

Genetic basis of complex behaviours biology essay

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SUMMARY

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ABBREVIATIONS

INTRODUCTION

Behaviour genetics is the field of study that examines the effect of genetic composition on the behaviour of an organism. It also considers the interaction between the genetics and environment and how it influences the organism's complex behaviour. The founder of this field of science is considered to be Sir Francis Galton, an English scientist who was first to mention the phrase "nature and nurture". Behaviour genetics is often associated with the "nature versus nurture" debate, where nature refers to

the genetics and nurture to the environment, respectively (Reviewed by Plomin et al., 1994). The actual behavioural genetics research began in 1920s. Experiments involving animal inbred strains, animal behaviour and twin studies of human behaviour (Plomin et al., 1994). The research was mostly concentrated on intelligence and mental illnesses. However, only in 1970s behaviour genetics acquired the balance in its definition as both genetics and environment and also the interaction between the two were considered. Early behaviour genetics studies were carried out in psychiatry and schizophrenia was the main phenotype that was investigated. In order to take into account both genetics and environment adoption studies were used to investigate schizophrenia (Plomin et al., 1994). Previous studies have shown that schizophrenia runs in families with a risk of 13% for offspring of parents who have schizophrenia (Plomin et al., 1994). Therefore, adoption studies shed the light on whether environment or genetics is responsible for the schizophrenia bias in certain families. The study was carried out in which adopted at birth children of schizophrenic mothers were compared to the control adopted group of offspring (Heston, 1966). The result was following: out of 47 adopted children from mothers who suffered from schizophrenia 5 developed the disease. However, none of the 50 control adoptees were diagnosed schizophrenia (Heston, 1966). This study clearly showed that there is a strong genetic influence on the development of schizophrenia and confirmed the "nature and nurture" hypothesis. Nowadays, human behavioural genetics have progressed much further and are under intensive research. Complex behaviours are quantitative traits. The driving force for these traits is the epistatic interactions of genes with pleiotropic effects. The

phenotype of the complex traits is strongly influenced by the environment and its interaction with the genes (Anholt and Mackay, 2004). Model organisms such as *Drosophila* and *Peromyscus* mice are valuable tools to study the genetic basis of complex behaviour because experimental crosses can be carried out with these organisms. In this review the genetic basis on basis of complex behaviours will be discussed on the model of *Drosophila* aggression. Moreover, the complex trait such as aggression will also be discussed in humans and compared to the model organism.

Genetic basis of aggression in *Drosophila melanogaster*

Aggression is a complex behaviour of the organisms which is essential for survival. In animals aggression is vital for choosing and protecting mates, for hunting and protection of food, for establishing the social status and more. As other complex behaviours aggression is a quantitative trait (Edwards et al., 2006). There are two genetic effects which determine the architecture of quantitative traits: epistasis and pleiotropy (Zwarts et al., 2011). Epistasis is associated with the expression of one gene being influenced by another gene. Pleiotropy is the effect when one gene determines several phenotypes. By studying the epistatic interactions it is possible to shed light on the complex genetics networks which determine the quantitative traits (Zwarts et al, 2011). Pleiotropy accounts for the variation in phenotypes of the complex traits (Zwarts et al, 2011). Inbred populations should be used to study epistasis and pleiotropy. Therefore, *Drosophila melanogaster* is a good model organism to study these effects. Diallel crosses are usually used to study quantitative traits in model organisms which involve crossing all parents in order to create hybrids in all possible combinations. In particular,

