Psychiatric genetics

Key objectives

- Knowledge of current progress towards identifying particular genetic risk factors for mental illness
- Knowledge of CNVs as risk factors for schizophrenia
- Knowledge of genetic risk factors for early and late onset Alzheimer's disease

Standard methods for investigating genetic contribution to disease

Assessing the extent of genetic versus environmental contribution can be done using twin studies and adoption studies. Certain classical modes of transmission, such as X-linked recessive, can be recognised by studying the segregation of diseases through pedigrees.

Genetic markers can be used to localise susceptibility genes to particular chromosomal regions. Linkage analysis identifies markers which segregate with disease through pedigrees and give a broad localisation. Association analysis identifies marker alleles which tend to occur more frequently in cases than controls and give a narrower localisation.

Genome-wide association studies (GWASs) use hundreds of thousands of markers to identify common variants associated with disease.

Copy number variant detection identifies deletions and duplications of chromosomal segments associated with disease.

Whole genome or whole exome sequencing identifies every variant present to see if any are commoner in affected subjects.

Detection of genetic variation associated with a disease is followed by studies to determine the effect on gene expression and/or functioning in animal models and cell cultures.

Familiality in the major psychoses

Examining the diagnoses which occur in relatives of probands with a given disorder may throw light on the classification of psychiatric illness. For example, in general manic depression and schizophrenia tend to "breed true", supporting the Kraepelinian distinction between these disorders. Relatives of manic depressive probands are also at increased risk of unipolar depression, and relatives of schizophrenic probands have increased rates of schizoid and schizotypal personality disorder, suggesting that the diagnoses may sometimes represent less severe forms of the same underlying disease process. Although it can be difficult to classify puerperal psychosis clinically, the fact that relatives tend to suffer increased rates of affective disorder suggests that in most cases puerperal psychoses are essentially atypical forms of affective psychosis.

Manic depression / bipolar disorder

Twin and adoption studies indicate a substantial genetic contribution to risk

Although it is possible to find some densely affected pedigrees the mode of transmission is unclear and it is assumed that a number of different genes may contribute to risk.

Linkage studies implicated candidate regions but did not produce conclusive results.

The genes most consistently implicated by GWASs are CACNA1C and ANK3. CACNA1C codes for a subunit of a voltage-gated calcium channel and there are results suggesting the involvement of other ion channel genes. ANK3 is located at the nodes of Ranvier and is involved with the localisation and functioning of sodium channels. Another GWAS implicated gene, NCAN, is involved in neuronal adhesion and neurite growth. Mice knocked out for either ANK3 or NCAN demonstrate mania-related behaviours such as overactivity or impulsivity.

Although there is a genetic contribution to the susceptibility to unipolar depression, it is less marked than for bipolar disease. A recent GWAS produced two hits but otherwise there is no strong evidence from linkage or association studies to demonstrate which genes might be involved.

Schizophrenia

Twin and adoption studies have demonstrated a genetic influence on predisposition. Also, children of the normal monozygotic cotwins of schizophrenics have a similar risk of schizophrenia as do the children of the schizophrenic parents (supporting a genetic contribution to aetiology). A number of environmental risk are also identified, including maternal influenza, maternal famine, birth trauma, winter birth, cannabis use.

The mode of transmission of schizophrenia is unclear and it is likely that a number of genes are involved.

A number of regions generated positive linkage results, although with little consistency.

A large Scottish pedigree has been described in which many subjects have a translocation between chromosomes 1 and 11 and suffer from schizophrenia or other psychiatric illness. The breakpoint on chromosome 1 goes through a gene named DISC1 ("Disrupted in schizophrenia 1"), and association studies of DISC1 have been positive in other samples. Abnormalities of DISC1 may interfere with neuronal development.

A deletion of part of chromosome 22 causes velo-cardio-facial syndrome (VCFS) and some patients with this also suffer from a psychosis indistinguishable from schizophrenia. Indeed in some cases the psychosis is the only abnormality which comes to attention and in a cohort of unselected schizophrenics approximately 1% will turn out to have VCFS. VCFS thus represents a rare genetic cause of schizophrenia. It is possible that genes in this region may influence susceptibility to psychosis in other cases. COMT lies in this region and was originally claimed to be associated with schizophrenia but is now thought to influence prefrontal cognitive function.

Studies of other copy number variants (CNVs - deletions and duplications) show that in addition to the VCFS deletion CNVs are generally more common in subjects with schizophrenia than in controls. CNVs affecting NRXN1 (neurexin 1) are associated with schizophrenia. Deletions at 15q11.2 and duplications at 16p11.2 increase risk. Altogether, CNVs might account for around 1-2% of cases of schizophrenia.

