Genetics

Charcot-Marie-Tooth syndrome
- Majority **autosomal dominant** (CMT1A) - also X-linked (CMTX1) and recessive forms
  - commonest inherited neuromuscular disorder - abnormal myelin causes **demyelination**
- Symptoms (insidious, progressive) - **muscle weakness** / sensory loss at extremities
  - starts at intrinsic foot muscles, ascends to lower thigh - muscle wasting, finger curling
  - **fine touch** and **proprioceptive sensory loss** (spinothalamic preserved)
  - in the feet - foot drop, pes cavus (high arch), tripping, cramps
- Investigations - nerve conduction studies (low peripheral velocities)
- Management - rehabilitation, orthotics, analgesics, fasciotomy / osteotomy / arthrodesis

Congenital adrenal hyperplasia (CAH)
- **Autosomal recessive** - majority 21-hydroxylase deficiency - mutation of chromosome 6
  - insufficient **cortisol** / **aldosterone**, excess androgens; boys more severely affected
- Symptoms - baby girls may have **ambiguous genitalia**; boys may have hyperpigmentation
  - early vomiting, lethargy, dehydration, weight loss; later **virilism**
- Investigations - U&Es (hyponatraemia, hyperkalaemia, hypoglycaemia), genetics
  - 17-hydroxyprogesterone - may be diagnostic if raised; also **corticotropin stimulation test**
- Management - **hydrocortisone** with **fludrocortisone**; salt supplementation if aged < 1m
- Complications - developmental delay, obesity, HTN, insulin resistance, PCOS, infertility

Crigler-Najjar syndrome
- **Autosomal recessive** inborn error of **bilirubin** metabolism causing **neonatal jaundice**
  - UGT deficiency leads to inability to conjugate bilirubin - mutation of chromosome 2
  - type I - subtotal deficiency, kernicterus, severe; type II - impaired activity, mild jaundice
- Investigations - bilirubin (very high), LFTs (normal)
- Management (type I) - **exchange transfusion**, long-term phototherapy, calcium phosphate
  - type II usually conservative; consider **phenobarbital** if consistently high bilirubin
  - consider **liver transplantation**

Dubin-Johnson syndrome
- **Autosomal recessive** inborn error of **bilirubin** metabolism mainly affecting Iranian Jews
  - cMOAT defect from mutation of chromosome 10 impairs **conjugated** bilirubin excretion
- Symptoms (in adolescents) - recurring non-pruritic jaundice, hepatomegaly
- Investigations - LFTs (normal), urinary coproporphyrin ratio, hepatic pigmentation
- No specific management required - no reduction in life expectancy
Ehlers-Danlos syndrome
- Majority **autosomal dominant** causing abnormalities of *structural proteins* in skin, CTs
- Symptoms - **bruising**, GI bleeds, herniae, aortic dissection, **joint laxity**, skin hyperelasticity
- Types - classic, hypermobile (commonest, tall stature, *blue sclerae*), vascular (ecchymoses)
- Investigations - X-ray (subcutaneous calcified spherules)
- Complications - high risk of obstetric complications in pregnancy

Fragile X syndrome
- **CGG** repeat expansion disorder of FMR1 gene; females more often carriers
- Symptoms - **learning difficulties**, developmental delay, ADHD, clumsiness, echolalia
  - appearance - high forehead, **macro-orchidism**, facial asymmetry, large jaw, long ears
- Management (normal life expectancy) - consider antipsychotics, SSRIs, anticonvulsants

Friedreich’s ataxia
- **Autosomal recessive** degenerative neurological disorder - **GAA** repeat on *frataxin gene*
  - produces a clinical syndrome near-identical to *vit. E deficiency*
- Symptoms (aged 2-16) - **progressive ataxia**, clumsiness, scoliosis, **cardiomyopathy**
  - later - dysarthria, **optic atrophy**, hearing loss, dysphagia, proprioceptive/vibration loss
  - also lower limb weakness, extensor plantars, **areflexia**, DM
- Investigations - ECG (LVH), vit. E (exclude deficiency), MRI (cerebrospinal atrophy)
- Management - consider **idebenone** (quinine analogue, antioxidant)
  - loss of ambulation after 15 years; life expectancy 40-50 years
- Complications - urinary urgency / incontinence, sexual dysfunction, depression

