**Genetic and Chromosomal Disorders by Dr. Koraya**

**Basic arrangement of DNA and Chromosomes**

* DNA is a double-helix structure, that is wrapped around histone proteins called the nucleosomes and then nucleosomes that gives chromosomes at the end. In short, chromosomes are both DNA and proteins.
* DNA, if stretched, is almost 1.5-2 meters long. In order to pack this very long strain in a small nucleus, an innovative packaging system is needed, what is exactly present in our bodies.
* Chromosomes are very loose in the nucleus. It looks like spaghetti, but it’s not, if one end is pulled, it is a single strand. DNA is transcribed to meaningful information by RNA polymerase enzyme to mRNA. RNA polymerase identifies the gene of interest, and transcribes it.
* Chromosomes are not only the packaging of DNA, they’re also for regulation.
* DNA is the same in all cells, RNA is very different in different cells; hence, the diverse cells of the body. E.g. RBCs vast majority of RNAs are made to make hemoglobin.
* Arrangement of DNA to allow the access of RNA polymerase to function is different between the cells, and this is called the chromatin signature. Meaning, if stretched, DNA is the same, but the way it’s packaged differs between cells.
* Difference between autosome and sex chromosome?
  + 23 pairs of chromosomes. From each chromosome, there are 2 homologues, one from each parent. Diploid chromosomes are both paternal and maternal, and haploid are either maternal of paternal. Therefore, all cells are diploid with few exceptions e.g. megakaryocytes, which have multiple nucleoli or gametes (sperms and eggs).

**Down syndrome (47, XX, +21 or 47, XY, +21)**

* Commonest cause of intellectual disability (but depends on the location, because the incidence drops in areas legalizing Down syndrome abortions).
* Commonest autosomal trisomy in live births, but not the commonest trisomy at conception (trisomy 16 which is not compatible with life). Down is compatible with life, but has reduced viability i.e. the number of Down at time of conception is much higher than the actual live births due to spontaneous abortion. Therefore, Down is also not fully compatible with life.
* Commonest form (95%) of Down is trisomy 21 (instead of the normal disomy), which is present in all the cells. The remainder 5% of forms of Down syndrome are translocations and 1% mosiacism.
* Must determine the exact type of Down by karyotyping because of the recurrence risk, because it differs in the different forms of Down. Even if the case is a clear clinical textbook Down, karyotyping is still done to each case. It’s not a matter of confirming the diagnosis (even though this is actually important).
* Risk of Down maternal age is the only proven risk
  + Age-adjusted risk: risk is very low until the age of 30, it increases exponentially.
  + Previous child: It’s roughly 1%. Depends on the karyoptyping of that child, to specify the exact increase of risk. Egg or sperm may have mosiasim, which increases the risk.
  + 45 year old has a 1.5-2.5% age-adjusted risk, and if she already had a child with Down, the risk of having another child with Down becomes 2.5-3.5%.
* How trisomies occur
  + Start with diploid cell, and then disjoin the homologues. Disjunction is critical in meiosis 1, and meiosis 2 is like mitosis. Duplicated chromosomes will be separated to 2 chromatids.
  + In case of an error ‘non-disjunction’, 1 gamete will have 2 chromosome 21s and the other gamete will be nullisomic (compared to the normal gamete which has 1 chromosome 21). Nullisomic gametes are rarely fertilized, but if they do, they become monosomic, which are incompatible with life. If a disomic gamete is fertilized by a normal gamete (monosomic), a trisomic pregnancy results. In order to get trisomy 21, non-disjunction must occur.
  + There are 2 ways for non-disjunction: meiosis 1 and 2 errors. Meiosis 1 errors are more common.
  + Meiosis 1 in males starts at puberty and commences well throughout life. While in females, meiosis 1 starts in utero, and gets suspended; homologues get stuck together until time of menstruation as the egg is about to be shed from the ovary, meiosis 1 is continued (can’t say puberty, because not all eggs mature at the same time). Therefore, if a 50-year-old woman gets pregnant, the egg has been in meiosis 1 stuck together for 50 years, explaining the increased risk of error with age.
  + In case of males, there is a time limit for sperms, oldest sperm being 60-70 days old. Therefore, the meiotic non-disjunction error is more likely to come from a female rather than a male.
* Dysmorphic features of Down
  + Up-slanting palpebral fissures; very slacked nasal bridge (extremely helpful in US during pregnancy); large tongue; small mouth; epicanthal fold; single palmar crease; and intellectual disability (almost always present); etc.
* Diagnosis
  + 2nd trimester screening was first possible with only 85% sensitivity. 1st trimester screening was then possible by the nuchal thickness with 92-93% sensitivity. Nowadays, diagnosing Down without any invasive procedures is possible.
  + Amniocentesis is done late (after 15 weeks of gestation) and she’s already showing, which makes it psychologically difficult to terminate the pregnancy then. Chorionic-villous sampling (CVS) is done at 11 weeks, when the mother is not yet showing. Both are invasive procedures, with 1% risk of losing the pregnancy.
  + Nowadays, blood sample from the mother and isolating the fetal DNA, and determine if the fetus has any trisomies. Maternal plasma will contain trisomies instead of disomies. It has extremely high sensitivity and specifity (99-100%).

