14 - Sex linked disorders

Sex-linked disorders

© SPMM Course penetrance increases the likelihood of having an unaffected child. The variable expression refers to differences in severity of the disease expressed. A mildly affected parent may have a severely affected child. Spontaneous disease-causing mutations can often present as diseases that are known to occur in autosomal dominant fashion. For example, achondroplasia and tuberous sclerosis are commonly due to spontaneous mutations, but families show AD pattern. Often the abnormal gene in autosomal dominant diseases codes for structural proteins such as receptors or cytoskeleton proteins. Sometimes such aberrant production of an autosomal dominant disorder without family history may be due to a phenotypically indistinguishable disorder without the genotype – this is called phenocopy. (Goldschedt, 1935) e.g., anti-psychotic medication causes patients to manifest the same symptoms as the genetically determined Parkinson’s disease. Another example is genotypically determined Pendred syndrome being mimicked by endemic cretinism. Autosomal recessive disorders These disorders manifest themselves only when an individual is homozygous for the disease allele; i.e. both chromosomes carry the mutated gene. In this case, the parents are generally unaffected, healthy but carriers (heterozygous for the disease allele). There is usually no family history, although the defective gene may be passed from generation to generation (skipping). The offsprings of an affected person are healthy heterozygotes unless the other parent is also a carrier. If carriers marry each other, the offspring has a 1 in 4 chance of being homozygous and affected and a 1 in 2 chance of being a carrier, and a 1 in 4 chance of being genetically normal. Consanguinity increases the risk. Often the abnormal gene in autosomal recessive diseases codes for enzymatic proteins. Sex-linked disorders Genes carried on the X chromosome are said to be 'X-linked', and can be dominant or recessive in the same way as autosomal genes. Normally males inherit an X chromosome from their mother and a Y chromosome from their father, whereas normal females inherit an X chromosome from each parent. The Y chromosome contributes very less genetic material to a man’s genetic makeup. Hence, there must be a mechanism to simulate this deficiency in females too to preserve natural equality. This phenomenon is now known to be ‘X inactivation’. This occurs very early in the development of female embryos. When an X chromosome is inactivated, it could be visualized under the microscope as a highly condensed Barr body in the nuclei of interphase cells. An inactivated X chromosome does not get transcripted to produce mRNA. X inactivation is random process. In other words, some cells of the female embryo have paternally inherited X inactivated while the other cells have maternally inherited X inactivated. It is an irreversible, fixed process and once inactivated these chromosomes do not get reactivated life long. The entire cell’s progeny will have same inactivation replicated. All X chromosomes in a cell are inactivated except one, irrespective of original number of X chromosomes in a cell. Thus females with trisomy X will have two Barr bodies. X inactivation occurs via DNA methylation.

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