Gastrointestinal

Familial adenomatous polyposis (FAP)
- **Autosomal dominant** mutations in *APC* tumour-suppressor gene (chromosome 5)
  - colonic polyps develop from aged 20 years; **adenomas** subsequently develop
- Symptoms - PR mucous / bleed, obstruction / overflow diarrhoea, abdominal pain
  - also epigastric pain (gastric polyps), obstructive jaundice (duodenal polyps)
- Associated with **CHRPE** ("bear tracks"), **supernumerary teeth**, osteomas, thyroid masses
- Investigations - **colonoscopy** / biopsy, FOB, CEA (CRC), LFTs (metastasis), genetics
- Management - **aspirin**, consider NSAIDs / COX2I; ultimately **proctocolectomy** with IPA
- Complications - **CRC** (by age 40 years), pancreatic / thyroid malignancy, GI haemorrhage
Hereditary non-polyposis colorectal cancer (HNPCC; Lynch syndrome)

- **Autosomal dominant** mutations in *DNA mismatch repair* genes; commoner than FAP
  - majority linked to *MSH2* (chromosome 2); also *MLH1* (chromosome 3), *MSH6*
  - patients develop no more adenomas than general population but likely carcinogenesis
- Screening - *Amsterdam criteria* > 2 family members aged < 50 years across 2 generations
  - polyps may be tested for micro-satellite instability (MSI)
- Presents with CRC in aged 40 - 50 years; investigate as for FAP
- Management - *(sub)total colectomy* with IRA / IPA; biannual surveillance colonoscopy
- Complications - CRC (80% lifetime risk), endometrial / ovarian / ureteric / gastric cancers
  - Turcot syndrome - HNPCC / FAP with primary glioblastoma

Peutz-Jeghers syndrome

- **Autosomal dominant** - *mucosal pigmentation*, intestinal non-neoplastic polyps
  - usually attributed to *STK11* tumour-suppressor gene mutation (chromosome 19)
- Symptoms - pigmented lesions on lips, buccal mucosa, palms, soles, anus, genitalia
  - also GI obstruction / intussusception / bleed, *nasal polyps*, precocious puberty
- Investigations - FBC (iron deficiency anaemia), FOB, endoscopy / colonoscopy, genetics
- Management - genetic counselling, *polypectomies*; biannual colonoscopy screening
- Complications - malignancy (60% by age 60 years) pan-GI, pancreatic, breast, thyroid

Hereditary haemorrhagic telangiectasia (HHT; Osler-Weber-Rendu)

- **Autosomal dominant** - vascular dysplasia, telangiectasia, arteriovenous malformations
- Symptoms - recurrent epistaxis, mucocutaneous lesions - usually occurring in teenagers
  - GI - acute-on-chronic bleeds, iron deficiency anaemia, cirrhosis (uncommon)
  - cardiorespiratory - dyspnoea, cyanosis, clubbing, high-output cardiac failure
  - neurological - aneurysm, headache, epilepsy, stroke, intracranial haemorrhage
- Investigations - fingernail capillary microscopy, CT / MRI to identify AVMs
- Management - embolisation / ligation / resection of AVMs, nasal septoplasty, liver transplant
  - consider oestrogens in premenopausal women e.g. COCP, tamoxifen

Kartagener’s syndrome

- Autosomal recessive triad of primary ciliary dyskinesia, situs inversus, sinus abnormalities
  - leads to bronchiectasis, recurrent sinusitis / otitis media, COPD, male infertility
  - signs - dextrocardia, asplenia, *nasal polyps*, conductive deafness, clubbing
- Nasal nitrous oxide screening test - inhale and measure exhaled gas - low in Kartagener’s
  - nasal mucosal membrane sampling and examination gold standard diagnostic test
Klinefelter’s syndrome

