Lewis phenotypes, insulin resistance, and risk of ischaemic heart disease

The Lewis blood group has been described as a new genetic marker of ischaemic heart disease and alcohol has been claimed to be particularly protective to those with the Lewis phenotype associated with the highest predicted risk. These results come from the Copenhagen Male Study, which has followed a cohort of 5249 men since 1970. In 1985 all survivors were traced and 3387 men aged 53–75 years agreed to participate in a further four year prospective study. Several factors were recorded including alcohol and tobacco consumption, physical activity, height, weight, and blood pressure. Blood was taken for several investigations including lipids and Lewis phenotypes. At baseline those who had Lewis blood group Le (a− b−) had a higher serum triglyceride, higher body mass index (BMI, weight/height²), and a lower high density lipoprotein (HDL) cholesterol concentration than those of other Lewis phenotypes. Over the following four years the relative risk of death from ischaemic heart disease was significantly increased in Le (a− b−) individuals, even after correction for baseline age, BMI, HDL cholesterol, and triglyceride. Daily consumption of 1 to 4 units alcohol was reported to have a protective effect in those at highest risk of ischaemic heart disease as predicted by their Lewis blood group.

The Lewis group on red blood cells was first described by Mourant who was investigating red cell agglutination. It is the result of a complex interaction between several genes on chromosome 19 that are closely linked to the secretor status of the blood group antigens in saliva. There are three possible Lewis phenotypes: Le (a + b−) (20% of Europeans, almost always non-secretors); Le (a− b +) (70% of Europeans, almost always secretors); and Le (a− b−) (10% of Europeans, usually but not always secretors).

The findings of the Copenhagen study could indicate that the Lewis phenotypes are in linkage disequilibrium with a locus determining susceptibility to ischaemic heart disease on chromosome 19. Subjects with Lewis blood group Le (a− b−) were shown to have a disease profile similar to that proposed by Reaven in his confusingly named “syndrome X”. Reaven’s syndrome X comprises insulin resistance, hypertension, and glucose intolerance, together with increased concentrations of very low density lipoprotein (VLDL) and decreased HDL concentrations. The central pathogenetic event and its association with hypertension and heart disease remains the subject of much debate. Patients have usually been insulin resistant for several years before diabetes becomes apparent. Thus insulin resistance may be the initiating factor, with hyperinsulinaemia occurring as a consequence and diabetes becoming evident when the beta cell fails.

Though they did not measure insulin resistance, the group that did the Copenhagen study suggested that individuals with Reaven’s syndrome X or insulin resistance may have had an abnormality linked genetically to the Lewis phenotype on chromosome 19.

Subjects characterised by a particular pattern of LDL particles have recently been shown to have several features of Reaven’s syndrome X and significant linkage of this phenotype with the LDL receptor locus on chromosome 19 has been demonstrated. The insulin receptor gene is also known to be located on chromosome 19 and some studies have reported an association between insulin receptor polymorphisms and insulin resistance or type II diabetes mellitus. Abnormalities in the insulin receptor itself have been found in only a handful of cases of insulin resistance and are not responsible for the vast majority of cases. Groop et al found that the glycoprotein synthase gene is also encoded on chromosome 19, and that a polymorphism within it is associated with non-insulin dependent diabetes mellitus (NIDDM) with a strong family history. The activity of the enzyme itself seemed to be unrelated to the polymorphism, which was due to a single base change in an intron. It is possible that these polymorphisms are close to a hitherto unidentified gene causing insulin resistance on chromosome 19.

Insulin resistance as a marker of hypothalamic or sympathetic activation

Counter-regulatory hormones to insulin, such as adrenaline, noradrenaline, cortisol, growth hormone, and glucagon, can cause insulin resistance through a direct effect on the enzymes involved in glucose homoeostasis in many tissues. The hypothalamic arousal and neuroendocrine dysregulation scheme proposed by Björntorp proposes that “stress” may cause insulin resistance by increased hypothalamic arousal. The resulting increase in sympathetic activity raises blood pressure, increases hepatic glucose production, and suppresses glycogen synthesis. Several negative feedback loops involving many neurotransmitters are present in the hypothalamus, and abnormalities in pre or post synaptic receptors may affect baseline hypothalamic activity. Genes that cause increased baseline sympathetic outflow will cause hypertension and insulin resistance simultaneously. Such thrifty genes will favour lipogenesis at the expense of glycogenesis. The hypothesis that such thrifty genes may confer a selective advantage at times of starvation would explain their high apparent prevalence worldwide.

Barker et al suggested that insulin resistance may be
programmed by changes in the intrauterine and early fetal environment. This thrifty phenotype hypothesis stems from epidemiological evidence linking low birth weight with Reaven's syndrome X in later life. The intrauterine and early fetal environment may modulate insulin resistance, perhaps by altering the set point of hypothalamic activity. Insulin resistance may therefore be determined by a combination of genetic influences and early fetal environment, which together determine the set point of hypothalamic activation.

The Copenhagen study found that alcohol was particularly protective in Le (a−b−) individuals. The Lewis gene may be very close to a gene influencing sympathetic activation, and hence insulin resistance. Alcohol may have a modulating effect on hypothalamic or sympathetic tone and may therefore be of most benefit to individuals with high sympathetic tone. Though this theory is highly speculative, Razay et al found that women drinking alcohol had lower insulin concentrations than non drinkers and that in a study of insulin-resistant, hyperphagic and obese rats, animals given ethanol had a substantial reduction in insulin resistance.

In summary, four genes on chromosome 19 (those determining the Lewis phenotype, the glycogen synthase gene, the insulin receptor gene, and the LDL receptor gene) have shown a weak association with the clinical features of insulin resistance. There may be a hitherto unidentified gene close to these loci on chromosome 19 causing insulin resistance and Reaven's syndrome X. This gene may primarily determine hypothalamic activation, which in turn may cause insulin resistance. Other minor genes, changes in the intrauterine and fetal environment, and environmental factors in later life may modulate this activity. The finding of another possible genetic marker for ischaemic heart disease in the form of Lewis phenotypes is a link to chromosome 19—which seems a good place to start the search.

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*Br Heart J* 1994 71: 305-306
doi: 10.1136/hrt.71.4.305

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