Reviewer's report

Title: Adipose Transcript Networks Across Finns and Mexicans Identify Novel Triglyceride Genes

Version: 2 Date: 11 July 2012

Reviewer: John Whitfield

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This paper sets out to identify significant associations between gene expression in human adipose tissue and serum triglyceride concentration, with the aim of identifying gene products or pathways which contribute to variation in circulating triglycerides. The results show significant and consistent findings across two Finnish samples and a Mexican one.

The authors use a bioinformatic method for clustering and summarising co-expression of multiple genes. I am unwilling to comment on the validity of this method but it is intuitively appealing and appears to have been described and used in many previous studies, referenced in this paper.

The points below constitute Major Compulsory Revisions in the sense that the authors need to consider and either refute or adopt them before publication.

1. The authors refer to ‘triglyceride genes’ in the title and to ‘novel TG genes’ in the first paragraph of the Discussion. This implies that the genes affect triglycerides, which may well be the case, but the method is based on association between two phenotypes and does not necessarily identify the direction of causation. For example, this method might well find associations between the level of a hormone in the serum and expression of a group of genes in its target tissue but they would not be ‘insulin genes’ or ‘oestriadiol genes’ in the sense implied by ‘triglyceride genes’ here. Moreover it is possible that an association between gene expression and the phenotype (in this case triglyceride) could depend on some unmeasured and confounding variable.

The causation issue can also be seen in relation to BMI. Figure 1 shows that both the blue module and the yellow module are associated with BMI as well as with triglycerides. Therefore gene expression in subcutaneous adipose tissue varies with adiposity, i.e. the total mass of adipose tissue. This is interesting in itself, and also raises the question whether total fat cell mass changes gene expression or gene expression changes total fat cell mass.

The authors should give a little more space to their concept of ‘triglyceride genes’ and say that inferences about causation based on this method must be supported by biological arguments as well by statistically significant associations.

2. The Abstract uses the term ‘independent’ and the Background states that ‘triglyceride levels have been implicated as an independent risk factor for CHD’, but whether triglycerides are independent has long been controversial. Statistical
independence has mostly been judged through multiple logistic regression, and most (but not all) studies have found that adjustment for other risk factors removes the association with triglycerides. (See, for example, Major lipids, apolipoproteins, and risk of vascular disease, JAMA 2009;302:1993-2000.) The Mendelian Randomisation approach taken in reference [1] is subtly different because it addresses causation; it too has its problems because it is necessary that APOA5 variation has no effects on anything except triglycerides and it is hard to be sure of this. There is no problem in saying that triglycerides are metabolically important and their variation is of interest, but because the article starts by justifying study of triglycerides with reference to CHD the second sentence of the Background needs some qualification.

3. The fourth paragraph of Background says ‘Previous studies have analysed gene expression data from subcutaneous adipose tissue …’ It would be desirable to have references to these studies.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests