogen synthesis and degradation occur at the tips of branches, with

the branching structure increasing the number of sites at which glucose residues can be added or removed. Pompe's disease or acid maltase deficiency (glycogen storage disorder type 2): is a deficiency in alpha-glucosidase. It produces a myopathy , restrictive cardiomyopathy and hepatomegaly. Glycogen storage disorders: • Muscle involvement (muscle glycogenoses): Types II, III, IV, V • Liver involvement (liver glycogenoses): Types I, III, IV • Types III and IV (late-onset type) may present with both muscle and liver involvement • NO liver involvement V Notes & Notes for MRCP
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Deficiency of iduronate-2-sulfatase Aggressive behavior, Hyperactivity No corneal clouding Carpal tunnel syndrome

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• Autosomal recessive • All types of glycogen storage diseases result in abnormal metabolism and product accumulation within cells. • Type IV (Andersen's disease) is the only one GSD involved in Glycogen Synthesis. The rest are involved in Glycogen degradation. Diagnosis • Periodic acid-Schiff stain is helpful in diagnosing glycogen storage disorders. Type I (Von Gierke's disease) • Relative frequency: ~25% • Deficient enzyme Type 1a → Glucose-6-phosphatase Role of the enzyme →Hydrolysis of glucose-6-phosphate to glucose and inorganic phosphate Type 1b → Glucose-6-phosphate translocase Role of the enzyme →Transport of glucose-6-phosphate into the endoplasmic reticulum where it is hydrolyzed by glucose-6-phosphatase • Characteristic features Hepatomegaly Severe fasting hypoglycemia, mild ketosis Severe hyperlipidemia → doll-like facies Hyperuricemia Lactic acidosis Anemia Failure to thrive Type II (Pompe's disease) • Relative frequency: ~15% • Deficient enzyme: Lysosomal acid maltase deficiency • Role of the enzyme: Glycogenolysis within the lysosome • Characteristic features Hypertrophic cardiomyopathy and/or conduction blocks Proximal myopathy Macroglossia Failure to thrive Type III (Cori's disease) • Relative frequency: ~25% • Deficient enzyme: debranching enzyme (alpha-1,6-glucosidase). • Role of the enzyme: Glycogenolysis • Characteristic features Generalized muscle weakness and/or cramps Hepatomegaly Possibly cirrhosis (ascitis, splenomegaly) Mild, fasting hypoglycemia and ketosis Hyperlipidemia Type IV (Andersen's disease) • Relative frequency: ~3% • Deficient enzyme: Glycogen branching enzyme • Role of the enzyme: Glycogenesis • Characteristic features Proximal myopathy Hepatomegaly Possibly cirrhosis (ascites, splenomegaly)

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Type V (McArdle's disease) • Relative frequency: ~2% • Deficient enzyme: Muscle phosphorylase (myophosphorylase) • Role of the enzyme: Glycogenolysis • Characteristic features Generalized muscle weakness, exercise intolerance (with a second wind phenomenon) , Rhabdomyolysis and myoglobinuria

McArdle's disease (Type V glycogen storage disease) Pathophysiology • Autosomal recessive mutation in myophosphorylase (PYGM) gene on chromosome 11 → myophosphorylase deficiency (myophosphorylase is involved in the breakdown of glycogen to glucose) → unable to release glucose from glycogen in muscle (decreased muscle glycogenolysis). Features • Muscle pain and stiffness following exercise (reversible) in the first few minutes of activity. Characterised by 'second wind' phenomenon after about 8 minutes most patients achieve a 'second wind' and can then continue exercise with less difficulty. Second wind is a phenomenon in distance running, such as marathons (an athlete who is too tired to continue suddenly finds the strength to press on at top performance with less exertion). Mechanism →metabolic switch When non-aerobic glycogen metabolism is insufficient to meet energy demands, physiologic mechanisms utilize alternative sources of energy such as fatty acids and proteins via aerobic respiration. muscle fibers use fat as a source of energy. Investigations • Creatine kinase levels are elevated in more than 90% • NO increase in venous lactic acid levels following exercise testing. • Urine study →Myoglobinuria following exercise • Muscle and/or liver biopsy →↑glycogen→ PAS-positive granules (initial tests) • DNA testing for the gene defects (Gene sequencing): the gold standard for the diagnosis Often presents in adolescence with exercise intolerance, cramps and weakness A history of painful muscle cramps that occur within a few minutes of initiating activity and which subside rapidly with rest, in conjunction with a raised serum CK, is highly suggestive of McArdle's disease

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Basic sciences Genetics Management • No specific treatment • Dietary therapy (e.g., uncooked corn starch, glucose preparations) with the aim of preventing hypoglycemia and/or muscle symptoms • Foods rich in fructose and galactose should be avoided in patients with GSD type I • Advised to ingest snacks containing sucrose before exercise. • Tourniquets should not be used during operative procedures The exertional thigh cramps, the presence of myoglobin and change in colour of urine after exercise suggests glycogen storage disease type V - McArdle's syndrome. the next most appropriate investigation → Muscle biopsy which reveals subsarcolemmal deposits of glycogen appearing at the periphery of fibres.

Linkage disequilibrium • Linkage disequilibrium is the non-random association of alleles at different loci in a given population. • Loci are said to be in linkage disequilibrium when the frequency of association of their different alleles is higher or lower than what would be expected if the loci were independent and associated randomly. • Consider the scenario of two separate genetic loci A and B, where each locus carries two possible alleles. If these two loci A and B are in linkage disequilibrium →An individual with locus A is likely to have locus B • Linkage disequilibrium almost always, occurs between alleles at genetic loci that are closely linked in the genome.

Imprinting Definition • imprinting is a phenomenon by which certain genes are expressed in a parent-of-originspecific manner. the term 'imprinting' refers to →Differential expression of alleles contingent on their parental origin If the allele inherited from the father is imprinted, it is thereby silenced, and only the allele from the mother is expressed. If the allele from the mother is imprinted, then only the allele from the father is expressed. Mechanism • poorly understood but does involve DNA methylation. • Disease may occur as a result of a defect in one allele if the other

allele is imprinted and hence not expressed. Examples • diseases involving genomic imprinting include: Prader–Willi syndrome (paternally imprinted) Angelman syndrome (maternally imprinted)

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Prader-Willi syndrome Overview • Prader-Willi syndrome is an example of genetic imprinting where the phenotype depends on whether the deletion occurs on a gene inherited from the mother or father: Prader-Willi syndrome if gene deleted from father Angelman syndrome if gene deleted from mother • Prader-Willi syndrome is associated with the absence of the active Prader-Willi gene on the long arm of chromosome 15 , this may be due to: Microdeletion of paternal 15q11-13 (70% of cases) Maternal uniparental disomy of chromosome 15 • The mode of inheritance is →Non-Mendelian Features • Hypotonia during infancy • Dysmorphic features • Short stature (Growth hormone deficiency) • Hypogonadism and infertility (risk factor for osteoporosis) • Cryptorchidism (undescended testis) • Learning difficulties • Childhood obesity due to Hyperphagia (abnormally desire for food →overeating → obesity) • Behavioural problems in adolescence • Associated with elevated ghrelin Ghrelin is a hormone produced in the fundus of the stomach and in the pancreas Ghrelin levels increase before meals and decrease afterwards Receptors for ghrelin are found in the arcuate nucleus and the hypothalamus Treatment • Administration of growth hormone and sex hormones (testosterone) is the treatment of choice • Calorie restriction MRCPUK-part-1-September 2017 exam: Which one of the following is the most common genetic cause of Prader-Willi syndrome? Microdeletion of the paternal 15q11-13 Chromosome 15 is implicated in Prader-Willi, Angelman, and Marfan syndromes. Deletion of chromosome 15 Prader-Willi – paternal Angelman syndrome - maternal

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Angelman syndrome Overview • Angelman syndrome is a genetic condition characterized by a mutation on the maternal copy of chromosome 15. • occurs as a result of a phenomena known as genomic imprinting. • The imprinted copy of the gene is silenced through methylation or histone modification. • Normally, certain paternal alleles on chromosome 15 are silenced and only the maternal alleles are expressed. However, in Angelman syndrome, the maternal alleles are mutated. Hence, the patient will have disease since only the mutated maternal alleles are active. Features • Developmental delay • Intellectual disability • Seizures, Ataxia • Unprovoked laughter • Large mouth with tongue protrusion. • Hypo-pigmentation with blond hair Diagnosis • genetic studies showing loss of function of the UBE3A gene.

Mutations • Missense mutation substitution in one amino acid in a protein e.g: glutamic acid is substituted by valine in sickle-cell disease • Nonsense mutation the altered DNA sequence prematurely signals the cell to stop building a protein. This type of mutation results in a shortened

protein that may function improperly or not at all. • Insertion mutation changes the number of DNA bases in a gene by adding a piece of DNA. As a result, the protein made by the gene may not function properly. • Frameshift mutation insertions or deletions of nucleotides e.g: cystic fibrosis • Point mutation a change in a single nucleotide e.g: C282Y mutation responsible for haemochromatosis • Splicing mutation results in larger nonfunctional protein e.g: β-thalassemia • Large Segment Deletion Unequal crossover at meiosis results in loss of large segment of DNA Loss of function mutation e.g., α-thalassemia (deletion of α-globin gene) • Termination mutation generation of a premature stop codon e.g: Hurler syndrome

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Chromosome abnormality • Chromosome anomalies usually occur when there is an error in cell division following meiosis or mitosis. Types • Numerical disorders called aneuploidy (an abnormal number of chromosomes), occurs when an individual either is: missing a chromosome from a pair (monosomy) e.g: Turner syndrome, (born with only one sex chromosome, an X). has more than two chromosomes of a pair (trisomy, tetrasomy, etc.). e.g: Down syndrome (trisomy 21) Unbalanced autosomal translocation most likely to cause a severe phenotype As a rule, the clinical effects of a chromosome abnormality reflect the amount of imbalance of genetic material. For example: all autosomal monosomies and most autosomal trisomies are incompatible with life, the exceptions being trisomy 13 (Patau syndrome), trisomy 18 (Edward syndrome) and trisomy 21 (Down syndrome); only the last of these carries a reasonable life expectancy. Sex chromosome aneuploidy: This is associated with comparatively less severe phenotypes, e.g. Klinefelter syndrome (XXY) and Turner syndrome (XO). • Structural abnormalities: e.g: Duplications: A portion of the chromosome is duplicated, resulting in extra genetic material. e.g: Charcot-Marie-Tooth disease type 1A, caused by duplication of the gene encoding peripheral myelin protein 22 (PMP22) on chromosome 17.

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List of common Chromosomal disorders: Chromosome disorders Chromosome 1 variegate porphyria chromosome 3 von Hippel Lindau (VHL) Chromosome 4 Polycystic Kidney Disease (PKD2) Huntington's disease Achondroplasia Chromosome 6 hereditary haemochromatosis Chromosome 7 Cystic Fibrosis Chromosome 9 Fredrich's ataxia Chromosome 11 Sickle Cell Disease Beta-Thalassemia Chromosome 12 Phenylketonuria von Willebrand’s disease Chromosome 13 Patau Syndrome. Wilson Disease. retinoblastoma Chromosome 15 Marfan’s Syndrome Angelman Syndrome Prader-Willi Syndrome Tay-Sachs Disease. Chromosome 16 Polycystic Kidney Disease (PKD1) alpha- Thalassemia Chromosome 17 Celiac Disease. Charcot-Marie-Tooth Disease. Neurofibromatosis (NF1) Chromosome 18 Edward Syndrome Chromosome 19 Myotonic Dystrophy Chromosome 21 Down Syndrome Chromosome 22 DiGeorge Syndrome. Neurofibromatosis (NF2)

McCune–Albright syndrome (MAS) McCune-Albright syndrome: • Triad of patchy skin pigmentation, bone abnormalities, and endocrine abnormalities. • McCune-Albright syndrome is a form of mosaicism • Due to a mutation in the GNAS1 gene

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Significance tests Null hypothesis (H0) • A null hypothesis (H0) states that two treatments are equally effective (and is hence negatively phrased). • A significance test uses the sample data to assess how likely the null hypothesis is to be correct. • The null hypothesis is always that there is no difference between the variables we would like to test for a difference. • For example: 'there is no difference in the prevalence of colorectal cancer in patients taking low-dose aspirin compared to those who are not' The alternative hypothesis (H1) • is the opposite of the null hypothesis, i.e. There is a difference between the two treatments P value • The p value is the probability of obtaining a result by chance at least as extreme as the one that was actually observed, assuming that the null hypothesis is true. • It is therefore equal to the chance of making a type I error (see below). • the p-value is the probability of obtaining the observed results or results which are more extreme if the null hypothesis is true • Example: if p=0.03. What does ‘p=0.03’ mean? • It means the probability that a difference between the two sample groups occurred by chance is 3% Statistical errors • Two types of errors may occur when testing the null hypothesis

1. type I: the null hypothesis is rejected when it is true, ‘the null hypothesis is falsely rejected’. i.e. Showing a difference between two groups when it doesn't exist, a false positive. This is determined against a preset significance level (termed alpha). As the significance level is determined in advance the chance of making a type I error is not affected by sample size. It is however increased if the number of end-points are increased. For example if a study has 20 end-points it is likely one of these will be reached, just by chance. i.e. the result is just a statistical fluke.
2. type II: the null hypothesis is accepted when it is false, ‘the null hypothesis is falsely accepted’.- i.e. Failing to spot a difference when one really exists, a false negative. The probability of making a type II error is termed beta. It is determined by both sample size and alpha. This can happen if the sample size is too small. Increasing the sample size reduces the standard error, meaning the estimate is more precise and the probability of a type-2 error is reduced. This type of error can be avoided by making explicit power calculations before embarking on any study. This will answer the question ‘if I am studying an

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outcome that occurs in (say) 20% of a conventionally treated group and want to show a (say) halving in the rate of this outcome, then how many patients do I need to study?’ Study accepts H0 Study rejects H0 Reality H0 Type 1 error (alpha) Reality H1 Type 2 error (beta) Power (1 - beta) Error: type I (alpha) vs. type II (beta) Type I (Alpha) Error: "There Is An Effect" where in reality there is none.

The power • The power of a study is the probability of (correctly) rejecting the null hypothesis when it is false, i.e. the probability of detecting a statistically significant difference power = 1 - the probability of a type II error power can be increased by increasing the sample size • As the power decreases, type II error (= 1-power) will increase. Therefore, the chance of type II error will increase if the same sample size is used. • The statistical power will decrease if the standard deviation increases. • Power of the study' refer The probability of a statistically significant treatment effect if the true treatment difference is at a prespecified level • Power is determined by sample size, effect size, and its standard error. • The statistical significance of a result is the probability ('p value') that the observed relationship (eg between variables) or a difference (eg between means) in a sample occurred by pure chance and that in the population from which the sample was drawn, no such relationship or differences exist • The sample size can be reduced if the level of significance is increased. • The power increases with the set level of significance, if other variables remain the same.