GWAS results indicate a large number of regions associated with a small effects on risk. These effects can be summed to produce a "polygenic risk score", which also shows that some genetic risk factors are shared with other psychiatric disorders.

Exome sequencing studies imply that multiple rare variants are involved but have not identified specific genes definitively.

Cumulative evidence points towards glutamatergic transmission, calcium channels, synaptic functions and histone modification.

The strongest GWAS signal is in the HLA region, which contains the gene for complement component 4, C4. This occurs in two form, C4A and C4B, each of which can be long or short and commonly there may be

one or two copies of the gene on each chromosome. There are four common haplotypes: BS AL-BS, AL-BL and Al-AL, associated with different levels of expression of C4A. This correlates with increasing risk of schizophrenia (AL-AL versus BS OR=1.3). C4 is located on dendrons, axons and at synapses and mice lacking C4 have reduced synaptic pruning. Risk of schizophrenia is associated with C4 haplotypes and the effect may be mediated through increased C4 expression and increased synaptic pruning.

Loss of function variants in SETD1A were observed to occur *de novo* in schizophrenic offspring of normal parents and this observation was confirmed in larger case-control samples. These variants account for 0.2% of cases. SETD1A is a histone methyl transferase, modifying expression of other genes.

Alcoholism

Family, twin and adoption studies have demonstrated a genetic influence on the predisposition to alcoholism. The mode of transmission is unknown and it is not clear whether single gene effects or polygenic effects occur.

A number of associations have been reported with the dopamine D2 receptor gene (DRD2), but the status of these findings remains uncertain.

Note the following example of the influence of genetic polymorphism on the development of psychiatric illness:

A mutation common in orientals inactivates mitochondrial aldehyde dehydrogenase 2 (ALDH2), which is involved in the normal metabolism of ethanol. In such individuals the consumption of small amounts of alcohol produces circulating acetaldehyde leading to unpleasant symptoms (facial flushing, etc.) and this causes them to avoid alcohol. So the mutation which deactivates ALDH2 indirectly protects against the development of alcoholism.

A variant in the gene for alcohol dehydrogenase 1B causes a gain in function of the enzyme, leading to excess acetaldehyde production and, again, the avoidance of alcohol.

It is expected that there will be other genetic variants which influence susceptibility to alcoholism through psychological mechanisms such as reward-seeking, compulsivity. For example, GABA receptor variants can strongly influence alcohol preference in mice.

Gilles de la Tourette syndrome

This is a rare syndrome characterised by motor and vocal tics and sometimes involving coprolalia. Although some families appear compatible with the segregation of a major gene, none has yet been identified.

Attention deficit hyperactivity disorder (ADHD)

There is good evidence for a genetic contribution to the risk of ADHD. There have been reports that large, rare CNVs are commoner in cases. No specific genes are definitively implicated.

Learning disability

40% of cases have unknown aetiology. Can be divided into neurodegenerative, syndromic and non-syndromic. Many chromosomal (Downs syndrome) and genetic (phenylketonuria) abnormalities cause learning disability.

Note the example of phenylketonuria showing the way in which genes and environment (phenylalanine in the diet) can interact.

The mutation responsible for the fragile X syndrome has been identified and the gene in which it occurs has been named FMR1 (Fragile-X Mental Retardation). Its transmission is complex, since although the mutation can act as an X-linked recessive it "gets worse" as it passed on through different generations - a trinucleotide repeat sequence (CGGn) enlarges.

Autism

There is strong evidence for a genetic basis for this condition, and it is appears that abnormalities of a many different genes contribute to disease risk. There is an excess of de novo mutations - variants seen in cases but not their parents. Rarely, cases are due to mutations affecting the neuroligin or neurexin 1 genes. The autism phenotype can also occur with fragile X syndrome and mutations of MECP2 which cause Rett syndrome. 1% of subjects with autism have a deletion at 16p11.2 and 5% have CNVs at other locations. Exome sequencing implicates synaptic formation, transcriptional regulation and chromatin-remodelling pathways.

Alzheimer's disease

Late onset Alzheimer's disease is a common cause of dementia with a similar prevalence to multi-infarct dementia. Early onset Alzheimer's disease is a rare presenile dementia which is inherited as an autosomal dominant disease and causes similar changes in the brain, notably neurofibrillary tangles (rich in tau protein) and amyloid plaques. Identical lesions also occur in patients with Downs syndrome (trisomy 21) in middle-age. The gene which codes for the protein forming this amyloid is on chromosome 21q, and following linkage studies it was shown that mutations in this gene (for APP - amyloid precursor protein) account for a small minority of cases of presenile Alzheimer's disease. Other presenile cases are due to mutations in genes on chromosomes 14 and 1, named presenilin 1 (PS1) and presenilin 2 (PS2). The presenilins are involved in the processing of APP.