**Trisomy 18**

* Not extremely dysmorphic features, and diagnosis can be missed at birth, but neurological detoriated
* Overriding of the thumb and 5th finger, and is only seen in trisomy 18 clasping of the hands is classical.
* Hypo or hypertonic, depending on their brain involvement.
* Typically die very soon at 16-18 months due to apnea, and many associated abnormalities, but not facial ones.

**Trisomy 13**

* Dysmorphic features
  + Extremely dysmorphic (as opposed to trisomy 18).
  + Nose is very unique to trisomy 13 with very broad nasal bridge; micro-ophthalmia (makes opening eyes difficult); polydactyl.

**Turner syndrome (45, X and not XO!)**

* As mentioned previously, monosomies aren’t compatible with life, except sex monosomies.
* Even though it’s compatible with life, it’s very prone to spontaneous abortion. Out of 100 conceptions of Turner syndrome, 1 makes it to term.
* Best time to examine is at birth because of the loose and redundant skin that used to cover the cystic hygroma in utero (which disappears at birth). If feto-scope was used, an impressive cystic hygroma will be found.
* Generalized swelling of the body due to defective lymphatic drainage that tends to disappear at birth, except for the feet (almost don’t see the nails due to the very swollen toes), which also disappears with time.
* If all this is missed, patient goes unnoticed until the time of puberty. Therefore, it’s critical to pick them up at birth.
* Very high risk of mosaicism.
* Features
  + Webbing of neck: as they grow, redundant skin becomes tethered, leading to webbing of neck, which is characteristic.
  + Shield-like chest: absorption of the swelling is believed to cause the nipples to part, known as shield-like chest.
  + Short stature.
  + Amenorrhea: any short female presenting with amenorrhea, Turner must be ruled out.
  + Intellectually normal (normal IQ) but learning disability for spatial and geometric issues (specific things).
* Management
  + Early diagnosis helps the parents and the patient, and saves them the trouble of misdiagnosis, and help inform them of the natural history of the disease.
  + Offering hormonal-replacement therapy:
  + Sex hormones (estrogen) at puberty: because they have discrete gonads and don’t produce estrogen, leading to the absence of secondary sexual characteristic after puberty.
  + Growth hormone (GH) early: studied have proved that very early administration of GH is not a cure, but will increase their height and improve their psychological wellbeing.

**Micro-deletion syndromes**

**22q11.2 micro-deletion syndrome**

* Pronounced as follows: twenty two (chromosome number 22)/q (long arm of chromosome. Whereas “p” is the short arm)/one (band 1, because the chromosome is divided into bands)/one (sub-band 1 because the band is also divided into sub-bands)/point two (sub-sub-band 2 of sub-band 1 of band 1).
* Also called velocardiofacial syndrome, also called DiGeorge syndrome (DiGeorge is when they typically have abnormality of the parathyroid glands causing hypocalcaemia).
* Velo (palate): cleft palate. Cardiac: left-sided heart defect; interrupted aortic arch; Teratology of Fallot.
* 22q11.2 is the commonest micro-deletion syndrome.
* In 22q11.2 micro-deletion syndrome, 11.2 piece of the chromosome is deleted, leading to the loss of multiple genes with it.
* Micro-deletions causing multiple genes to be lost are also called contiguous (next to each other) micro-deletion syndromes. The phenotype of contiguous micro-deletions is the result of the collective loss of the genes, and not a single gene.
* Dysmorphic features
  + Typical facies is uncommon.
  + It’s the commonest associated syndrome with cleft palate; therefore, it should always be suspected in a patient with a cleft palate (cleft lip is uncommon).
  + Eyes: short palpebral fissures.
  + Nose: tubular nasal bridge (diagnostic).
  + T-cell abnormalities: part of their workup.
  + At birth, they present with cleft palate; hypocalcaemia; cyanotic heart disease; and intellectual disability.

