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Searching for genes responsible for human behaviour

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Summary

The paper presents issues connected with mapping new genes responsible for personality and instinctive traits in humans. The research focused on selecting appropriate investigation methods. An attempt was made to clarify some problems arising in the process of mapping genes responsible for behaviour.

Key words: personality traits, instinctive traits, strategies of mapping, methodology problems

Introduction

Instinct and personality

Temperament is characterized by a relatively simple genetic architecture [1], which seems to be interesting in sport. However, investigating the genetic background of human behaviour, even experienced researchers are bound to face numerous problems. Already at the very start of their work the first doubts arise concerning the nature of the analyzed trait, i.e. whether it is personality or instinctive. Instinct is a deeply imprinted algorithm used in solving the most basic problems [2]. It should be noted that the life of an individual consists of a series of problems (physical, emotional, intellectual, or those connected with coordination or volition, etc.), which the organism attempts to solve. However, it is not crucial for the process of survival whether or not they are actually solved. Those problems which need to be resolved in order for the individual or species to remain alive, are solved automatically using instinctive behaviour. Such behaviour is inborn and is not dependent on the environment. The differentiation between personality and instinctive features is not clear-cut. Let us consider aggression as an example here. It is instinctive. On the other hand, some forms of behaviour, such as irritation or dislike towards another person, while being manifestations of personality traits, are also connected with aggressive behaviour. For this reason, it is

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quite difficult to distinguish one from the other. Similarly, it is not easy to differentiate between instinctive sexual drive and such psychological features as excessive sexual excitability or sexism (sexoholism), etc. [3].

Another problem in the investigation of genetic background of personality traits (which will be further discussed in greater detail), or of instinctive traits in animals, is also to select an objective test. Let us assume that a researcher intends to map gene(s) responsible for shyness in hens. What could be an objective test classifying animals as shy or shyless? For example, in the simple "pencil test", the experimenter moves a pencil towards the animal's cage watching the reaction of the hen. This test makes it possible to determine shyness without removing hens from their cages. Shyness is measured by determining the degree to which the animal is withdrawing or escaping in its cage as a result either of a person approaching it or of being shown unfamiliar objects (e.g. a pencil) in front of the cage [4, 5, 6, 7]. This test is easy to administer and does not disturb the animal's life, which is important in the production process on a farm. May such a test, however, be used to assess – without a reasonable doubt – if a given animal was properly classified as belonging to the suitable experimental group. Thus, it is evident that while investigating genetic background of animal behaviour, the researcher faces numerous difficulties, which seem to multiply at the stage of interpretation of experiment results. In the case of mapping genes responsible for human behaviour it seems to be a little simpler.

Investigation of genetic markers – linkage or association?

Mapping is a term which refers to the determination of a gene locus on a chromosome (i.e. physical mapping) or the determination of the distance (measured in cM) between specific genes or markers (i.e. genetic mapping). When complex human behaviour is investigated, the most common procedure is to analyze candidate genes. Mapping of genes responsible for behavioural traits is not different from mapping other characteristics. There are two dominant approaches. The association analysis and linkage analysis.

The most commonly used method, applied so far to search for genes responsible for genetic diseases, has been linkage analysis, which thanks to the development of an increasingly accurate genetic map makes it possible to indicate the locus for the investigated diseases caused by one gene and heritable according to the Mendelian laws. So far, approximately 400 diseases have been mapped in this way. Linkage analysis turns out to be difficult in case of traits that are determined by several genes, where a single gene has a limited effect on the phenotype, and in which the phenotype is additionally modified by environmental factors. In such complex genetic determinations segregation analysis does not make possible the unambiguous fitting of the inheritance model of the trait, thus rendering linkage analysis impossible to perform. In such a case methods, which do not require the determination of the inheritance model, such as the allele sharing method or association studies, prove to be useful [8, 9, 10, 11].

Extended families with inherited susceptibility to a disease are not used in association studies, as it is the case in linkage analysis, but a large group of unrelated patients

suffering from the disease is formed, together with a control group. Investigations include a comparison of the distribution of alleles of different polymorphisms between these groups (case-control studies). If it is attempted to find the genetic basis for a quantitative trait, then the analysis is usually conducted on a population group and it consists in finding significant differences in the intensity of a given trait between subgroups of people with different genotypes for a given polymorphism. In both cases the application of larger groups of patients subjected to the examination makes it possible to detect genes with a less significant effect on the trait or the development of the disease, or to obtain larger reliability of the results.

