

**A step towards unravelling the genetics of polycystic ovarian syndrome**

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A 19-year-old lady presented to endocrine outpatients in 1990 with a one year history of hirsutism, oligomenorrhea and ultrasound evidence of polycystic ovaries. She had a raised random glucose of 10.2. Her BMI at this time was 27 and a diagnosis of impaired glucose tolerance linked to polycystic ovarian syndrome was made. She was advised on diet and exercise and asked to lose weight. Over the course of the following two years, she managed to lose 5kg. Her hirsutism and oligomenorrhea continued and she was therefore started on hormonal treatment in the form of Dianette with initial good results. However due to adverse effects on her lipid profile and blood glucose readings this was subsequently stopped. Spironolactone was substituted but this too had to be stopped due to postural hypotension. Over the course of the next few years, it became apparent that our patient had a progressive metabolic syndrome with increasingly abnormal lipid profile (total cholesterol 6mMol/L triglycerides 5mMol/L in 1997) and deterioration into frank diabetes (fasting plasma glucose 9.7mMol/L and HbA1C 7.9% by 1997). She was treated with metformin and this initially controlled her HbA1C and a fibrate to control her raised triglycerides. Both her blood sugar and lipid profile continued to deteriorate such that by 2003 her HbA1C was 8.4% on 1.5g metformin (maximum tolerated) and her cholesterol was now 7.1mMol/L with triglycerides of 4.97mMol/L on 200mg bezafibrate.

Due to her young age of onset and progressive symptoms she was referred for gene analysis, which revealed the presence of PPAR (peroxisome proliferator-activated receptor) gamma co-activator 1 (PGC-1) heterozygosity. PGC-1 is a co-activator of a number of nuclear hormone receptors including the PPARs and was demonstrated to coordinately activate a programme of adaptive thermogenesis in adipocytes and muscle. Subsequent work also showed it is involved in the regulation of Glut 4 expression and insulin stimulated glucose uptake in skeletal muscle and in the coordinate regulation of hepatic gluconeogenesis. There are associations with the development of type 2 diabetes, dyslipidemia, hypertension, polycystic ovaries and possibly an increased risk of breast cancer and decreased aerobic exercise capacity with abnormalities of the gene.

The optimum treatment for patients with this condition is as yet unknown and we expect prognosis is linked to cardiovascular risk. Our patient has been encouraged to maintain lifestyle measures such as adherence to a low-fat diabetic diet and regular exercise schedule as these are thought to be beneficial. A thiazolidinedione and statin were added to her metformin and fibrate in 2003 but a similar pattern has repeated itself with initial benefit and subsequent deterioration and the direction further treatment should take is still somewhat uncertain. Our case demonstrates that progressive metabolic syndromes can be due to novel gene mutations, which may lead to new targets for treatment in future.