diallel crosses are being carried out in *Drosophila* to study aggression (Zwarts et al., 2011). P-elements are used for mutagenesis in order to identify the genes determining the aggression (Zwarts et al., 2011). Epistatic interactions of mutant genes which exhibit hyperaggression It has been identified that there are 38 P-element associated mutations which account for hyperaggressive behaviour in *Drosophila melanogaster* (Rollmann et al., 2008). Out of the 38 mutations there are ten mostly characterized ones which lead to increased aggression. These genes encode important biological processes: protein kinases Darkener of apricot (Doa) and Btk29A; an NMDA receptor subunit (Nmdar1); a guanine exchange factor, schizo (siz); a UDP-glucose transferase, sugarless (sgl); an extracellular matrix protein, Laminin A (LanA); a transcription factor, muscle blind (mbl); a cell adhesion molecule, echinoid (ed); two genes regulating Notch signaling, the E3 ubiquitin ligase neutralized (neur) and the protein tyrosine phosphatase Gp150 (Zwarts et al., 2011). Diallel crosses of all possible heterozygous mutant F1 progeny show that four mutations are partially dominant (Gp150, mbl, sgl and Nmdar1), three mutations are partially recessive (ed, Doa and siz) and six mutations exhibited epistatic interactions (Figure 1) (Zwarts et al., 2011). The double heterozygotes that exhibit enhancing epistasis (more aggressive behaviour) are, LanA and Nmdar1, neur and sgl and Gp150 and Btk29A (Figure 1) (Zwarts et al., 2011). The mutants that displayed suppressive epistasis (less aggressive behaviour) are sgl and LanA, LanA and Gp150 and Btk29A and Nmdar1 (Figure 1) (Zwarts et al., 2011). Pleiotropic effects of the mutant genes on brain morphology Mutant flies which have hyperaggressive behaviour also exhibit the unusual morphology of the mushroom bodies and

ellipsoid body (Rollmann et al., 2008). This means that mutant genes display the pleiotropic effect on brain phenotype. In particular, Gp150, Btk29A, LanA, and sgl homozygous mutants exhibit lower length of α -lobes of the mushroom bodies, and Gp150 together with Btk29A have β -lobes of decreased width compared to wild-type (Zwarts et al., 2011). Moreover, double heterozygotes show an increased variation in the width of β -lobes, both width and length of α -lobes and area of ellipsoid bodies. Again, there is an epistatic interaction between the specific genes which affect the length and width of mushroom heads in *Drosophila*. Specifically, the epistasis between LanA and Btk29A genes diminishes the length of α -lobes and the epistatic interaction between *neur* and *Nmdar1* decreases the width of α -lobes (Zwarts et al., 2011). Therefore, these pleiotropic effects of the mutant genes on brain morphology show that the mushroom bodies play an important role in the aggressive behaviour of *Drosophila melanogaster*.

Pleiotropic effects of mutant genes on expression of other genes
The whole-genome expression profiling shows that hyperaggression homozygous mutants have a different transcription profile from wild-type flies (Zwarts et al., 2011). In particular, there are 613 down-regulated transcripts in mutant flies and 556 up-regulated ones (Zwarts et al., 2011). All down-regulated transcripts include the genes for neural development, brain morphology and activity of the nervous system (Huang et al., 2009). The up-regulated transcripts, on the other hand, include the genes which code for metabolism, transcription and translation. The double heterozygous *Drosophila* mutants exhibit a different transcription profile as well. Specifically, the double heterozygotes show dominance and epistasis towards the expression of

other genes (Zwarts et al., 2011). However, there is a great deal of variation for the epistatic interactions which affect the gene expression profile.

Overall, the homozygous mutant genes exhibit significant pleiotropic effects on the expression of other genes in the genome of *Drosophila melanogaster*, specifically down-regulating the genes which are important in neural development that is associated with hyperaggression. Moreover the double heterozygotes amplify the pleiotropic effects even more.

Genetics of aggression in mice

Mouse is another outstanding model organism for behaviour genetics experiments because, not only, it allows the research based on experimental crosses but also this organism is genetically closer to human. Selected and inbred strains of mice demonstrated that aggressive behaviour shows the patterns of inheritance. Effects of chromosomes on male aggressionThe first evidence comes from the mouse strain *Mus domesticus*. The studies have shown that in Italy there are mice with four different chromosome number variants: 20, 13, 12 and 11 (Miczek et al., 2001). The latter three genomes are yielded from the first one due to the centromeric fusion of the chromosomes (Miczek et al., 2001). The mouse population with 13 chromosome pairs is increasing and replacing the population with 12 pairs. This is happening due to the differences in aggression levels between two populations. In particular, mice with 13 chromosome pairs have more elevated offense levels than the ones with 12 (Miczek et al., 2001). Moreover, there are hybrid mice arise due to the hybridization between populations with 11 and 20 chromosome pairs. The resulting mice show lower aggression levels than the parental populations (Miczek et al., 2001). Another example