- Extra X chromosomes affecting males (e.g. 47XXY); nuclear chromatin mass (Barr’s body)
  - classically tall (long legs, wide hips), gynaecomastia, micro-orchidism, subfertility
- In children - delayed milestones, learning difficulties, rapid growth, truncal obesity
- Management - testosterone replacement from puberty
- Complications - osteoporosis, breast cancer, leukaemia, CVD, VTE

Noonan’s syndrome

- Autosomal dominant Turner-like disorder - usually PTPN11 gene mutation
  - may be detected antenatally - polyhydramnios, pleural effusion, oedema, nuchal fluid
- Symptoms - neck webbing, short stature, pectus excavatum, scoliosis, cubitus valgus
  - also low-set ears / sensorineural hearing loss, ptosis, wide-spaced eyes, triangular face
  - neurological symptoms - learning difficulties, strabismus, refractive errors, seizures
- systemic features - congenital heart disease, coagulopathy, delayed puberty
- Management - consider rhGH

Osteogenesis imperfecta (OI)

- Majority autosomal dominant affecting collagen type I (bone, teeth, sclerae, joints, skin)
  - types - I (mild, 60%), II (lethal), III (slowly progressive) and others
- Symptoms - tendency for recurrent pathological fractures, discoloured teeth, blue sclerae, early corneal arcus, aortic regurgitation, mitral valve prolapse, joint hypermobility
- Management - bisphosphonates, surgery, physiotherapy

Phacomatosis

- Characterised by hamartomas (disordered non-neoplastic tumours) of multiple tissues

Neurofibromatosis

- Autosomal dominant (but often sporadic) genetic disorder of skin, nerves, skeleton
  - associated with pulmonary hypertension, renal artery stenosis, phaeochromocytoma
- Type I - chromosome 17 (NF1) mutation - low neurofibromin, peripheral / cutaneous lesions
  - diagnosis - café-au-lait spots, axillary freckles, neurofibromas, scoliosis
  - also optic nerve glioma causing asymmetrical visual field defects, cognitive difficulties
  - iris hamartomas (Lisch nodules) may be seen on slit-lamp in 95% aged > 10 years
- Type II - chromosome 22 mutation - central / CNS lesions
  - diagnosis - bilateral acoustic neuroma, menigioma, glioma, Schwannoma
  - causes deafness, tinnitus, vestibular problems
  - presents later around aged > 20 years
- Complications - brain malignancy, epilepsy, cerebral aneurysm, leukaemia, ADHD
Tuberous sclerosis
  • **Autosomal dominant** multi-system genetic disorder of **TSC1/2** (tumour suppressor genes)
    • characterised by hamartomas of brain, skin, kidneys, eyes, heart, lungs
  • Symptoms - *infantile spasms / epilepsy* (65%), *ash-leaf* spots (pale, show up with UV)
    • other skin lesions - *adenoma sebaceum* (red facial papules), *Shagreen patches* (rough lumbar skin), ungual fibromas, poliosis (white hair), skin tags, café-au-lait spots
    • also WPW, renal cysts, **global developmental delay**, ASD / ADHD, schizophrenia
  • Complications - subependymal giant cell astrocytomas (SEGA), *angiomyolipomata*, RCC

Sturge-Weber syndrome
  • Sporadic disorder causing foetal hypoxia, ischaemia (vascular steal), thrombosis
    • may be *cutaneous* and / or *neurological* lesions; complete if both, incomplete otherwise
    • neurological - *leptomeningeal angiomas* leading to **severe epilepsy** (up to 90%)
    • cutaneous - *port-wine stain* (trigeminal area, unilateral, *not* specific to SWS)
    • also glaucoma, developmental delay, headache
  • Management - carbamazepine, *pulsed dye laser* for PWS

