Regulation of insulin gene expression by the IDDM associated, insulin locus haplotype

Lucassen AM, Screaton GR, Julier C, *et al. Hum Molec Genet* 1995;4:501–6.

Insulin dependent diabetes mellitus (IDDM) or type 1 diabetes has become the focus of intense research into the possible genetic factors underlying this multifactorial condition. This team have previously identified nine single base substitutions and a single VNTR in and around the insulin gene locus (INS) at 11p15.5. These polymorphisms are found as just two predominant haplotypes only one of which is associated with IDDM. In this paper, these authors transfected a hamster insulinoma cell line with genomic fragments containing the whole polymorphic region including the INS gene and assessed mRNA transcription by RT-PCR. RNAse protection assays confirmed that levels of INS message were 1·5 to 3 times higher in the diabetes assocated haplotype which contains a shorter VNTR polymorphism. This VNTR lies 365 bp upstream of the start of INS transcription and an accompanying Editorial cites a study (in press) of human pancreatic islets in which short VNTR lengths were again correlated with increased INS mRNA. The authors speculate that the VNTR might exert its effect through conformational DNA alterations and propose at least three possible mechanisms for the assocation of increased insulin levels and IDDM. These include β cell oxidative stress as a result of over transcription, secretion of immunogenic INS precursors, or breakdown of immunological tolerance as a result of overproduction.

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Health supervision for children with achondroplasia

American Academy of Pediatrics Committee on Genetics. *Pediatrics* 1995;**95**:443–51.

This set of guidelines was designed to assist paediatricians in caring for children with achondroplasia and also covers prenatal diagnosis of achondroplasia and diagnosis of the condition in the newborn period. Overall, it presents a very positive picture of achondroplasia, but does not shy away from mentioning the significant complications which may occur. The information is presented in the form of checklists for paediatricians to refer to at each stage of development, because different issues will arise at different ages. The topics which are covered include accurate diagnosis, phenotypic features and complications, assessment of growth and development, specific treatments such as leg lengthening procedures, genetic counselling, social issues surrounding achondroplasia, support for the family, and home and school adaptation, for example, for toileting. The text is interspersed with growth charts specific for achondroplasia and information on normal developmental milestones for this group of patients. The paper stresses that most people with achondroplasia will have normal intelligence and normal life expectancy. Severe complications such as restrictive pulmonary disease, severe upper airways obstruction, and hydrocephalus only occur in a minority of patients. Other problems such as otitis media, spinal stenosis, orthodontic problems, and development of thoracolumbar kyphosis are more common. As regards the latter, great emphasis is placed on the importance of back support during the first year of life. Unsupported sitting and the use of "soft" buggies and baby carriers is positively prohibited. Swimming and biking are acceptable activities for an achondroplastic child, but not gymnastics or contact sports because of the risk of neck or back injury. The discussion of issues arising during adolescence and early adulthood includes the areas of vocational planning, sexuality, and reproduction and stresses the need to foster independence. These guidelines certainly prompt one to consider aspects of achondroplasia hitherto often forgotten. The introduction mentions the recent discovery of the FGFR3 mutation as the cause of achondroplasia but it is interesting that thereafter it is stated that the diagnosis is a radiographic one. There is no mention of mutation analysis in the section on prenatal diagnosis. This is yet another issue which we have to address, and the more fully informed we are about achondroplasia the better we will be able to do this.

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