5. Maternal or paternal X chromosome can effect genetic imprinting and the random pattern of inactivation in each

Impact of genetic mutation on behaviour lecture 2

Mutation – very rare
Polymorphism – found more commonly (>1%) – only difference in definition is frequency

Types of mutations:

- Silent – same amino acid
- Missense – different amino acid
- Nonsense – stop codon

Specific language impairement:

- When language does not follow normal developmental course and not due to hearing loss, physical abnormality or brain damage
- Normal development and other areas
- Difficult to pin down cause as multiple different variations of condition

Causes:

- Seen that language difficulty rates higher in relatives of those with SLI compared to the controls
- Family aggregation as opposed to segregation suggesting that it is a multifactorial defect and not necessarily caused by a single disease
- Does not prove it is genetic as it can be due to common environment eg diet.

KE family pedigree:

- 50% of children of those with SLI also have SLI; DOMINANT DISORDER – if half of siblings do not have it is shows that it is not simply environmental and has a genetic aspect to it.

Three methods of research of FoxP2 involvement in language:

1. ***Evolution – analysis of how FoxP2 sequence has changed across species***
2. ***Phenotype refinement – in humans refining phenotype to include neural structure and functional correlations***
3. ***Animal models – look at cellular and molecular level***

1. ***Evolution***

- Suprisingly FoxP2 is very highly conserved with only 3 AA positions differing in rat and human FoxP2 – suggesting that it is not simply the 'language/speech' gene as our language is significantly more complex than that of the rat. Does it even have anything to do with speech?
- Suggesting foxp2 plays an evolutionary conserved role in the development of corticostriatal circuits of both human and mouse brains however also suggested that it is involved in neural circuitary underlying speech which is unique to humans from people who have disruptions in this gene? How is this possible?
-
- Shows these changes also occurred relatively late during evolution with changes in human FoxP2 occuring after separation from chimpanzee – positive selection
- Change in base pair sequence despite being minor must have been an evolutionary advantage otherwise it would not have spread so rapidly and human FOXP2 changes seem to have concided with estimated time of emergence of spoken language in human populations

- Their effects manifest in different ways so that there are different symptoms and siagnoses in different carriers
- Particular mutation could be required but not sufficient to cause disease in individual carriers – may require additional 'hits' to result in diseased phenotype.
- Non genetic factors may also be important: **environmental** and **intrinsic developmental variation** – hence why not 100% concordance in MZ twim phenotypes

Genome wide complex trait analysis (GCTA)

- Doesn't look at individual sections of DNA but instead finds similarities between all DNA **using all of the SNPs** to find index of **relatedness**
- Comparision of SNPs to measure relatedness seen whether or not it maps onto phenotypic similarities.
- It is used to identify the **percentage variance** in the phenotype a**ccounted for by SNPs** <u>without having to identify the SNPs</u> involved
- This is a limitation to some extent as it leads you back without telling you what the genes are.
- Higher estimates of heritability but still less than twin studies.
- Based on methods from animal breeding

Interpretation of genetic findings:

DCDC2 gene:

- Gene thought to disrupt normal formation of brain curcuits necessary for fluent reading
- misnterpreted as this gene being possible to screen for in children and prevent misdiagnosis

This is wrong:

1. DCDC2 is only a gene which has been associated with dyslexia, there is no causativity confirmed and only in a few studies
2. Scerii et al (2001) - association was not great with an SNP found on the gene where the association was significant at p=0.05
3. Risk allele was found in 23% controls and 27% of dyslexics and is therefore only higly significant in a large sample.
4. Cannot simply just translate back such a rare association with cause as most people with the risk allele will not have dyslexia and those with dyslexia most likely wont have a risk allele.

Typical study =

1. Take SNP that has been shown to be associated with a disorder
2. Compare brain structure of those with different genetic variants
3. Many non replicable results which are underpowered are produced

Solution is to replicate the associations.