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A Review of Egan et al. 2004: New Frontiers for IVF and Gene Therapy?

Author: Ben Michael Mathews
www.Michaelmathewsart.com

A paper on genetic engineering, designer babies, in vitro fertilisation (IVF), gene therapy, new medical opportunities and the ethical issues and value judgements surrounding.

A Review of Egan et al. 2003: New Frontiers for IVF and Gene Therapy?

A review of a study by Egan, Kojima, Callicott et al. (2003) shows that it may have important implications in terms of preventing illnesses associated with the hippocampal function. In this paper they write that their results are important for four reasons: the results demonstrate the feasibility of studying, *in vivo*, the effects of specific genes on hippocampal biology and memory; that the basic mechanisms of long term potentiation (LTP) and spatial memory in lower species have been conserved in the highly evolved episodic memory of humans; a specific genetic polymorphism may be a factor which is likely to have an impact on the susceptibility to or expression of illnesses that involve hippocampal neuronal integrity; and finally that the single nucleotide polymorphism (SNP) examined is important in intracellular trafficking and secretion of Brain-derived neurotrophic factor (BDNF). Perhaps the greatest implications from this study at the moment are found in the finding that this SNP may impact the susceptibility to or expression of illnesses that involve hippocampal neuronal integrity. To put it simply the paper says there are two alleles: met and val, and an individual can inherit either of the two varieties on either chromosome; e.g. perhaps they may have 2 of either variety or one of each variety. Specifically it is shown that those with the met/met or val/met genotype showed abnormal activation of the bilateral caudal hippocampus and, on average, lower scores on episodic memory tests than those individuals with the val/val allele. This may put the population with the met genotype at higher risk in terms of developing problems or illness related to these functions at some stage in their life. Given that we now have the technology such as *in vitro* fertilisation (IVF), preimplantation genetic diagnosis, and gene therapy, this technology gives us the ability to use the information about the advantages of the met allele to either select the healthier embryo in IVF or to change the allele postnatally. This article will focus on the implications in this area because of what is believed by the author to be the greater relative importance of these implications.

One of the implications that has an effect on our choices in life is that this knowledge in conjunction with IVF may give some the opportunity to select against this gene in their children. IVF is a procedure that was initially developed to treat infertility, though it has become apparent that this procedure may have other applications too. In this procedure fertilisation takes place outside the potential mother's body and sperm and egg are put together in a laboratory to form an embryo. However, instead of directly transferring embryos to the prospective mother's womb, the embryos can first be tested for faulty genes. This testing is known as preimplantation genetic diagnosis (PGD). Of course, what is and is not a faulty gene is an arbitrary assessment. Given that Egan et al. (2003) have found that one gene that gives lower episodic memory scores and may increase susceptibility to illnesses that involve hippocampal neuronal integrity, we could consider this a faulty gene that we wish to avoid. PGD is currently being employed for the purposes of detecting chromosomal abnormalities or inherited genetic abnormalities (Lee, 2002). Furthermore the case has been argued

on moral grounds for the selection of non-disease genes that will produce children that will have the best life (Bandura, 2006; Baylis & Robert, 2004; Salvulescu, 2001). It is warned however, that there must be equal access to “intelligence selection” in order to avoid creating greater inequality in the world (Birch, 2005). As such the case may be more problematic than it appears superficially. By lessening suffering in those families that select for such beneficial genes, we may also run the risk of making others relatively worse off. Contrary to this argument however is the theory that everyone would be functioning at a higher level and productivity would increase (Newson & Williamson, 1999). Despite these theories the direct implications of this research for the area is that now we actually have a gene that could potentially improve cognitive abilities and decrease susceptibility to illness. Putting aside the value judgements about whether the greater indirect consequence on society would be a worthy outcome, the only factors holding us back are related to ethical considerations due to any possible risks of the procedure. Nick Bostrom (2005) argues that if safe and effective alternatives are available, it is irresponsible to risk starting someone off in life with the misfortune of congenitally diminished basic capacities or an elevated susceptibility to disease. Since it is now believed that we have evidence to suggest that the Val gene confers an advantage and may decrease susceptibility to illness, that the technology is there and that the procedure is safe, it seems that we should be offering the option to use PGD to screen for the presence of a Met on this nucleotide.

