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NEWS AND COMMENTARY

Complex Disease

Pleiotropic gene effects in obesity and type 2 diabetes

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The idea that a common set of genes with pleiotropic (multiple diverse) effects might influence obesity, type 2 diabetes, and related traits such as sensitivity to the effects of insulin, is not novel,[1] but examples of specific common genetic determinants have been lacking. A recent paper in *Nature Genetics* now provides just such a link.

The new work shows that the gene *ENPP1* (which encodes ectonucleotide pyrophosphatase/phosphodiesterase 1, also known as plasma cell membrane glycoprotein PC-1) mediates some of the effects of the hormone insulin on glucose metabolism while simultaneously being associated with obesity and type 2 diabetes.[2] This finding supports the idea that a common molecular mechanism underlies features of the body's response to the effects of the hormone insulin as well as the predisposition to develop obesity and type 2 diabetes. These results also highlight the possibility of novel common avenues for treatment of these conditions.

Obesity and type 2 diabetes are metabolic disorders whose prevalence has risen in parallel over the past two decades to epidemic proportions. Western lifestyle and diet have certainly had a role in this rise but it is also well established that genetic determinants influence both of these conditions. Furthermore, it is likely that some of those genetic determinants are common. However, the identity of the molecular 'missing link(s)' between obesity and type 2 diabetes has been hard to pinpoint. In fact, 4 years ago work carried out in mice suggested the hormone resistin as a possible link between obesity and type 2 diabetes.[3] However, despite widespread initial excitement, this finding has not been corroborated in humans.

In their investigation Meyre *et al*[2] used family studies of childhood obesity to identify a gene on chromosome 6q with DNA variants that impact on obesity predisposition, as well as on type 2 diabetes risk. In those families for which there was prior evidence that their predisposition to obesity was linked to chromosome 6q, the authors observed that the obese children and their parents were more likely to also have problems with their glucose metabolism than other obese subjects. Based on these observations the authors hypothesized that a single gene with pleiotropic effects was likely to predispose these families to obesity, abnormal glucose metabolism and type 2 diabetes. Armed with this hypothesis and taking advantage of other 'gene hunting' experiments in obesity, insulin resistance and type 2 diabetes,[4–10] the authors could delineate a smaller interval on chromosome 6q that was more likely to harbour the gene of interest. Within this region the *ENPP1* gene had a number of features which made it a good 'suspect'.

Interest in *ENPP1*, within the context of glucose metabolism, was first raised when Maddux *et al*[11] found that *ENPP1* activity was raised in a proportion of type 2 diabetes subjects. They also showed that overexpressing *ENPP1* in cultured cells reduced insulin-induced activity of its receptor, possibly through the direct interaction of ENPP1 with one of the insulin receptor's subunits.[12] Subsequently, a polymorphism in this gene that underlies an amino-acid substitution, K121Q, was suggested to be associated with resistance to the effects of insulin on glucose metabolism.[13] However, subsequent findings were equivocal: some studies supported the initial hypothesis while others did not.

The debate over whether *ENPP1* is or is not involved in these metabolic disorders appears to be resolved in this new study, which is the largest of its kind that focuses on this gene. Detailed sequencing of *ENPP1* in obese children with evidence for linkage to the chromosome 6q locus and nonobese adult controls identified a number of polymorphisms in this gene. Further detailed testing in families with obesity indicated that the K121Q polymorphism is associated with obesity and identified two other polymorphisms as additionally contributing to obesity risk. These three polymorphisms were found to comprise a risk haplotype for obesity. Population and family studies indicated that this haplotype is associated with childhood obesity, morbid obesity in adults and less severe forms of adult obesity.

The authors went on to measure serum levels of ENPP1 and found that in children there was a positive correlation between measures of body fat and ENPP1 levels. When lean children were studied the presence of at least one of the polymorphisms from the three polymorphism haplotype was associated with a significant increase in the levels of ENPP1. Lastly, the authors assessed the effect of the risk haplotype on variation in glucose metabolism traits in 474 obese children, their parents and additional subjects with type 2 diabetes from two different European population studies. This assessment provided evidence for a role of this haplotype in glucose metabolism.

Based on their findings the authors hypothesized that genetic variants within *ENPP1* influence circulating levels of this protein, and that increased levels of protein inhibit the actions of insulin on its receptor in the brain and muscle. This in turn, could lead to increased deposition of fat. So it seems that *ENPP1* could be the link between resistance to the effects of insulin, obesity and type 2 diabetes.

Although this presents an exciting hypothesis how the specific genetic variants might be acting is not known and further experiments to explore this will be invaluable. Moreover intriguingly it seems that inactivating *ENPP1* mutations also lead to arterial calcification: a condition that has no features of abnormal energy or glucose balance.[14] This raises questions relating to the normal function of *ENPP1* and how different mutations might be leading to such distinct phenotypes. Also the exact cause–effect relationship between the presence of these genetic variants, increased levels of *ENPP1* and the effect of this on obesity and type 2 diabetes requires further validation studies. These would preferably assess levels of this protein in subjects prior to obesity and type 2 diabetes onset and follow those subjects overtime. Such a study would be able to establish whether individuals with these genetic determinants had higher levels of ENPP1 protein and furthermore whether those subjects with the highest levels of ENPP1 would also have a higher chance of developing obesity and type 2 diabetes. Lastly, although the genetic determinants described in *ENPP1* appear to associate with obesity they do not fully account for the original linkage signal on chromosome 6q. So further work is still required to fully understand the original 6q linkage results: other genetic determinants that impact on human obesity might still be at large in this region… However, this is an exciting beginning: a common molecular link between insulin resistance, obesity and type 2 diabetes has been substantiated■

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