Association studies detect differences in the distribution of alleles, and they may be the result of five basic causes: (I) direct association – the allele of a given polymorphism is found more frequently in diseased patients when it is the direct cause for the increased risk of the disease, e.g. it causes the change of the essential amino acid in the protein, thus changing its activity or structure in the protein, changing in this way its activity or structure, or affecting gene expression. (II) linkage disequilibrium – the allele does not affect the development of the disease, but it is in the state of linkage disequilibrium with the allele of another polymorphism located in the vicinity and directly affecting the development of the disease. (III) natural selection – the allele does not affect the development of the disease, but it improves the chances of survival or having children for patients with the disease. (IV) heterogeneity of the population – the difference in the distribution results from an improperly selected control group, which does not reflect the actual distribution for the investigated population, which may be connected with the population stratification. (V) statistical artefact – the observed difference in the distribution is a statistical artefact. Obviously, the first situation is the most advantageous, as it identifies not only the gene, but also the polymorphism directly responsible for the increased risk of the incidence of the disease. However, in order to exclude the possibility of linkage disequilibrium, which may well equally be the cause of the observed association, additional functional studies are necessary, which will confirm the effect of the polymorphism on the expression of the protein function. In the second case, i.e. linkage disequilibrium, only the locus on the chromosome is localized, and the respective polymorphism of the investigated gene may be located at the distance up to approx. 1cM. Then it is necessary to continue the search in the DNA segment with the length of approx. 2 million base pairs. The three other cases are disadvantageous, as they do not identify the true genetic background of the disease or even an approximate location of genes responsible for it. In order to avoid false positive results caused by the population stratification two methods may be applied at a slight increase in the costs of the study. These methods are going to be described below. However, the best method to limit the errors connected with the statistical artefact is to increase the size of the investigated groups.

Association studies have one major disadvantage in comparison to linkage analysis. The latter makes it possible to search for completely unknown genes in the whole genome, whereas performing association studies for the whole genome would require the examination of several thousand markers. Such a large number results from the fact that linkage disequilibrium concerns polymorphisms located at the distance not bigger

than approx. 1cM from one another. If the level of significance p=0.05 is assumed, then it results from pure statistics that for each 100 investigated polymorphisms five alleles falsely associated with the disease are obtained. In order to avoid such a situation the so-called Bonferroni correction needs to be applied, i.e. to lower the level of significance to p=0.05/n, where n is the number of examined markers (the Bonferroni correction should be applied if more than one marker is investigated). At three thousand markers the required level of significance would be such that only very big associations would be meaningful. Additionally, a lack of association in the investigated region does not exclude the possible presence of the given gene. In linkage analysis it is possible to exclude the region of a chromosome from further investigations, thus limiting the area in which the gene may be located. The above mentioned obstacles resulted in the fact that association studies are conducted primarily for polymorphisms in the sequence of the so-called candidate genes or in their immediate vicinity. Such genes are usually already well researched and on the basis of the functions of their protein products they are suspected to be responsible for the development of a disease or an investigated trait. Then association studies are much easier to perform thanks to the limitation of the analyses to a small number of polymorphisms. However, it needs to be stressed that in such a case obtaining an association is not certain and depends on the selection of "appropriate" candidate genes [12].

As has been mentioned earlier, genetic stratification of a population may be an obstacle in the selection of an appropriate control group. Thus, in order to avoid the problem the HRR (haplotype relative risk) or TDT (transmission test for linkage disequilibrium) methods are used [13, 14].

The formation of a control group in the HRR method consists in the determination of genotypes for the investigated polymorphisms in the parents of the diseased proband. The genotype of an "artificial" control individual is composed of the alleles, which were not transmitted to the diseased child. Such a control is completely appropriate. Possible disorders may result only from a recombination between the locus of the marker and the locus connected with the disease. However, appropriate statistical tests take into account these disorders and the effect is only a slight loss of power in these tests without any risk of false positive results. In case of the TDT approach the frequency of alleles transmitted to the diseased child is compared to the frequency of non-transmitted alleles. In this analysis due to the applied statistical tests, only parents heterozygous in the marker locus are used.

Both methods require the examination of 50% more people; however, the elimination of the false positive results compensates for the increased costs. A serious disadvantage of these methods is connected with the difficulties with their application in case of the diseases, which are developed at an old age, as at that time the parents of the diseased patients are no longer alive.