shows that there is specific t region on the chromosome 17 which possesses the genes associated with offense behaviour in male mice (Miczek et al., 2011). The array of the genes which lie in that region is a haplotype. There are two possible haplotypes: + and t. When male mouse with haplotype +/+ is put in the cage with another male mouse but with haplotype +/t, the latter one showed more signs of aggression and started more fights (Lenington et al., 1996). What is more, the mice with +/t haplotype usually win the fights. The haplotype t/t is homozygous lethal. Therefore, because +/t mice are more offensive they have the reproductive advantage and this maintains both haplotypes in the population of *Mus domesticus* (Miczek et al., 2001). Y chromosome also plays the role in mice aggressive behaviour. This chromosome consists of two parts: first part that is specific to males; and another one which participates in recombination with X chromosome (Miczek et al., 2001). The region which recombines is called the pseudoautosomal region. Specifically, the non-pseudoautosomal region plays the role in mice aggression (Maxson 1996). The sex determining region on Y chromosome (Sry) is thought to be a candidate for the Y gene which is responsible for the offensive behaviour (Maxson 1996). However, this candidate gene doesn't show any pleiotropic effects on the testosterone levels which is always elevated during aggressive behaviour in male mice. The phenotype of this gene shows a strong dependence on the genetic background of the mouse and, in particular, there is a link between the non-pseudoautosomal and pseudoautosomal regions on Y chromosome (Miczek et al., 2001). Polygenic basis of mice aggression

The mutagenesis studies have identified a number of genes which play role in mice aggressive behaviour. By changing the

expression of these genes it is possible to elevate or diminish the aggressive responses in mice. Moreover, knocking out a particular gene doesn't have the uniform effect on the aggressive phenotype (Miczek 2001). For example, knocking out the neuronal nitric oxide synthase (nNOS) gene increases the aggressive behaviour. However, knocking out the oxytocin (OT) gene decreases the mice aggression. This clearly shows that aggressive behaviour exhibits the polygenic inheritance. The effects of the serotonin levels on aggressive behaviour Studies have shown that brain serotonin levels are one of the main characteristics of mouse aggressive behaviour. Clinical studies provide the facts that hyperaggressive individuals exhibit lower brain serotonin levels. This is either achieved by decreased levels of serotonin acid metabolite in cerebrospinal fluid or by diminished prolactin response (Mann, 1999). Moreover, pharmacological experiments on animal models have shown that it is possible to decrease the aggressive behaviour by inhibiting the activity of serotonin. Inhibition can be done by certain substances: l-tryptophan, dietary precursor of the serotonin, inhibitors of serotonin uptake or releasing agent such as fenfluramine which disrupts the vesicular storage of neurotransmitter and reverses the serotonin transporter function (Miczek et al., 2001). The serotonin antagonists are known to decrease the levels of aggressive behaviours as well, specifically at 5-HT_{2C} receptors (Miczek et al., 2001). This receptor is a G protein-coupled receptor which is one of the many binding sites for serotonin. However, serotonin agonists which act on the 5-HT_{1B} receptor are known to reduce aggressive behaviour more efficiently. Specifically, the substances such as anpirtoline and zolmitriptan, which act on this receptor as serotonin agonists, diminish the aggressive

response very effectively (Fish et al., 1999). The experiments have been carried out with mutant mice. Particularly, the KO mice were generated deficient in 5-HT_{1B} receptor and these mice displayed much more vigorous aggressive behaviour than the wild type mice (Miczek et al., 2001). Overall, it is clear that serotonin plays vital role in establishing aggressive behaviour in mice.

Genetic basis of human aggressive behaviour

Just as in animal models, human aggressive behaviour is an important complex trait which determines the success of an individual in a competitive human population. Back in the Stone Age the most aggressive males had the highest status in the society and mated with the best female in the tribe. Nowadays, the morals have changed however the concept of the competitiveness stayed the same. Therefore, even today, aggressive behaviour is an important quality which drives the social environment. Considering such an important role of aggressive behaviour throughout human evolution it is clear that this complex trait has a genetic basis. Human aggression can be divided in two subdivisions. The first type of aggression results from the lack of emotional sensitivity and is characterized by violent behaviour without any empathy (Craig and Halton, 2009). The second type, on the other hand, occurs due to the excess of emotional sensitivity which is associated with rage and elevated anxiety (Craig and Halton, 2009). It has been shown that there is a strong evolutionary relationship between aggressive behaviour and anxiety; moreover, the same region in the brain, called amygdala, is responsible for both responses (Craig and Halton, 2009). Specifically, the disruption of the neural circuits in

