Genes and the placebo effect

Are you easily pleased? The effectiveness of a placebo may depend on someone's DNA

Give someone who is sick a sugar pill that you have told him is a powerful drug, and it will often make him feel better. Even if you tell him what it really is, he may still feel better. The placebo effect, as this **phenomenon** is known—from the Latin for "I shall please"—is one of the strangest things in medical science. It is a boon to doctors and a bane of those running clinical trials, who must take account of it in their **designs**. But how it works is obscure.

Knowing that would open up a new field of medicine. If placebos could be **exploited rationally**, perhaps in conjunction with **functional** drugs, better treatments might be effected. Drug testing would also be simplified if trial **designers** were able to **select** those more and less susceptible to the effect as the needs of the trial dictated. That would save effort, time and money.

One thing that is known about the placebo effect is that it **involves** several brain systems, each under the control of a particular type of messenger molecule, called a neurotransmitter. These systems, like everything else in the body, are **regulated** by genes. This has led some **researchers** to ask whether different **versions** of the genes in question might modulate a person's susceptibility to placebos.

A review of these researchers' studies, **published** recently in *Trends in Molecular Medicine* by Kathryn Hall of Harvard Medical School, and her colleagues, suggests genes do indeed seem to matter. Dr Hall looked for **links** between the placebo effect's strength and certain mutations, known as single nucleotide polymorphisms (SNPs), in which a single DNA "letter" in a gene is changed. Altogether she found 11 genes, in four neurotransmitter systems, where SNPs made a difference. Five were in the system **mediated** by dopamine, which includes the brain's reward centres. Four were in the system mediated by serotonin, which **regulates** mood. And the opioid and endocannabinoid systems had one each.

As their names suggest, these two systems are **affected** respectively by opium and its **derivatives**, and by cannabis and its derivatives. The other two are affected by cocaine, which blocks the retrieval of dopamine into nerve cells, thus increasing its power as a messenger; and Prozac, which has the same effect on serotonin, and is used as an antidepressant. It is not hard to imagine a **similarity** between the workings of these drugs and what happens in the brain when the placebo effect is operating.

The genes for which most placebo-related SNP **evidence** exists encode enzymes called catechol-O-methyltransferase and monoamine oxidase. Both of these are parts of the dopamine system, and both are responsible for metabolising dopamine, and thus **regulating** the **amount** of it around. (Indeed, monoamine oxidase is the **target** of a second type of antidepressant, which has a different mechanism from Prozac.) People with different versions of either of these genes experience the placebo effect to different **degrees**. These various versions, moreover, are all commonplace, suggesting differences in placebo **perception** may be widespread.

The studies Dr Hall drew on are all **preliminary**, so they are better regarded as pointers for further investigation than as prescriptions for action. But if such investigations confirm these results, it may be possible to **predict**, on the basis of a genetic test, whether someone will **experience** a strong placebo effect or not. That could allow a doctor to **lower** the prescribed dose of a drug, if a strong placebo effect is expected. It could also permit drug companies **conducting** trials to **exclude** the placebo-susceptible, and thus to get a better sense of the **underlying** efficacy of what is being tested.

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