26 - 11. Hardy Weinberg equilibrium

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> 80 Major depression Generalized anxiety Panic disorder Phobia Alcohol dependence *Based on DSM-IIR diagnosis. The estimates must be treated as approximations only. Autism and Tourette’s may have around 90% heritability. (From Owen, MJ., Cardno, AG. &O’Donovan, MC. Psychiatric genetics: Back to the future Molecular Psychiatry (2000) 5, 22–31) The Big Five personality traits have following heritability: Openness: 57%; Extraversion: 54%; Conscientiousness: 49%; Neuroticism: 48%; Agreeableness: 42%

11. Hardy Weinberg equilibrium In the absence of mutation, non-random mating, selection and genetic drift, the genetic constitution of the population remains the same from one generation to the next. This principle can be used mathematically to determine frequency of an abnormal gene or genotype in the population. If p is the frequency of the normal gene in the population, q is the frequency of the abnormal gene, p2 is the frequency of the normal homozygote, q2 is the frequency of the affected abnormal homozygote, 2pq is the carrier frequency, and p + q = 1. The equation can be used, for example, to find the frequency of heterozygous carriers in an autosomal recessive disease XYZ. If the incidence of disease XYZ is 1 in 3600 live births, then q2 = 1/3600, and therefore q = 1/60. Since p = 1 - q, then p = 59/60. The carrier frequency is represented by 2pq, which in this case is 1/30. Thus 1 in 30 individuals in the whole population is a heterozygous carrier for disease XYZ. Hardy Weinberg equilibrium does not always hold true. Consider the following circumstances; Natural Selection: Genes which hinder survival and fertility are not maintained in the genetic pool of a population. This is because the abnormal genes are not passed on to next generation when reproductivity is low or if the patient dies at very young age. Similarly some mutations that offer survival benefits are

maintained in higher than expected rates in the population. For example, GENOTYPE FREQUENCY For a given locus, the genotype frequency measures the proportion of each genotype in a population. In a population of 100 individuals assume 33 have AA, 45 have AB and 22 have BB genotypes. The genotype frequency is obtained by dividing the count for each genotype by the total number of individuals. i.e genotype frequency for AA = 0.33, AB = 0.45 and BB = 0.22. The term gene frequency refers to the proportion of chromosomes in a population that contain a specific single allele. In the above example, frequency of allele A = 2x33 (where A occurs twice) + 45 expressed as percentage = 111% or 1.11. Similarly the gene frequency of B is 2X22 + 45 = 89% or 0.89.

© SPMM Course sickle cell carriers are protected against sever falciparum malaria, cystic fibrosis carriers may have an advantage against typhoid, etc. Genetic Drift: Genetic drift refers to gene frequency change caused by limitations in population size. Genetic drift explains why some genetic diseases are unusually common in small, isolated populations. In a small population, the chances of random distribution is limited as probabilities of the combination are restricted. This is very close to what is termed as ‘founder effect’. Gene Flow: Gene flow refers to the exchange of genes between populations. Due to migration or other social reasons, the populations studied are not ‘closed’ populations anymore. Consanguinity: Non-random mating occurs, and mutations are preserved within a closed pedigree due to consanguinity. Autosomal recessive diseases are more often seen in consanguineous families. High frequency of mutations: Environmental exposure can provoke mutations at a higher frequency than expected in a stable population e.g. living near a nuclear reactor leak.

EPISTASIS, HETEROGENEITY & PLEIOTROPY Gene- gene interaction particularly between different alleles at different genes is called epistasis. This can occur at the same step or at different stages of the same biochemical pathway. Locus heterogeneity exists when the same disease phenotype can be caused by mutations in different loci. It becomes especially important when genetic testing is performed by testing for mutations at specific loci. For example early onset Alzheimer’s could be caused by mutations in chromosome 1, 14 or 21. Allelic heterogeneity refers to the same disease phenotype resulting from different types of mutations at the same loci. Consider cystic fibrosis, here nearly 600 different mutations at the same site of chromosome 7 results in same disease. Pleiotropy exists when a single disease-causing mutation affects multiple organ systems. Pleiotropy is a common feature of genetic diseases. For example, consider Marfan’s syndrome. Cardiovascular system, connective tissue, skeletal system etc. are affected by a single genetic aberration.

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