Journal of Physiology - Paris 105 (2011) 190–194

Contents lists available at ScienceDirect

Journal of Physiology - Paris

journal homepage: www.elsevier.com/locate/jphysparis

Good use and misuse of "genetic determinism"

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ARTICLE INFO

Keywords:
Epistasis
Interactions gene × environment
Alternative splicing
Pleiotropy
Brain
Behavior

ABSTRACT

After sequencing the human genome, scientists believed it would be possible to draw up a list of diseases, morphological characteristics and behavioral traits linked to each gene, but the post-genome era has shown that while links between genes and phenotypes, including behavioral phenotypes, do exist, they are more complex than was previously thought. There is no linear connection between genotype and brain and between brain and behavior; consequently, genomic and behavioral levels of organization are not isomorphous. There is no isomorphism because one gene plays many different roles, which means that the integrative processes needed for the development and functioning of an organism inevitably occurs in situations of non-linear multiple causality. Pleiotropy and epistasis, interactions between genes and the environment, alternative splicing and neuronal integration are all crucial mechanisms contributing to the many and varied aspects of brain-related genes.

1. Introduction

Freud was firmly convinced that heredity plays part in the etiology of mental disorders. He proposed an "etiological equation" in which he inserted several parameters that were consistent with his theory of the neurosis and the "heredity" took a significant part in this equation (Chiland and Roubertoux, 1975–1976). Freud conception of heredity was stamped by his time and it was not surprising to observe that he trusted the Lamarck and Darwin concept of "heredity of acquired characters". The considerable energy that he developed to decipher the processes by which the dynamic factors might interact with heredity gives evidence for an exceptional open mindedness. Unfortunately, his scientific descent forgot often this important idea.

A century after, there is ample evidence for an implication of genes in behavioral traits and mental states (i.e., via brain states) in different species. We know now that the genotype modulates cognitive traits in pathological and non pathological levels (Carlier and Roubertoux, 2010). An extra-copy of HSA21 (trisomy 21 or Down syndrome), a hemizygous deletion of HSA7 at 7q11.23 (Williams–Beuren), a mutation of HSAX at Xq27.3 (Fragile-X) and an hemizygous deletion of HSA22 at 22q11 (Di George or cardio-velo-facial syndrome) induce brain and cognitive disorders (Carlier and Ayoun, 2007; Roubertoux and Kerdelhué, 2006; Roubertoux and Carlier, 2009; Vogels et al., 2002; Lacroix et al., 2009; Schubert, 2009). The brain modifications and the altered cognitive performances differ across the chromosomal aberrations indicating that the cognitive profile seems specific of a chromosomal pathology. Several genes are linked to autism, manic depressive illness or schizophrenia. Genes contribute also to the normal range of variation. The nicotinic receptor gene, the dopamine receptor 4 gene and the dopamine transporter gene modulate attention processes. The *COMT* (catecholamine O methyltransferase) gene mapped on HSA22 contributes to the dopamine circuit. Allelic forms of the gene are linked with cognitive flexibility. Gene targeting reveals that the addition, subtraction of one gene may change the brain or neuronal functioning and behavior in animal models of genetic research – mouse, drosophila or *Caenorhabditis elegans*. Pharmacological treatments correct the protein defect. The quarrel about the prominent role of genes or environment is not a scientific topic. The question is not to deny the contribution of genes to brain and to behavioral or psychological traits. Facts are stubborn. The question is not to know whether genes and psychological traits are linked but what is the nature of the link.

2. Multifunction of the gene

Several researchers saw the possibility to superimpose normal or pathological psychological traits on the genome map in the days following the human genome sequencing and even in the special issues of *Nature* and *Science* that presented the human genome sequence. They assumed a strict matching between genes and behavior. However, other authors expressed doubts about linear relationships between genes and phenotypes (Roubertoux

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doi:10.1016/j.jphysparis.2011.07.004

et al., 1990; Roubertoux and Nosten, 1990; Roubertoux, 2004; Roubertoux and Carlier, 2007).

The comparison of neuronal properties in different species confirms the non-linearity. Fig. 1 demonstrates that there is no correlation between the number of genes in a species and the complexity of the neuronal circuitry. We see that the complexity of behavior does not depend on the number of genes. The small worm *Caenorhabditis elegans* (*C. elegans*) has more genes than drosophila but drosophila behavior is more complex. Mouse and human have a similar number of genes and human behavior is richer than mouse behavior. Drosophila has more neurons and lesser genes than *C. elegans* that has only 302 neuronal cells. The number of ion channel families is similar in *C. elegans*, mouse and human species that have different number of genes. The number of G protein binded receptors is quite similar in *C. elegans*, mouse and Human. The published number of links between gene and behavior or brain functioning is twice higher than the number of existing genes in the mouse (Roubertoux, 2004; Roubertoux and Carlier, 2007).