OGOD or QTL?

It is worth considering which type of inheritance occurs in case of genes determining behaviour in humans. Quality traits are often determined by a single gene. For

instance, if a single gene is responsible for a disorder (quality trait), only one type of inheritance is taken into account, i.e. one gene one disorder (OGOD) (Fig. 1). In the OGOD type inheritance it is assumed that single gene is necessary and sufficient, to develop a disorder [15]. Quantitative traits (QTL), determined by multiple, unspecified number of genes (none of which is sufficient for the disorder to develop) requires a completely different approach. The OGOD and QTL approaches characterized by both advantages and disadvantages for identifying genes that affect complex behaviours. In case of quantitative traits, it is possible to identify genes with major effects. The probability of gene detection depends, among other things, on the investigated population, its size, structure, gene effect and frequency, as well as the chromosomal localization in relation to the marker.

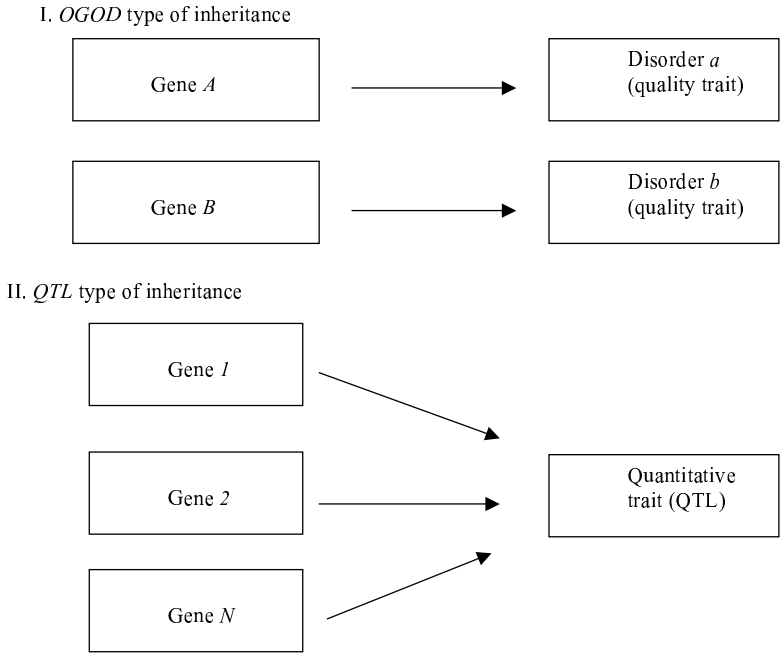

Figure 1. **The OGOD (I) and QTL (II) approaches of inheritance**

Markers which seem to be associated with human behaviour are repetitive micro satellite sequences [16]. It is assumed that 3-nucleotides CAG and CCG play a significant role here [17].

The research concerning the vasopressin receptor gene (V1a) suggests that it is associated with social behaviour [18]. The starting point for the investigations described in Nature were the differences observed in the behaviour and expression of V1a-receptor gene in prairie vole (Microtus ochrogaster) which is affiliative, biparental and monogamous, and montane vole (Microtus montanus) which is relatively asocial, non-paternal, and promiscuous. The neuroanatomical distribution of vasopressin V1a

receptors varied markedly between species with different forms of social organization. The species differences in the promoter structure of vasopressin receptor gene containing numerous repeated di- and tetranucleotide sequences and gene duplication in prairie vole may contribute to specific differences in V1a-receptor gene expression, and as a consequence differences in social behaviour. Mice (males are aggressive, polygamous and characterized the very similar pattern of V1a-receptor gene as in the montane vole) that were transgenic for the prairie vole receptor gene exhibit increased affiliative behaviour after injection with arginine vasopressin [18]. This effect was not observed in non-transgenic mice.

These findings indicate that the pattern of V1a-receptor gene expression in the central nervous system may be functionally associated with species-typical social behaviours in male vertebrates [18]. However, the methodology of animal behaviour studies presented in the above mentioned work may raise some doubts, as the animals were anesthetized during the 5-minute long monitoring, and the females were additionally tethered.

