

Genes to Cognition: A Neuroscience Consortium for the Scientific Community

The Genes to Cognition (G2C) Programme (www.genes2cognition.org) is a systematic integrative research program that bridges basic and clinical neuroscience and was initiated by support from the Wellcome Trust. G2C is an international consortium of scientists studying synaptic molecules and their role in behaviour and disease. The G2C Programme collects and integrates data in the areas of psychiatry, human and mouse psychology, cellular neurophysiology and cell biology, proteomics and biochemistry, molecular biology, human and mouse genetics and genomics.

As neuroscientists we seek to tackle one of the great scientific challenges - understanding the mechanisms of human behaviour – as well as help relieve the enormous burden of neuropsychiatric disease on our community. Lessons learned from the study of cancer and cell growth have told us that there are far more molecules, cell biological processes and ultimately disease types than ever expected. Importantly these insights have emerged not from one technique or investigator but from integrating a diverse range of studies. There is no reason to suppose that the biology of brain diseases will be any less complex.

In several areas of biology it is now clear that large scale projects with publicly available data and

distributed resources make an important contribution alongside traditional individual projects and collaborations. Large scale projects, through economy of scale, can expedite progress and remove the need (and cost) for many basic experiments in specialist laboratories.

G2C scientific strategy

The central theme of the G2C project is the study of multiprotein complexes, called NRC (NMDA Receptor Complex) or MASC (MAGUK Associated Signaling Complex), found at excitatory synapses in the mammalian brain. These complexes were isolated from a mouse brain and found to have a surprisingly large number of proteins (~185). Over 50 of these proteins have been implicated in human diseases. In experimental animal models such as the knockout mouse or drug studies there have been ~50 genes reported to alter the properties of synaptic plasticity and forms of behavioural plasticity. These behaviors include learning and memory, pain, visual and somatosensory plasticity amongst others. G2C scientists are conducting a systematic study of mutations and polymorphisms in mouse and human genes encoding postsynaptic proteins, and exploring how these genes influence a broad range of phenotypes, especially cognition.

Modular organisation of the consortium

The consortium has a modular architecture incorporating specific scientific disciplines or activities (Figure 1). Details of people involved with these modules can be found on the G2C website www.genes2cognition.org. These modules provide a natural way for collaborators to join the program.

The connection between mouse and human genetics is central to the strategy. In brief, the human genetics involves clinical investigators interested in diseases of the brain (e.g. cognitive disorders; mental retardation, Alzheimer's, schizophrenia, bipolar disorder) and normal cognition (e.g. cognitive ageing and individual differences). Human DNA samples are sequenced and analysed for the NRC/MASC genes and variants identified. Because of the extensive information on these molecules in the G2C program from basic science studies the human genetic variants can be rapidly evaluated. Thus there are several complementary aspects to the collaboration between clinical and basic scientists.

The study of the genes in mice typically involves the generation of knockout mice followed by the G2C phenotyping pipeline (Figure 2). This involves molecular, neuropathology, electrophysiological and behavioral phenotyping. The data and all reagents are made available to collaborators and widely distributed. One important vehicle for distribution of data is the G2Cdb.





G2Cdb: an integrative databases for synapse biology

The G2C program has created an integrative database (G2Cdb) that stores data from the G2C research and links multiple databases including human genetic, expression and proteomic databases. We curated a comprehensive database of mouse knockouts that have been studied in synaptic plasticity and a behaviour database. We aim to make these databases repositories for published data (curated manuscripts), data generated in the G2C program as well as place for data submission directly by external groups.

Education and training in G2C

Scientific research into the basis of behaviour and disease is of great interest to lay people. We recognise the importance of education on all aspects of the research program and rather than develop educational material after the research has been completed we are developing that material from the outset. The major collaborator in the educational program is the Dolan DNA Learning Centre at Cold Spring Harbor (www.DNALC.org). They are developing an education website and materials for schools and colleges called 'G2C Online', which will contain extensive information, videos and interviews that inform on all aspects of the G2C research program.

Participating in the G2C program

The G2C program welcomes new collaborators. The interactions, sharing of information and reagents through the program, are proving to be very helpful in speeding progress. Using the modular framework of the program provides a simple way to identify connections. There are also training opportunities for students and scientists wishing to learn new methods. Send any enquires directly to Seth Grant (sg3@sanger.ac.uk) or through the website contact our collaborators.

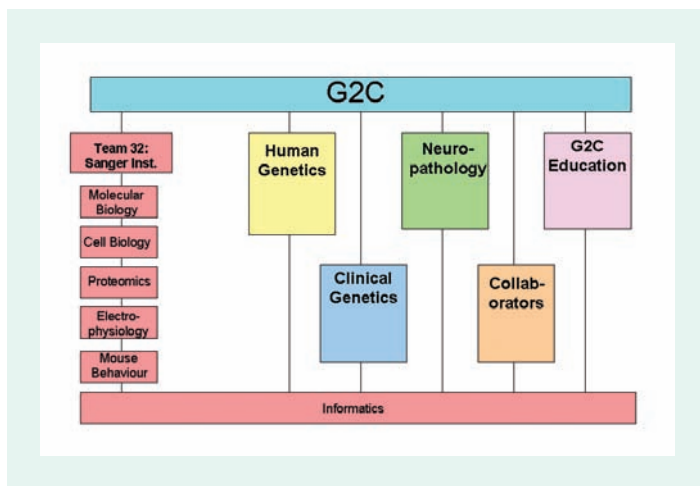


Figure 1. G2C's modular organisation.

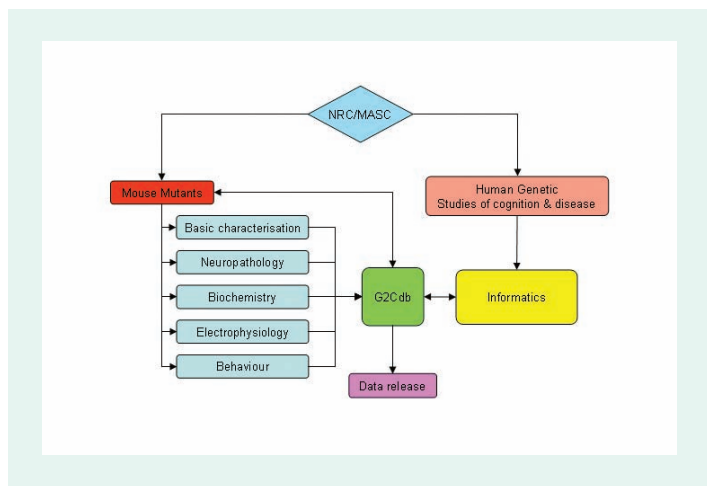


Figure 2. The G2C analysis pipeline.