Is human insulin imprinted?

Sir — In the March 1994 issue of *Nature Genetics*, Giddings *et al.* report that insulin is preferentially expressed from paternal alleles in the yolk sac of mouse embryos[1]. The human insulin gene may also be imprinted. Previous studies have shown that susceptibility to insulin-dependent diabetes is associated with paternal transmission of a 4.1 kb region that includes the insulin gene[2,3]. This is the most direct evidence for an imprinting effect at the human insulin locus, but other evidence is also suggestive. There are no published reports of homozygous null mutations of insulin, nor indeed of heterozygous null mutations. Two explanations suggest themselves: either the null phenotype is lethal during early prenatal development and thus is not detected, or null mutations are strongly selected against when heterozygous. The first possibility is less plausible in light of the live birth of infants without functional insulin receptors[4] and of infants with congenital absence of the endocrine pancreas[5]. These infants suffer severe intrauterine growth retardation with exceptionally low levels of subcutaneous fat[6].

A similar phenotype — intrauterine growth retardation and low adiposity — is found in the rare condition of transient neonatal diabetes (TND)[7,8]. As neonates, TND infants do not produce detectable levels of insulin in response to usual stimuli. Their diabetes is treatable with exogenous insulin, and is transient because normal insulin responses appear after some days, weeks or months. TND is usually interpreted as the result of delayed maturation of pancreatic β cells, but the condition would also be explicable if insulin was imprinted during prenatal development. In this scenario, only one of the parental insulin alleles is active before birth so that infants who inherit a null mutation from this parent would produce no insulin until the other allele is activated postnatally. Multiple cases of TND have been reported in at least two sibships[9,10], one of which is quite remarkable. In this sibship, TND occurred in three successive children of a father, by three unrelated mothers[10]. The pedigree clearly suggests dominant inheritance from the father, but does not allow conclusions to be drawn about maternal transmission, although one of the affected daughters has given birth to an unaffected son. A molecular study of insulin genes in patients with TND should provide evidence for or against the hypothesis that the condition is caused by a defective paternal insulin allele.

Fetal insulin appears to have an important role in the deposition of fat during the third trimester[6]. It is at this stage of pregnancy that the nutitional demands on a mother are greatest. Therefore, silence of the maternal insulin allele would be compatible with the theory that genomic imprinting has evolved because paternal alleles have been selected to make greater demands on a mother than have maternal alleles[11,12].

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ApoE-ε4 and early-onset Alzheimer's

Sir — Alzheimer's disease (AD) is by far the most common cause of dementia in humans. Accumulation of massive senile plaques and neurofibrillary tangles are characteristic neuropathological manifestations of AD. Recent investigations have revealed that apolipoprotein E (apoE) is present in these structures[1,2] and, furthermore, one particular allele APOE-ε4, is frequently associated with late-onset familial AD and sporadic AD[3–10]. Although apoE is one of numerous plasma lipoproteins, it is of particular interest because, unlike other lipoproteins that are mainly synthesized in the liver, apoE is also synthesized in astrocytes and oligodendrocytes in the central nervous system[11–13]. Three isoforms, corresponding to alleles ε2, ε3 and ε4,

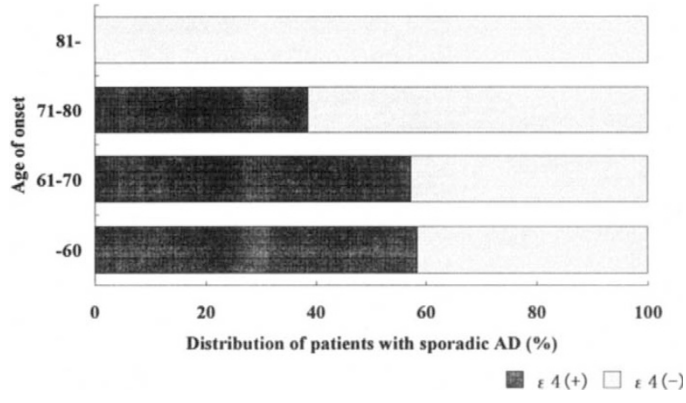

Fig. 1 Distribution of patients with sporadic AD having at least one APOE-ε4 allele in various age of onset groups.