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Significance tests: types Correlation • parametric (normally distributed): Pearson's coefficient • non-parametric: Spearman's coefficient • The type of significance test used depends on whether the data is parametric (something which can be measured, usually normally distributed) or non-parametric Parametric tests (the data follow normal distribution) (quantitative variables) Student's t-test - paired or unpaired* Pearson's product-moment coefficient (Pearson correlation coefficient) used to assess correlation (strength of association) between two variables Non-parametric tests Mann-Whitney U test - unpaired data used to compare medians or rank orders of two groups with nonnormal distribution. Wilcoxon signed-rank test: compares two sets of observations on a single sample The data in the study is non-parametric, paired and comes from the same population. chi-squared test: used to compare proportions or percentages (eg: prevalence) between two categorical variables for example, comparing the proportion of children developing measles between a group receiving a new measles vaccine and a group not given the vaccine Should be used for 2 independent samples. Spearman, Kendall rank: measures the correlation between the ranks of two variables which do not follow a normal distribution. compares ranks and not values, such as the perception of pain (ranked on a scale of 1-10) • Paired data refers to data obtained from a single group of patients, e.g. Measurement before and after an intervention. Unpaired data comes from two different groups of patients, e.g. Comparing response to different interventions in two groups In a scenario looks at whether the values are correlated, and the data is non-parametric, (e.g: pain scale), Spearman's rank correlation coefficient should be used.

Choosing the appropriate test • Choosing of a test to examine a statistical problem depends upon the scale of measurement (nominal, ordinal, interval, ratio) and the type of question being asked • a non-parametric test would give less power Student's t- test • Paired t test Compares a single measure (variable) recorded on a single group of individuals on two different occasions. Is used to compare means in a single sample, for example, before and after treatment. comparing means (not proportions) in the same subjects paired t-test is used to compare post-treatment and pre-treatment result of a single group. eg: the same subject measured before and after a process change, or the same subject measured at different times. As both sets of measurements were made on the same patients, the measurements are not independent • Unpaired t-test (independent sample t-test) is the most appropriate statistical test to compare means of two independent samples. compare the means of two different populations An independent sample t-test may be used in a study of two independent treatment groups, and the sample sizes are relatively large (>30 in each group) and the variable is Normally distributed. eg: Blood pressure is a continuous variable which is normally distributed; as such Student's t test is the most appropriate way to test for differences in the mean BPs between the two groups. For example, suppose we are evaluating the effect of a medical treatment, and we enroll 100 subjects into our study, then randomly assign 50 subjects to the treatment group and 50 subjects to the control group. In this case, we have two independent samples and would use the unpaired form of the t-test. eg: 2 groups (treatment group & placebo group) In a randomised controlled trial of drug A for treatment of hypercholesterolemia Log-rank test • Is the most appropriate test to compare two survival curves with censored data. • Log-rank test should be used to compare survival data between two groups, but not compare median survival. Mean survival is not known unless all patients have died. • If a question presented survival data and some observations are censored(ex: not came for follow up) and the outcomes are not known. We need to use survival analysis for such data and the log-rank test is the appropriate test to use to compare survivals in two independent groups. • can be used to test the difference in relapse rate between the two groups McNemar's test • is applied to binary data, but is only applicable to paired data, used to compare proportions • McNemar's test is used to compare paired samples - either case control studies where each case is matched to a control, or to studies where two treatments are given to matched subjects. • It cannot be used where the sample size differs. • is used to test for agreement of repeated observations.

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Regression techniques • are used to predict the value of one variable based on the other • Multiple regression is used to analyse the relationship between one dependent variable and one or more independent variables • Logistic regression (Log regression analysis) It is used to describe the relationship between one dependent binary variable and one or more metric independent variables. It is commonly used to assess plasma concentrations of a drug as it allows

examination of the relationship between possible confounding factors such as renal function or age. This would allow us to determine whether one variable is dependent on another, ex: in case whether drug concentration was dependent on body surface area. ANOVA (analysis of variance) is an example of logistic regression analysis. is a statistical test which tests for co-variance between populations and is useful when variables such as age, sex or race may be expected to affect the treatment's effectiveness. tests for a difference in mean values between a number of groups Is the most appropriate to compare the means of more than two groups. (used for more than two means) One-way analysis of variance is identical mathematically to the unpaired Student t-test when just two groups are being compared. The one-way (analysis of variance) (ANOVA) compares the means of the groups The means should be presented with confidence intervals to give the reader an idea of whether the differences between the groups were significant • The Cox (proportional odds) regression (Cox proportional hazards regression): this method was devised specifically for the type of study in which many patients fail to reach the end-point (ie in statistical terms, are 'censored') and in which follow-up time varies. Cox regression is designed specifically for the analysis of time to an event occurring.