Investigating complex behaviour forms in humans – genetic architecture of personality

It is obvious that describing personality is not an easy task. The problem results - among other things – from differences in temperament, being the dynamic organization of the psychophysical systems that regulate automatic responses to emotional stimuli [19]. To some extent individual traits are assumed to be inborn and permanent within a lifetime, irrespective of culture or ethnic origin [19, 20]. It can be observed that experiences accumulated in the course of time result in mutual dependencies between all its dimensions. Thus, even in case of weak correlation within the network of multiple heritable dimensions produces complex non-linear dynamics of temperament is created, as each individual responds to experience with different motivations, sometimes conflicting ones [1]. There are attempts to understand those dependencies and to design the algorithm of behaviour. Correlation between dimensions limits the development of character, so that the set of probable directions of its development is narrowed in a complicated, but – also in our opinion – predictable way.

The basic instruments used in the investigation of genetically determined personality traits discussed are questionnaires. For many years psychologists could not agree on which were the important traits of personality. Finally, five broad traits (“super factors”) were selected as necessary to describe human personality – extraversion, conscientiousness, agreeableness, neuroticism and openness [21].

It is assumed that a properly designed and filled in questionnaire provides complete and objective information concerning personality and behaviour of an individual. It is assumed that the correlation between the self-evaluation and the assessment of the observer is positive [22]. However, there are serious problems with obtaining repeatable results even with the same questionnaires and analogous observations [23, 24, 25]. Most probably it is caused by the complexity of human psyche. It consists of two fundamental structures: inborn, which may be called the core and compared to the stone

of a fruit; and the acquired, which is referred to as personality and may be compared to the flesh of the fruit. An individual's personality to a large extent is formed by imitating and repeating the behaviour of other people (formed by imprinting behaviour), especially those the individual feels emotionally attached to: parents, teachers, or generally speaking – authority figures. In consequence, as a result of assimilation and absorption processes, behavioural patterns are formed around the inborn structure as an effect of imitating the behaviour of other people. In time, this natural psychic core gets masked by environmental factors, and the individual personality traits are mixed with personality traits acquired from other people. In an adult, inborn psychic traits leading originally to automatic reactions and natural behaviour become thus modified by the impact of the environment. While conducting an interview, the interviewer most often notices acquired elements of personality, rather than the inborn ones. Volition and thinking processes pose an additional problem here, making it difficult to determine traits during the interview in a decisive and precise way. These processes may mask or dominate natural and automatic manifestations of inborn behaviour.

There are several controversial methods, which make the observation of an inborn element possible. One of the options is to provoke an altered state of consciousness using alcohol or drugs [26, 27]. In such difficult to accept experiments, personality undergoes a process of partial or sometimes even complete "disintegration". Similar effect is caused by extreme situations, in which an individual faces the real threat to their health or life. It is commonly described as showing oneself in one's true colours.

Conditioning complex instinctive systems - an animal model

Some behaviourists assume that in case of animals, especially high vertebrate taxa, the mental states, as well as emotional [28, 29], volitional and consciousness processes occur [30]. However, it may be hypothesized that in several vertebrate taxa it is possible to talk even of subtle emotional states. Numerous disorders are caused by psychic factors: fear of separation, fear of isolation, isolation syndrome, separation depression, phobias, acquired aggressions, anxiety attacks, periodical fears, permanent fears, involutional melancholia, reactive depression appearing as a reaction to sudden emotion.

Some interesting observations may be included by an animal model. Modern breeding aims mainly at improving of performance traits. However, there is a tendency also to modify instinctive traits [31], and such a selection is sometimes successful even though our knowledge concerning genes responsible for animal behaviour is still limited. Numerous experiments conducted by Price [32] indicate that the process of domestication elevates the level of expected behaviour.

Observations of complex behaviour in animals were already carried out quite a long time ago [33]. A characteristic example of response to selection is the brooding instinct. It is necessary for a given species to survive. The use of incubators resulted in the weakening of this instinct. The group headed by Goodale in the course of only five years of selective breeding managed to reduce the broodiness instinct in leghorn hens from 90% to 20% [34]. Those were the pioneering works conducted in the 1920's. In

time the broodiness instinct disappeared completely in Leghorn hens and in Japanese quail [35]. However, in other species, such as the turkey, the effectiveness of such selection was low. It is assumed that the coefficient of heritability in case of broodiness is low and equals h^2=0.11 [36].

Conclusions

In behavioural genetics it is almost universally assumed that personality and instinctive characters are genetically determined [37]. Traits that seem worth mapping in humans are aggressiveness, intelligence, specific and general ability. The coming years will probably bring new results, broadening our knowledge of the subject. For this reason it is worth considering far-fetching consequences of such research, both social and legal.

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