15 - X linked recessive disorders

X-linked recessive disorders

© SPMM Course X-linked recessive disorders If a recessive disease-causing mutation occurs on the single X chromosome of a man, this is sufficient to cause disease, as another X chromosome is not existent to compensate any deficiencies. As females have two copies of the X chromosome, they need a double identical mutation for disease expression, which is extremely rare. But during random X inactivation if most X chromosomes carrying normal alleles are inactivated (called unfavourable Lyonisation), then these females can manifest the disease phenotype – termed as manifesting heterozygotes. But nevertheless the severity of expressed disease is mild and can go unnoticed too. Skipped generations are commonly seen because an affected male can transmit the disease-causing mutation to a heterozygous daughter, who remains normal phenotypically but carries and transmits the disease-causing allele to her sons. From McGuffin et al. (ed) Psychiatric genetics and genomics. Oxford Press: 2002 Male-to-male transmission is not seen in X-linked inheritance. Affected male mates with a homozygous normal female, all of the daughters will be heterozygous carriers; all of the sons will be homozygous normal. If a carrier female mates with normal male (which is often the case in this transmission), then half Disorder Location and mode of transmission Features Tuberous sclerosis 9q34 / 16p13 Auto.dominant (but most are spontaneous) 1 in 30 000 Adenoma sebaceum, normal to sever MR, ash leaf macules, brain hamartomas, heart and kidney cysts Treacher Collins syndrome 5q31 Auto.dominant 1 in 40 000 Maxilla-mandibular hypoplasia, malformed pinna, down slanting palpebrae, mild to moderate MR Apert syndrome 10q Auto dominant Variable MR, cranio synostosis, shallow orbits, trapezoid mouth, ‘mitten’ hands and feet. Noonan syndrome Chr 12 Auto.dominant 1 in 1 500 Mild MR, short stature, nuchal edema/webbed neck, pulmonary stenosis, cryptorchidism Hurler syndrome 4p16 Auto. recessive 1 in 100 000 Deteriorating IQ after age 2, coarse facies, clouded cornea, joint stiffness. Lesch-Nyhan syndrome Xq 26-27 X linked recessive Deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) Poor muscle control, and moderate mental retardation – year 1. Self-mutilating behaviors, characterized by lip and finger biting – by year 2. Hyperuricemia and hyperuricosuria -severe gout and kidney problems – can present anytime.

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