MEDICAL GENETICS: ADVANCES IN BRIEF

Two drosophila receptor-like tyrosine phosphatase genes are expressed in a subset of developing axons and pioneer neurones in the embryonic CNS

Yang X, Scow KT, Bahiri SM, Oon SM, Chia W. *Cell* 1991; 67:661-73.

Three receptor-linked protein-tyrosine phosphatases are selectively expressed on central nervous system axons in the drosophila embryo

Tian S-S, Tsoulfas P, Zinn K. *Cell* 1991;67:675-85.

Central nervous system development in insect embryos is characterised by growth of neurones on stereotyped pathways along pre-existing axon bundles to reach their targets. These two papers describe the identification of two genes (DPTP99A and DPTP10D) and their protein products that are implicated in the axonal outgrowth and guidance. The genes, through alternative splicing, code for multiple forms of receptor linked protein tyrosine phosphatases (PTPases). The isoforms of the proteins differ in their C-terminal tails. The expression of these proteins is restricted to CNS axons and show distinct patterns specific to different subsets of CNS neurones. The expression of DPTP99A coincides with the onset of axonogenesis and is observed in several pioneer neurones. Transient expression of DTP99A proteins is observed in intersegmental and segmental nerves. This expression pattern suggests that they are involved in axon outgrowth and guidance. The structure of the receptor linked PTPases indicates that they may be involved in transduction of cell surface signals provided by extracellular matrix molecules or neural cell adhesion molecules. The PTPases have extracellular fibronectin type III repeats and intracellular protein tyrosine kinase domains. Thus, they may link cell recognition to tyrosine phosphorylation.

N S THAKKER

Epidermolysis bullosa simplex: evidence in two families for keratin gene abnormalities

Bonifas JM, Rothman AL, Epstein EH Jr. *Science* 1991;254:1202-5.

Epidermolysis bullosa simplex (EBS) is one of a group of hereditary conditions in which relatively gentle friction disrupts the basal epidermal cells of the skin causing painful blistering. Noting that blood cell disorders such as elliptocytosis share autosomal dominant inheritance and temperature sensitivity with EBS, and result from cytoskeletal protein mutations, this team set out to find analogous mutations affecting the keratin components of the intermediate filaments which form the main cytoskeleton in epidermal basal keratinocytes. They have found that the underlying cause of an EBS causing blisters mostly on the hands and feet is a point mutation within the K14 keratin gene

on chromosome 12. Linkage with the K5 keratin gene on chromosome 17 has been established in a second family with an EBS which causes blisters only acrally. As the K14 and K5 proteins combine to form a heterodipolymer it seems significant that the K14 point mutation produces a kink in one of the helical domains of the K14 protein which may interfere with this process. This work establishes the molecular basis for another clinical entity, makes prenatal diagnosis possible for some EBS families, and throws light on the function of intermediate filaments in maintaining cellular integrity.

JOHN C K BARBER

Iron overload in Africa

Gordeuk V, Mukiibi, J, Hasstedt SJ, *et al.* *N Engl J Med* 1992;326:95-100.

In contrast to haemochromatosis, which in white populations is inherited through a gene linked to the HLA locus, iron overload in Africa is believed to result from increased dietary iron derived from brewing beer in iron pots. Gordeuk *et al* examined the possible role of genetic factors by studying 236 members of 36 African families containing a proband with iron overload. Among family members with increased dietary iron, transferrin saturation was distributed bimodally. Pedigree analysis provided evidence that both genetic background and increased dietary iron had an effect on transferrin saturation. In the most likely model, increased dietary iron raised the mean transferrin saturation from 30% to 81% in subjects heterozygous for the 'iron loading locus'. There was evidence against tight linkage of this locus to HLA. Thus, iron overload in Africa may be caused by an interaction between the amount of dietary iron and a gene distinct from the HLA linked gene. This finding should lead to increased awareness of the disorder in affected populations and implies that genetically predisposed Africans living elsewhere may suffer iron overload from other sources. Increased awareness of hereditary haemochromatosis in general is necessary, because the diagnosis is often overlooked, though easy to confirm, and treatment is straightforward and effective.

A M NORMAN

Familial and sporadic hyperinsulinism: histopathologic findings and segregation analysis support a single autosomal recessive disorder

Thornton PS, Summer AE, Ruchelli ED, Spielman RS, Baker L, Stanley CA. *J Pediatr* 1991;119:721-4.

The authors of this paper have reviewed clinical, histological, and family data on 32

infants that have presented in Philadelphia with neonatal hyperinsulinism over the last 15 years. Four of 32 had discrete pancreatic adenomas and as these appear to represent a separate cause of neonatal hyperinsulinism they were excluded from further analysis. The remaining 28 cases were from 22 families (five of the families had more than one affected child). A comparison of the clinical data of cases from multiplex and simplex families showed no differences in the mode of presentation or severity of disease between these two groups which were, therefore, combined for further analysis. Segregation analysis was then carried out using the direct a priori method on the 14 suitable pedigrees and the expected number of affected sibs (19.65) was found to correlate very well with the 20 that were observed. In conclusion, this excellent paper provides further, compelling evidence that hyperinsulinism (nesidioblastosis) is an autosomal recessive trait and that appropriate genetic counselling should be offered to parents of a child with this condition.

DAVID FITZPATRICK

p53 germline mutations in Li-Fraumeni syndrome

Santibanez-Koref MF, Birch JM, Hartley AL, *et al.* *Lancet* 1991;338:1490-1.

Li-Fraumeni syndrome (LFS) refers to the familial association of breast cancer, soft tissue sarcoma, and other tumours, most commonly brain, adrenal, and leukaemic. Following recent reports of germline mutations within exon 7 of the p53 tumour suppressor gene in families with this inherited tendency to malignancy, Santibanez-Koref and colleagues have sought similar mutations in eight families with documented LFS. Mutations were detected in two of the pedigrees tested. This brings to four the number of LFS families documented wherein a CpG mutation at codon 248 of the p53 gene appears to be causally related to the malignant propensity. However, six of the families tested showed no evidence of mutation within exon 7 of p53. Comparison between LFS families with exon 7 p53 mutation and LFS families without such mutations evinced a higher prevalence of soft tissue sarcomas, brain tumours, and multiple cancers in the p53 mutation related pedigrees. Observations of this nature are provocative and apt to have a pulse quickening effect. Mature reflection suggests that the place of exon 7 mutations of the p53 gene in LFS as an aid to counselling and screening remains ill defined. To this observer, p53 mutation in LFS is not yet ready to make the momentous leap between thought provoking research observation and useful laboratory aid to the clinical situation.

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