**Williams syndrome (7q11.2 micro-deletion syndrome)**

* Typical facies
  + 1 line, instead of 2, for the eyelashes and eyelid (which is also normally found in people of far Eastern ancestry) because of laxity, so their eyelid droops and end up seeing 1 line.
  + Prominent cheekbones.
  + Full lips: cute in young age, but as they grow, gives them very course appearance.
  + Iris abnormalities.
  + Spaced teeth.
* Characteristic behavior
  + Extremely friendly and have no stranger anxiety (hug strangers out of nowhere).
* Musical: they love music.
* Characteristic cardiac findings: in supravalvular aortic stenosis, Williams must be ruled out.

**Chromosomal rearrangements (number is normal, but structure isn’t)**

* Examples are translocation, inversion, and insertion.

**Translocation**

* Reciprocal: swapping of chromosomal material between 2 non-homologous chromosomes i.e. equal contribution without any net loss or gain of DNA, but the structure is abnormal.
  + Balanced: without any net loss or gain of DNA.
  + Unbalanced: end or net gain or loss.
* Robertsonian: balanced translocation because even if they lose the short arm its not significant cause of its small size , they are phenoypically normal until age of reproduction where they may pass it to their offspring with chromosomal abnormalities.
  + Acrocentric chromosomes are chromosomes with the centromere on the far periphery, leading to a very short ‘p’ arm.
  + In Robertsonian translocation, 2 acrocentric chromosomes join end to end, leading to a giant chromosome ‘Robertsonian chromosome’ with the loss of the little material on both the original short arms.
  + If the mother is a carrier of a balanced Robertsonian translocation (e.g. 45, XX, rob (14; 21)). During meiosis, the disjunction will be confusing and the translocated chromosomes will be counted as a single chromosome (hence, 45 and not 46). She is normal and the problem is with her offspring.
  + Example
    - If you have a mother with 45, XX, rob (14; 21), and a normal father, what is the percentage that they will get a child with Down syndrome (DS)?
    - There are six possibilities, three of which are not viable and will end up in abortion out of the remaining three one will have DS, one will be normal, and one will be a rob carrier; therefore, they have 33% risk of having a child with DS. Refer to figure 8.4 page 118 in textbook. However, this is hypothetically and not what happens in reality because trisomy pregnancies are rare, and most defective eggs will not fertilize.
    - If both parents are carrier of the Robertsonian translocation, the risk that the female passing the translocation is higher (10-15% recurrence risk) than the male passing it (6-7% recurrence risk). This goes to the concept that female release one egg per cycle, which most likely will carry the translocation where as males release millions of sperms and the fittest sperm will most likely fertilize the egg (survival of the fittest).
    - To calculate the recurrence risk we have to karyotype the mother and father.

**Inversion**

* Paracentric: when the genetic information on the same side of the centromere gets inverted
* Pericentric: when the inversion is on both sides of the centromere.

**Mendelian Inheritance**

**Autosomal recessive (AR)**

* Both genders are equally likely to be affected (autosomal).
* Horizontal transmission (doesn’t affect all generations).
* Consanguinity: because for each gene, there are 2 alleles for AR to occur, 2 defective alleles are needed from each parent to be affected. Consanguinity increases the risk of marrying a carrier spouse by 1/8th because 1st degree cousins share 1/8th of the genetic make-up, which increases the risk of genetic rare diseases that can normally have an inheritance risk of (1/100,000).
* Majority of marriages in SA are consanguineous marriages (56%). Even if they don’t express the disease for multiple consanguineous generations, they remain carriers; therefore, families must be educated.
* If both parents are carriers, they have a 25% risk of affected offspring with each pregnancy. All cells have the defective allele, with the exception of the sex chromosomes.

**Homozygous vs. compound heterozygous**

* Homozygous is when both the alleles have the same mutation, but when both alleles carry 2 different mutations, it’s compound heterozygous. Therefore, shouldn’t be a homozygous to be affected, and can be a compound heterozygous.
* You need to introduce a defect to the allele to shut it off, whether the defect identical (homozygous) or different (compound heterozygous). Heterozygous is a different terminology in which only one allele is defected whereas the other allele is normal. Therefore, in order to express autosomal recessive disease, you are either homozygous or compound heterozygous.