Association studies show that the risk of late onset Alzheimer's disease is strongly influenced by the genotype of apolipoprotein E. Three alleles are commonly found: e2, e3 and e4. Inheriting one copy of the ApoE-e4 allele trebles the risk of Alzheimer's, while inheriting a second copy trebles the risk again. Apolipoprotein E does bind to the amyloid precursor protein and to neurofibrillary tangles, and this may provide some clue to the aetiology of late onset Alzheimer's disease.

GWASs have implicated CLU, PICALM, CR1 and BIN1.

Sequencing studies demonstrate that very rare variants in other genes involved in processing APP, including SORL1, are responsible for a small proportion of cases of late onset Alzheimer's disease.

Molecular genetic insights have allowed the construction of mouse models of Alzheimer's disease, so that new treatment approaches can be tested.

Fronto-temporal dementia

Rare cause of presenile dementia. 10% caused by single gene mutations in MAPT (which makes tau protein), GRN, TARDBP, VCP or CHMP2B.

Prion diseases

These are very rare (1:1,000,000) degenerative brain diseases with spongiform changes in which variable degrees of amyloid deposition occur as a result of the accumulation of prion protein derivatives. Most cases of CJD occur sporadically, with no known risk factors.

Some forms of these diseases occur as autosomal dominant disorders within families: Gerstman-Straussler syndrome, fatal familial insomnia, familial Creutzfeld-Jacob disease (CJD). In these cases there are mutations in the prion protein gene which cause an abnormal form of the protein to be produced.

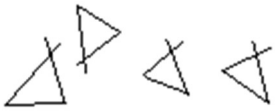
Other prion diseases, for example kuru, are transmitted horizontally and occur in subjects with the genetically normal form of prion protein. The abnormal prion protein acts as the "infective agent" and stimulates a conformational change in the host protein, thus setting off a chain reaction. In Britain the epidemic of bovine spongiform encephalopathy in cattle was followed by a small number of atypical cases of CJD. These cases show pronounced amyloid depositon, a longer time course, lack of characteristic EEG changes and were seen in unusually young subjects. This is now termed "variant CJD". Worldwide, around 200 cases occurred since 1995, only four since 2012. However, among those born before 1985 the UK prevalence of (so far) asymptomatic carriers is 1:2000.

Comparison of Alzheimer's and prion diseases

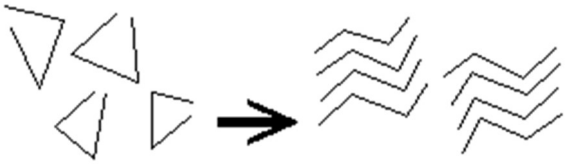
The diagram shows a simplified graphical representation of possible mechanisms leading to the deposition of amyloid in these diseases.

Alzheimer's disease

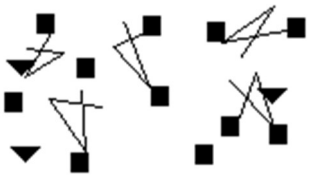
Normal amyloid precursor protein (APP) is soluble



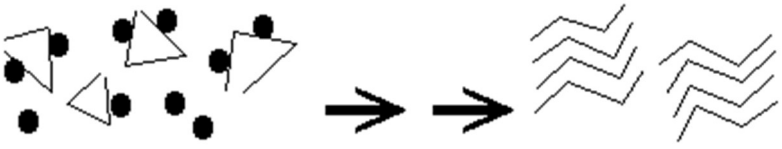
Mutations in the APP gene can lead to abnormal forms of the protein which can go on to form amyloid



ApoE e2 may reduce the probability of amyloid formation from APP



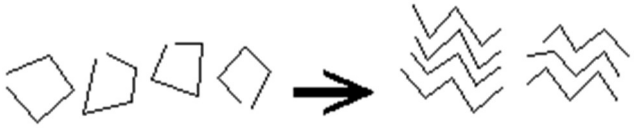
ApoE e4 may increase the probability of amyloid formation from APP



Prion disease

Normal prion protein is soluble

Mutations in the prion protein gene (PRIP) may lead to abnormal products which can form amyloid



In transmitted prion disease, prion protein in an abnormal conformation can induce a conformational change in the normal protein

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