Parametric tests and analogous nonparametric procedures Analysis Type Example Parametric Procedure Nonparametric Procedure Compare means between two distinct/independent groups Is the mean systolic blood pressure (at baseline) for patients assigned to placebo different from the mean for patients assigned to the treatment group? Compare two quantitative measurements taken from the same individual Was there a significant change in systolic blood pressure between baseline and the six-month followup measurement in the treatment group? Compare means between three or more distinct/independent groups If our experiment had three groups (e.g., placebo, new drug #1, new drug #2), we might want to know whether the mean systolic blood pressure at baseline differed among the three groups?. Estimate the degree of association between two quantitative variables Is systolic blood pressure associated with the patient’s age? • Categorical variables are not continuous, e.g. drug / placebo, dead / alive. They should be described as percentages or proportions and compared with a Chi-squared test. • Normally distributed continuous data should be described as mean and standard deviation and compared with a Student’s t-test. • Skewed continuous data should be described as median and range and compared using a test such as the Wilcoxon rank-sum test or the Mann-Whitney U-test. MRCPUK-part-1-May-2017 exam: A study is designed to assess severity of snoring before and after using a new mandibular device. What is the most appropriate statistical test to apply to this data? Wilcoxon signed-rank test

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Normal distribution • The normal distribution is also known as the Gaussian distribution or 'bell-shaped' distribution. It describes the spread of many biological and clinical measurements • Properties of the Normal distribution symmetrical i.e. Mean = mode = median 68.3% of values lie within 1 SD of the mean 95.4% of values lie within 2 SD of the mean 99.7% of values lie within 3 SD of the mean this is often reversed, so that within 1.96 SD of the mean lie 95% of the sample values the range of the mean - (1.96 *SD) to the mean + (1.96 * SD) is called the 95% confidence interval, i.e. If a repeat sample of 100 observations are taken from the same group 95 of them would be expected to lie in that range Notes & Notes for MRCP
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Two-sample t-test Wilcoxon ranksum test Paired t-test Wilcoxon signedrank test Analysis of variance (ANOVA) Kruskal-Wallis test Pearson coefficient of correlation Spearman’s rank correlation

Notes & Notes for MRCP
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MRCPUK-part-1-January 2019 exam: A study is designed to assess the efficacy of a new antihypertensive drug. Two groups of patients are randomly assigned, one to take the established drug for 3 months whilst the other takes the new drug for 3 months. blood pressure is measured before and 3 months .After period off medication the drug swapped around and again, blood pressure is measured before and 3 months later. Which one of the following significance tests is it most appropriate to apply? Student's paired t-test (comparing parametric data from the same patients (they swapped medication halfway through the study))

Standard deviation SD = square root (variance) Remember that around two-thirds of values lie within 1 SD of the mean, one-third will therefore lie outside 1 SD, and half of these (one-sixth) will be less than 1 SD below the mean • the standard deviation (SD) is a measure of how much dispersion exists from the mean • It is a measure of the spread of the sample distribution • SD = square root (variance) • The standard deviation is a sort of average of the deviations of each observation from the mean, whereas the range is simply the difference between the largest and smallest observations. • The standard deviation is affected by outliers and would be larger than expected if outliers are present • If the data are skewed, the standard deviation will tend to overestimate the spread in the data • If the standard deviation is reduced, the sample size required is smaller. • If SD increased the power of study is reduced . • The standard deviation would give the best estimate of a spread of a measurement about the mean • Variance is the square of standard deviation. Standard deviation is the square root of variance.

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