**Genetic heterogeneity**

* If both parents are deaf, what are the chances of having a deaf child as well, knowing that their deafness is an autosomal recessive disease?
* Most will think that it is 100%, but that is not necessarily true due to the fact that we have multiple genes that code for the same disease (in this case deafness), a concept known as Genetic Heterogeneity.
  + For example, mother has 2 defective alleles (homozygous) in gene A, whereas father has 2 defective alleles (homozygous) in gene B; the chance that they will have a child with deafness is 0%. But if they both had the mutation in the same gene the risk will be 100%.
  + The child; however, will be a carrier of a single defective allele in both genes A and B, which is defined as Double Heterozygosity.

**Autosomal Dominant**

* Vertical transmission (found in every generation; dominant), males and females are equally affected (autosomal)

**De novo vs. familial (inherited)**

* De novo: born to normal e.g. achondroplasia (a dominant mutation).
* De novo mutations are more likely to originate from males due to the higher replication in sperms (more chances of mutation). Meaning, de novo mutations will be the beginning of a dominant inheritance.

**Penetrance**

* When the mutation is expressed phenotypically. Incomplete penetrance when the individual carries the mutation but he doesn’t express it.
* Usually in AD and rarely in AR.

**Variable expressivity**

* Not everybody with the same mutation will have all the system involved.
  + For example, in Marfan syndrome, some only express ocular manifestation while others only have the cardiac defect and others have the full-blown picture.

**X-linked disorders**

* Females are carriers and males are affected.
* In certain conditions females manifest the disease

1. Turner syndrome (because they only have one X chromosome).
2. When one X chromosome in the female is inactivated.

* The risk of an affected child (any gender) is 25%, while the risk of an affected son is 50%, and 50% for a carrier daughter.
* There is never male-to-male transmission, because the male only gives rise to the Y chromosome.

**Mitochondrial**

* Comes from the mother and is completely different from x-linked. Matrilineal meaning that the mother will affect her offspring (sons and daughters), but her sons will give rise to normal offspring, and her daughters will have affected ones.

**Atypical mendalian inheritance:**

**Mociaism**

* Having cells of different genetic makeup in the same individual coming from the same zygote. This is seen in about 1% of patients with DS.
* The normal zygote gets the mutation somewhere during development. Once mutation is acquired, it will continue in all the following cells lines (somatic mociasism). Therefore, the earlier the mutation is acquired; the more cells are affected having higher chances for both germ-line (testicular/ovarian mocaisim) and somatic mocaisim. When the defect is late, then the child might only end up with germ-line mociaism.
* Germ-line mocaisim on biopsy of the testicles or ovaries the mutation will be present and this will give rise to a mutated egg.
* Conversely, you can have two different genetic make-ups from two different zygotes like in the case of bone marrow transplant patients known as “chimeric”.

**X-chromosome inactivation (lionization)**

* The female by definition is mosaic. Some cells have inactivation of either the paternal or maternal X chromosome, which is something the original cell line determines early on in development.

**Uniparental disomy/imprinting**

* [Refer to pg. 125 in textbook. Some genes are only expressed from mother and vice versa.]
* Prader-willi syndrome
  + There is paternal loss of chromosome 15.
  + Severely obese, intellectual disability, and dysmorphic features.
* Angelman syndrome
  + There is maternal loss of chromosome 15.
  + Severe intellectual and [developmental disability](http://en.wikipedia.org/wiki/Developmental_disability), sleep disturbance, [seizures](http://en.wikipedia.org/wiki/Seizures), jerky movements (especially hand flapping), frequent laughter or smiling, and usually a happy demeanor.

**Fragile X syndrome**

* They have intellectual problems; autistic features; large ears; macrocephaly; and very sensitive to water and sounds.
* It is the most common familial X-linked intellectual disability.
* Mutations occur in the exons of a gene (a gene consists of introns, exons and a promoter where the RNA polymerase binds the first exon, which is transcribed and later translated).
* Translation doesn’t go over the whole transcribed region; instead, it starts when the ribosome detects the start codon (ATG). Before the start codon, is the UTR (un translated region). In this UTR, there is a CGG repeat if there a large number of these repeats (beyond 200) the gene expression will separate from the RNA polymerase and will shut down.
* Atypical Mendelian/anticipation
  + When the grandmother has 50 repeats of CGG, she will not have the disease. During replication in the future generation, these repeats will expand and may manifest in the later offspring.
* Why would a female with X-linked recessive be affected?
  + The majority of lionization (inactivation) occurs in the defective X so most of the time females will not manifest the disease. However, according to the normal Gaussian distribution, there is a 5% risk of falling in the skewed region and the normal X of the female gets lionized and the defective X will be expressed, manifesting the disease.