Editorial

Rare Disease Day, our Roma cousins and the power of one

'Rare Disease Day' was first observed on February 29, 2008, to express solidarity with patients who have these rare diseases and their families, to highlight the importance of research on rare diseases, and to raise public awareness about them. This day was observed on February 28 in the subsequent three years.

Ribose-5-phosphate isomerase (RPI) deficiency is considered the rarest disease, with only one diagnosed case (Wamelink *et al.* 2010 *J. Mol. Med.* **88** 931–939). The patient suffered from progressive brain white-matter disease and peripheral neuropathy. Metabolic profiling showed elevated levels of D-ribitol and D-arabitol in his brain and body fluids. Genetic analysis revealed that both alleles of the RPI gene were mutant in the patient. One allele had a frameshift mutation that introduced a premature termination codon and represented a non-functional null allele, and the other had a missense transition mutation (c. C182T) that substituted an alanine for valine at codon 61 and generated a partially functional enzyme. The missense allele also showed cell-type-dependent expression deficits, such that some cells (lymphoblasts) showed residual RPI mRNA expression and enzyme activity but in other cells (fibroblasts) the deficit was complete. It was speculated that since the transition mutation was in the first codon of exon 3, its proximity to the splice acceptor site might affect the maturation of RPI mRNA in specific cells, or alter its binding to another regulatory molecule. The conjunction of three defects affecting RPI activity – a null allele, an allele with a cell-type-dependent reduction in RPI mRNA and a partially active RPI enzyme – is rarer than the natural and presumably lethal occurrence of double heterozygosity for two null alleles, and would account for the patient's uniqueness.

A disease may be rare in one part of the world yet common in another. Primary congenital glaucoma (PCG), an autosomal recessive eye disease, occurs at an unusually high frequency (1:1250 births) among the Roma. The Roma are descendants of small populations of people who migrated from northwest India to Europe as gypsies about 1000 to 1500 years ago. Their number in Europe now is about 8 million. They look so Indian that I even attempted speaking in Hindi to the few I saw panhandling tourists near the Paris Opera. A stop mutation in the LTBP2 gene has been linked to developmental glaucoma in a class of Roma. Ali *et al*. (2009 *Am. J. Hum. Genet.* **84** 664–671) found that this stop mutation, along with 14 flanking SNPs, was shared by eight Bulgarian Roma patients and a family from Pakistan, thus indicating a distant relationship via a common ancestor. Mendizabal *et al.* (2011 *PLoS One* **6** e15988) reported that several Roma mitochondrial lineages are of the M haplogroup that originated in the Indian subcontinent. These findings make a good case to grant the Roma 'persons of Indian origin' (PIO) status!

I do not study diseases, rare or otherwise, but some of my research was on a rare topic, not explored by anyone else: a PubMed search for 'dictyostelium *and* phytoalexin' turned up four papers, all from my lab, whereas each keyword used alone flagged 7289 and 1460 articles. If I may mix Henry David Thoreau with Donald Rumsfeld – had just one lab, in this case ours, not marched to the beat of a different drummer, phytoalexin effects on the cellular slime moulds would have remained buried among the unknown unknowns.

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Editor