A rapid survey of the papers on published gene targeting or overexpression in the model species indicates that each modification induces several phenotypes including neuronal and behavioral phenotypes. Targeting *Clk-1* in *C. elegans* modulates defecation, swimming, egg laying, crawling, pharyngian pumping (Felkai et al., 1999). Targeting the *5Ht1br* (serotonin receptor 1b) mouse gene induces a large set of physiological reactions (embryonic development, heart disorders, artery spasm, prostate cancer) and modulates brain and behavior (Learning, Long Term Potentiation – considered as an index of synaptic plasticity - drug consumption, aggression, ultrasound production, attention, aggression, depression). This is not an exception since the same observation can be made with other genes. The *αCaMKII* (alpha calmodulin kinase II) mouse gene impairs learning, Long Term Potentiation, increases aggression or reactivity to pain, favors epilepsy and modulates the development of the retina. The genetic of development provides other illustrations of the multiple functions that could be performed by an individual gene (Roubertoux et al., 2010). Genetic engineering offers the possibility to delete either a gene or an exon or to over-express one gene. The results from the genetic modifications demonstrate that there is no isomorphism between the genome level and the phenotypic level even if there is a link between the two levels.

The absence of isomorphism is not specific to the genome-behavior relationships. It is also the rule in the genome-brain, brain-behavior or nervous system-behavior relationships as shown by the two following illustrations. The same interneuron can induce two behavioral responses in the marine mollusk *Tritonia diomedea*: rhythmic swimming, which uses the muscles; or non-rhythmic crawling, which uses the ciliar system. The versatility or multifunctionality of the interneuron depends on the neuronal context; whether the interneuron triggers swimming or crawling depends on the activity of its adjacent neurons (Popescu and Frost, 2002). Similarly, the concept of a 'reflex' supported the hypothesis of ultra-specialized, hardwired neuronal networks. For example, the stretching reflex was seen as the prototype of an autonomous, specialized function, but it seems now that the sensory-motor units provide the appropriate response and are the elementary components of the stretching response, rather than the motor neurons (Clarac et al., 2000). The lack of isomorphism between the levels of biological organization appears as a general property of living systems.

3. Mechanisms resulting in the multifunction of the gene

What are the genetic mechanisms resulting in the multiplicity of the functions of the gene?

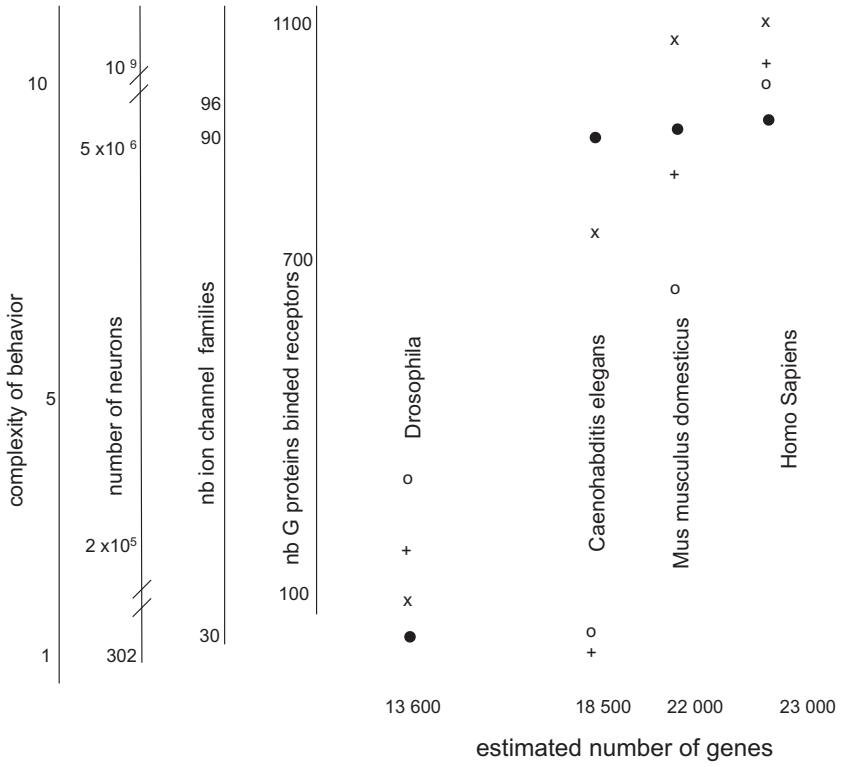

Fig. 1. Relationships between the number of genes and three neuronal properties in four species. The complexity of behavior is expressed first axis on the links. The number of neurons, number of ion channel families and the number of G proteins binding receptors are indicated on the second, third and fourth axes. The number of genes is indicated on the *X* axis. O represents the estimated complexity of behavior in the species; + represents the estimated number of neurons in the species; □ represents the number of ion channel families in the species; × represents the number of number of G proteins binding receptors in the species.