Polycystic kidney disease (PKD)
  • Both **autosomal dominant** (more common; 0.1%) and **autosomal recessive** forms
    • defects in *polycystin* impair renal development but also affect liver, brain, arteries
    • autosomal dominant - **PKD1** (majority; chromosome 16), PKD2 (chromosome 4)
    • autosomal recessive - chromosome 6; more often presents in infancy with liver disease
  • Symptoms - polyuria / nocturia / gross haematuria, *loin pain*, renal calculi, UTI, HTN, LVH
    • *extra-renal cysts* - early satiety, ascites / varices / jaundice, pancreatitis
  • Investigations - USS, FBC (polycythaemia - excess EPO), genetics
  • Management - control of CVD risk factors
  • Complications - IHD, renal failure, berry aneurysm / AAA, mitral valve prolapse

Prader-Willi syndrome
  • **Autosomal dominant** - partial deletion of *paternal* chromosome 15 / maternal disomy 15
    • characteristically Arian, associated with tantrums / OCD / psychotic behaviours
    • In newborns - **hypotonia**, poor suck, FTT, narrow face, almond-shape eyes, cryptorchidism
    • In children - *hyperphagia*, obesity, hypogonadism, delayed milestones, sleep apnoea
  • Management - rhGH, consider SSRIs

Angelman’s syndrome
  • **Autosomal dominant** - partial deletion of *maternal* chromosome 15 / paternal disomy 15
  • In children - **developmental delay** apparent by 6 months, microcephaly, *epilepsy*
  • Management - **piracetam**, sodium valproate
**Trisomy syndromes**

**Down's syndrome**
- **Trisomy 21**: risk roughly 1 in 400 at maternal age 35, up to 1 in 30 at age 45
- On USS - nuchal translucency, *absent nasal bone*, tricuspid regurgitation
- Symptoms - hypotonia / hyperflexibility, brachycephaly, small low-set ears, narrow palate
  - also flat nasal bridge, epicanthic folds, single palmar crease, large ‘sandal gap’
- Associations - AVSDs, hearing loss, cataracts, duodenal atresia, Hirschsprung’s, scoliosis

**Edward’s and Patau’s syndromes**
- Edward’s is **trisomy 18**; Patau’s is **trisomy 13** - second and third commonest after Down’s
- Risks - female foetal sex (miscarriage more likely in males), *advanced maternal age*
- Features - low birthweight, low-set ears, small facial features, cleft palate, clenched hands
  - majority have *congenital heart defects*; range of other abnormalities; *Wilm’s tumour*
- Median life expectancy is 4 days; 40% survival at 1 month, 5% survival at 1 year

**Turner syndrome**
- Abnormality / loss of paternal X chromosome affecting females (e.g. 45X / 46XrX)
  - highly variable phenotypes; characteristic *webbed neck* (affects 20%)
- In newborns - small for dates, hand/foot lymphoedema, nuchal fat, *aortic abnormalities*
- In children - FTT, short stature, behavioural difficulties, *recurrent OME* / deafness
- In adolescence - gonadal dysgenesis, obesity, HTN, learning difficulties, *ovarian failure*
- In adulthood - *autoimmune disease*, aortic dissection, osteoporosis, *infertility*
- Management - frequent monitoring, consider rhGH for short stature / HRT for ovarian failure

**Wiskott-Aldrich syndrome**
- Rare *X-linked recessive* inherited *immunodeficiency* - mutation of WASP protein
  - characterised by recurrent *bacterial infection*, eczema, *bleeding diathesis*
- Symptoms (first 25 years of life) - petechiae / PR bleed (90%), pneumonia, sinusitis
  - also autoimmune haemolytic anaemia, glomerulonephritis, vasculitis, IBD
- Investigations - FBC (thrombocytopenia), IgG / IgM (low), WASP protein
- Management - routine immunisations, antibiotics, Ig, transfusion; consider splenectomy
  - *stem cell transplant* may be curative; life expectancy typically 20-30 years
- Complications - *malignancy* (esp. NHL, leukaemia), haemorrhagic stroke