46 - D. Genetics of dementias

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© SPMM Course been postulated to be associated with decreased neurogenesis in the hippocampus, which is dependent on neurotrophic factors, including BDNF. Disrupted in Schizophrenia 1 (DISC1): This gene on chromosome 1q was identified in a Scottish family with a genetic translocation and with multiple cases of psychiatric disorders, primarily schizophrenia. This gene is expressed in multiple brain regions, including the hippocampus, where it is differentially expressed in neurons. It is associated with microtubules; in mice, disruption of DISC1 leads to abnormal neuronal migration and dendritic organization in the developing cerebral cortex. DISC1 appears to interact with phosphodiesterase 4B, which may play a role in mood regulation. 5HTT, MAOA, COMT: These three genes have been shown in meta-analyses to be associated with BP disorder. The effect size for each appears to be in the range of 10–20% increase in risk. Each of these genes is associated with other behavioral phenotypes, and each has been reported to interact with the environment to increase the risk of specific disorders (major depression, antisocial personality disorder, and schizophrenia respectively). Recent data in BP illness are more positive for 5HTT than for MAOA or COMT. Dysbindin: Also known as dystrobrevin binding protein 1 - involved in the formation of synaptic structures Neuregulin: Involved in neuronal migration and in the genesis of glial cells and subsequent myelination of neurons by these cells GRK3: This is the only candidate identified using animal model studies (a mouse model employing methamphetamine). This gene participates in the down-regulation of G-protein coupled receptors and is associated with Bipolar disorder. D. Genetics of dementias Alzheimer’s disease (AD) Mutations in the amyloid precursor protein (chr 21) and presenilin 1 (chr 14) and 2 (Chr 1) genes may be responsible for as much as 50% of familial (ie, autosomal dominant) AD beginning before 60 years of age (presenile). But this accounts for less than 1% of patients worldwide. The genetic factor with the highest attributable risk for AD is apolipoprotein E (APOE). The APOE gene on chromosome 19q has 3 codominant alleles, 2, 3, and 4, differing by single-base substitutions in the coding region of the gene. The ancestral allele, 4, is overrepresented, and 2 is underrepresented in AD (from Graff-Radford et al.: Arch Neurol. 2002;59(4):594-600). In Caucasian subjects, the odds of AD for those homozygous for 4 and for 3/ 4 heterozygotes are 14.9 and 3.2 times, respectively, greater than the odds associated with 3 homozygosity. The mean age of onset of AD is 2 decades earlier in 4 homozygotes. The APOE 4 allele has also been found to increase AD risk in nonwhite populations, including Afro-Caribbean, Chinese and Japanese. The increased risk associated with the 4 allele is greater in women than in men though this is not replicated in African

Americans. Chr 21 harbours mutant APP (Amyloid Precursor Protein) – this is related to Down’s syndrome and explains the higher prevalence of AD in patients with Down’s syndrome

Male Abs. risk% Female Abs. Risk % Relative risk (both sexes)

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