Of course it is not just children who have yet to be born that could potentially benefit from the research by Egan et al. (2003), but also people already living with the Met genes. Those already living could choose to undergo testing for the genes, and if they prove positive, perhaps someday gene therapy might provide an optional way of changing their genotype. Studies that have identified the complex regulatory mechanisms involved in the maintenance of normal cellular function and the roles assumed by different genes, such as those by Egan et al (2003) and Harri, Egan et al. (2002), have paved the way for a new type of therapeutic approach (Haim & Steiner, 2006). This new approach, called gene therapy, is based on the alteration of cellular phenotype by genotype manipulation. This method was originally contemplated for the wide array of monogenetic inherited disorders, such as cystic fibrosis and Duchene muscular dystrophy, for which conventional pharmacotherapy is unable to provide any adequate response (Haim & Steiner, 2006). Of course, in the paper by Egan et al. (2003), we are dealing with a monogenetic inherited polymorphism that may similarly be difficult to treat directly. Currently there have been over 1,300 gene therapy trials approved worldwide (<http://www.abedia.com/wiley/>, 2008), and several of these have been directed at treating neurological diseases such as parkinsons disease (Aminoff, 2003; Marks, 2006-07). Indeed as part of their study Egan et al. (2003) used some of the techniques involved in gene therapy in the manufacture of their Val- and Met- BDNF cultured cells from which they measured the BDNF expression. However the procedure in vivo is still not entirely risk free. The treatment is often performed by using modified viruses (vectors). These vectors are manufactured so that they deliver normal rather than viral genes

and, when treating an abnormality in the nervous system, they are usually delivered to the brain by direct intraparenchymal injection (Haim & Steiner, 2006). The risks involved then include: the viruses becoming virulent again; the vectors replacing the wrong genes and thus causing cancer; the body creating a dangerous immune response, even to avirulent vectors; tissue damage and secondary damage to the blood brain barrier by the needle tract. These were not issues as such in the study by Egan et al. (2003) partly because they were performed in simple cultures rather than in living humans. For living subjects this gene may not be pose as much of a threat as the procedure at the moment. As such, it may be awhile before medical professionals can say benefits this technology and information will outweigh the potential risks and costs.

Despite all of this it should be taken into account that Egan et al. (2003) state that the magnitude of BDNF genotype on in vivo measures of hippocampal function is small and they also state that such functions are likely to be constructed by many genes working together. For broad cognitive capabilities such as intelligence it has been hypothesised that individual genes will, on average, only account for 1% of variance (Plomin, 1999). As such altering this or other particular genes on their own is unlikely to create drastic changes, rather it symbolises the path ahead that may lead to a time when we have a much greater understanding of the function of genes, and perhaps greater control over there expression. It must also be taken into account that genes are not the only factors that influence levels of BDNF and memory, but that many environmental factors such as levels of exercise and diet are also important (File, Hartley, Alom, & Rattray, 2003; Gomez-Pinilla, Ying, Opazo, Roy, & Edgerton, 2001). None the less there are some among us who will inevitably attempt to use this technology and this information, and some of whom it may benefit, some of whom it may be of little benefit to. No matter the case we must be wary that our understanding of the function of these genes may not be complete. For instance, if we go ahead with using gene therapy and IVF to select against the gene on the basis of our current knowledge, we may later discover that there were other reasons to keep the gene. The met gene, may have beneficial pleiotrophic effects that counterbalance the problems examined in the article by Egan et al. (2003). We say a gene has pleiotrophic effects when a gene has two or more apparently unrelated effects. For example, a gene associated with cystic fibrosis may also confer advantage by increasing resistance to Salmonella typhi (Baylis & Robert, 2004). Enhancement efforts without knowledge of any undiscovered pleiotrophic gene effects could then potentially reduce human genetic diversity in dangerous ways. What is significant about this paper however is that it is the first step toward gaining meaningful knowledge of the function of single genes and their contribution to cognitive abilities. This interesting information then gives us the option to change this gene and thus alter the cognitive abilities should we value the change enough.

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