amygdala leads to elevated aggressive behaviour in humans (Davidson et al., 2000). Human aggression and heritability The studies have shown that heritability is responsible for 50% of the total variance (Rhee and Waldman, 2002). Moreover, the heritability for aggressive behaviour is higher for males than females. It is obvious that males exhibit the aggressive behaviour much more frequently than females and studies have proven this fact. A study involving 1000 individuals from age 3 to 21 years have shown that males are 2.4 times more likely to show the aggression than the females (Craig and Halton, 2009). Moreover, males show the most aggressive behaviour during the puberty when the levels of androgens is very high (Wilson and Daly, 1985). Therefore, it has been suggested that genes for human aggressive behaviour and androgen synthesis can be linked. What is more, the same as in mice models, Y chromosome is associated with human aggression (Craig and Halton, 2009). However, the Sry region on Y chromosome previously thought to be associated with hyperaggression is shown to have no effect on aggression (Gatewood et al., 2006). This means that other genes on Y or X chromosomes play the role in aggressive behaviour. The effects of certain genes on human aggressive behaviour The best evidence that certain genes are responsible for aggressive behaviour comes from a search of quantitative trait loci in mice. Quantitative trait locus is a region of DNA which possesses the genes that determine a complex quantitative trait. The study involved outcrossing and backcrossing the hyperaggressive mouse strain with the hypoaggressive one (Brodkin et al., 2002). The study identified two chromosomal regions which contain the candidate genes for aggressive behaviour (Brodkin et al., 2002). The identified regions

correspond to distal chromosome 10 and proximal chromosome X (Craig and Halton, 2009). The candidate genes identified on those regions are *Dagk1* gene coding for diacylglycerol kinase subunit and *Gria3* gene encoding glutamate receptor subunit AMPA3 (Craig and Halton, 2009). Indeed, both gene products play the role in neurotransmission which can account for their role in aggression. Candidate genes which determine the differences in aggression between sexes One of the best characterized loci for sex determination is the androgen receptor which contains two trinucleotide repeats (Craig and Halton, 2009). It has been reported that some Swedish males have shorter CAG repeats and those males exhibited increased verbal aggression (Jonsson et al., 2001). Moreover, recent studies involving Indian males that committed crime based on aggression show that they also have shorter CAG repeats. Therefore, it is evident that there is a linkage between androgen receptor gene and human aggressive behaviour. Candidate genes responsible for serotonergic effects on human aggressive behaviour Monoamine oxidases MAOA and MAOB are encoded by X-linked genes and participate in amines metabolism in CNS (Craig and Halton et al., 2001). MAOA oxidase catalyses the oxidation of epinephrine, norepinephrine and serotonin and is associated with human aggressive behaviour. Moreover, the MAOA mice null mutants exhibit an elevated aggression (Cases et al., 1995). Therefore, genetic markers such as SNPs and microsatellites within MAOA gene are good places to look for linkage to aggressive behaviour. Another candidate gene for aggressive phenotype is the gene encoding the tryptophan hydroxylase 1 (TPH1) which is involved in synthesis of serotonin. There are two SNPs in THP1 gene in intron 7: A218C and A779C

polymorphisms (Craig and Halton et al., 2001). In particular, 779A allele is associated with diminished levels of 5-hydroxyindoleacetic acid in males which is a main metabolite of serotonin in humans. Moreover, individuals homozygous for 779C allele have the lowest levels of 5-hydroxyindoleacetic acid and exhibit violent and aggressive behaviour associated with alcoholism (Nielsen et al., 1994).

Genetic basis of addictions

Addictions are mental abnormalities which are associated with an overuse of substances such as drugs, alcohol and nicotine. Addictions are also associated with aggressive and unsocial behaviour because the substances cause the adaptive changes in brain activity (Goldman et al., 2005).

Addictions are the worldwide problem which affects all aspects of life such as economy, families and society as a whole. It is believed that the both genetic factors and environment influence the likelihood that individual will be addicted to certain substances (Goldman et al., 2005). Different experiments were used to study the mode of inheritance of addictions however the most comprehensive knowledge comes from the study of monozygotic and dizygotic twins (Goldman et al., 2005). It has been shown that the more addictive the substance is the more inheritance it displays. For example, cocaine is one of the most addictive drugs and it shows the highest heritability (Figure 1), while the addiction for lesser addictive hallucinogens is less heritable (Goldman et al., 2005). The inheritance of addictions is same as for the complex diseases. Moreover, Mendelian pattern of inheritance is not applied in this case (Goldman et al., 2005). Two model of inheritance can be applied to the addictions: polygenic model and heterogenic model.

Polygenic model proposes that the vulnerability of an individual to be addicted to substances arises due to the influence of the variation at two or more genes (Goldman et al., 2005). This model also proposes that these several genes that affect vulnerability to the addiction must be inherited simultaneously. The second model of inheritance is heterogeneity. It proposes that variation at only one locus accounts for the likelihood that an individual will be addicted to harmful substances (Goldman et al., 2005). It is possible to distinguish between polygenicity and heterogeneity by comparing the concordance ratios of monozygotic and dizygotic twins. If the concordance ratio is high or very high it means that the trait is oligogenic or polygenic, respectively. Low concordance ratio, on the other hand, shows that the trait is heterogenic. In the case of addictions, there is no strong evidence that the complex trait shows polygenic inheritance (Goldman et al., 2005). The highest concordance ratio, equal to 4: 1, is shown by cocaine addiction which is associated more with oligogenicity than polygenicity (Figure 2) (Goldman et al., 2005). The inheritance of all other addictions is associated with concordance ratio of 2: 1 which implies the heterogenic mode of inheritance (Figure 2) (Goldman et al., 2005). Drug addiction is very often associated with comorbidity because it is common that when individual is addicted to one drug, he eventually develops the addiction to other drugs (Goldman et al., 2005). The genetic linkage studies shed light on the extent to which variation in the likelihood of a particular trait is shared or unshared (Goldman et al., 2005). This kind of studies is usually done in the relatives or, better, twins. The studies (Goldman et al., 2005) have shown that by comparing the risk for the two traits in twin pair it was found that there is a

variation in the bias towards a certain substance or different substances. That is some risk factors are shared between multiple drugs and some are specific to only one substance. Interestingly, there is comorbidity between the addiction to alcohol and to smoking (Goldman et al., 2005). The numbers alcoholics who are also addicted to smoking reaches 85% (Goldman et al., 2005). In order to identify the susceptibility loci for alcohol addiction and nicotine addiction linkage and association mapping were used (Li and Burmeister, 2009). Linkage studies were carried out with the population of American Indians and Caucasians which identified the locus on chromosome 4q responsible for the alcohol addiction (Li and Burmeister, 2009). The locus is linked to the alcohol dehydrogenase gene cluster composed of seven genes, of which alcohol dehydrogenase 1B (ADH1B) is the most important one in alcohol addiction (Goldman et al., 2005). Another important alcohol addiction gene was identified in Asian and Jewish American populations: aldehyde dehydrogenase 2 (ALDH2) gene (Li and Burmeister, 2009). Biochemically, ADH is responsible for converting alcohol in acetaldehyde and then ALDH metabolizes it further into acetate (Figure 3a). Both genes have the essential alleles: codominant His47Arg allele in ADH1B gene and dominant Glu487Lys in ALDH2 gene, respectively (Goldman et al., 2005). His47 allele increases the activity of alcohol dehydrogenase 1B, while Lys487 decreases the activity of aldehyde dehydrogenase 2. Both these events lead to accumulation of acetaldehyde (Figure 3b) which inhibits further alcohol intake (Goldman et al., 2005). Interestingly, both alleles are quite abundant in Japanese population. Therefore, majority of the population possesses either homozygous or heterozygous genome which protects against

addiction to alcohol (Goldman et al., 2005). It is thought that these protective alleles arose from a single ancient mutation; however it is unlikely that these altered genes were selected in order to give protection from alcoholism (Goldman et al., 2005). More probably, these gene variants were selected in order to give protection from the infectious protozoans: inhibition of alcohol metabolism kills the microorganisms (Goldman et al., 2005).

Genetic basis of human intelligence

Intelligence is a quantitative trait. The experiments were carried out which showed that when an individual carries out mental work, two factors determine his overall result: the level of cognitive ability of the individual and the increased ability for carrying out a particular mental exercise at the moment (Deary et al., 2009). The cognitive ability factor has been denoted with symbol g . Factor g influences thinking skills such as memory, language and mathematical skills (Deary et al., 2009). However, it is widely accepted that overall intelligence of an individual is determined by both genetic and environmental factors. In 1865 it was proposed that intelligence is a hereditary trait which is transmitted from one generation to another. Since that time it was concluded that intelligence is influenced by genetics with a variance ranging from 30 to 80% (Deary et al., 2009).