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GENES AND THE SKIN*

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Until recently the area of overlap between genetics and dermatology seemed confined to a few rare inherited skin disorders. However, the 'New Genetics' has touched every branch of dermatology from common conditions like acne, psoriasis and eczema to the susceptibility to certain infections, skin cancers and adverse drug reactions. Furthermore, lessons from the rare genetic defects have elucidated many aspects of normal skin biology.

CHROMOSOME LOCUS AND INDIVIDUAL DISEASES

To demonstrate the impact of molecular biology on dermatology, some of the more illuminating examples are summarised here, in the order of their chromosomal positions.

The convention for denoting the position of a gene is as follows: autosomes are numbered from 1 to 22 in descending order of size. Each has a short arm ('p') and a long arm ('q') joined at the centromere. Regions visible on a Giemsa stained preparation are numbered outwards from the centromere. Regions are subdivided into bands, and sometimes sub-bands, numbered in the same way. Thus 9q34.1 means sub-band 1 of band 4 of region 3, on the long arm of chromosome 9.

Chromosome 3 and dystrophic epidermolysis bullosa

In some families the blistering disorder dystrophic epidermolysis bullosa maps to 3p21, which is also the locus for the gene COL7AI which encodes 7.[1] These patients have defective anchoring fibrils, which are normally composed of collagen 7 and hold the epidermal basement membrane on to the dermis. The result is that the epidermis easily lifts off, forming a blister.

Chromosome 4 and piebaldism

Piebaldism is a rare dominant disorder characterised by a white forelock and large hypopigmented patches on the trunk and limbs. It has been mapped to 4q12-q21 by analogy with the mouse 'W' (white-spotted) phenotype, and by study of patients with chromosomal translocations affecting this region. In several families, piebaldism has now been shown to be due to mutations in the c-KIT oncogene at 4q12-21.[2] This gene encodes a mast cell/stem cell growth factor receptor which is probably also involved in normal melanocyte migration during embryogenesis. In these patients it seems that melanocytes migrating from the neural crest do not reach their furthest destinations on the forehead, on the anterior abdominal wall, and on the limbs.

Chromosome 9, nail-patella syndrome, tuberous sclerosis and skin tumours

Several conditions have been mapped by linkage with the ABO blood group genes at 9q34.

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Nail-patella syndrome, also known as hereditary onycho-osteodysplasia (HOOD) shows hypotrophic nails, absent patellae, other skeletal defects, and sometimes nephropathy. The gene responsible has not yet been identified, but a candidate in the 9q34 region is COL5A1, the gene for the alpha-1 chain of collagen 5.[3]

Tuberous sclerosis also segregates with ABO blood group, and has been more precisely mapped to 9q34.1-2. However, some families do not show linkage with 9q, and three other loci have been established at 11q22-q23, 12q22-q24.1 and 16p13.[4] So far it has been impossible to distinguish phenotypically between families with tuberous sclerosis mapping to the different loci. Candidate genes include the pigment related genes dopamine beta hydroxylase on 9q, tyrosinase on 11q, and phenylalanine hydroxylase on 12q, as well as the gene for a cell adhesion molecule N-CAM on 11q.

Two skin tumour prone conditions map to 9q22.3-q31. They are Gorlin's syndrome (naevoid basal cell carcinoma syndrome)[5] and self-healing epitheliomas of Ferguson–Smith:[6] they may represent allelic variants, that is different phenotypes due to different mutations of the same gene. Allelic loss at this locus has been found in sporadic basal cell carcinomas, supporting the idea that this is the site of a tumour suppressor gene.[7]

Chromosome 11 and type I albinism

The gene for tyrosinase, a key enzyme in melanin metabolism, lies at 11q14-q21. Numerous mutations have been documented in this gene, all of which result in type I (tyrosinase negative) oculocutaneous albinism.[8]

Chromosome 12 and keratin abnormalities

Keratins are important structural skin proteins. Keratin filaments are heterodimers, each composed of a type one (acidic) and a type two (basic) keratin. A cluster of genes encoding type 2 keratins lies at 12q11-q13, and the corresponding type 1 cluster is at 17q12-23.

Three skin conditions are associated with keratin gene mutations.[9] The superficial blistering disorder epidermolysis bullosa simplex is characterised by mutations in keratins 5 and 14. These keratins form the tonofilaments responsible for the integrity of basal epidermal cells. When they are defective, minimal friction splits the epidermis creating a blister. In patients with bullous ichthyosiform erythroderma, mutations in the keratins characteristic of suprabasal epidermal cells (keratins 1 and 10) result in hyperkeratosis as well as blistering. The same pathology is found in some patients with keratoderma confined to the palms and soles, who have mutations in the keratin 9 gene. Two disorders characterised by nail dystrophy have been mapped provisionally to the keratin cluster loci, namely Darier's disease[10] and pachyonychia congenita.

Chromosome 15 and type 2 albinism

Another form of oculocutaneous albinism, the type 2 tyrosinase positive form, has been mapped to 15q11-q13. This area is deleted in patients with Prader–Willi syndrome and Angelman syndrome. In the former the deletion is on the paternally derived chromosome 15 and in the latter it is on the maternal chromosome, a phenomenon known as genomic imprinting (the difference in behaviour of an autosome depending on whether it came from the sperm or the ovum). The occurrence of tyrosinase negative albinism in patients with either of these syndromes provided a clue to its localisation. The relevant gene is the 'p' gene, so called because mutations in this gene in mice produce a pink-eyed variant.[11] The product of this gene facilitates the transfer of tyrosinase across melanosome membranes.

Chromosome 17 and neurofibromatosis

The mapping of von Recklinghausen's neurofibromatosis (NF1) was hampered by the lack of any convenient biochemical marker nearby.[12] Finally a conference was arranged at which all those trying to map NF1 pooled their negative data and built up an exclusion map: they were able to discount most of the genome and were left with a small number of candidate sites upon which attention was then focussed. Soon afterwards a patient was identified with NF1 and a chromosomal breakpoint in one of these candidate regions at 17q11.2, thus localising the disorder. The function of the very large gene product 'neurofibromin' has not yet been established, although part of it encodes the GAP protection which inactivates the RAS oncogene. This could explain the tendency to malignancy seen in patients with NF1.[13]

Chromosome 18 and porphyria

Most types of porphyria have now been mapped, for example erythropoietic protoporphyria which is caused by mutations in the ferrochelatase gene at 18q21.3.[14]

Chromosome 19 acanthosis nigricans, and DNA repair disorders

Acanthosis nigricans (thickened pigmented skin in the flexures) is a marker of gastrointestinal malignancy when it develops for the first time in a non-obese adult, and of hyperinsulinism when seen in a child. Several patients with syndromes featuring acanthosis nigricans and hyperinsulinism have mutations in the insulin receptor gene at 19p13.2-p13.3.[15] The excess insulin somehow produces skin overgrowth, perhaps by its effect on insulin-like growth factor receptors.

At 19q13.3 lies one of the excision repair genes, ERCC2, which removes photo-damaged DNA. Mutations in this gene are found in two different skin disorders. Xeroderma pigmentosum (XP) is characterised by extreme sensitivity to the ageing and carcinogenic effect of sunlight with early development of skin cancers on exposed areas, and neurological degeneration. Patients with trichothiodystrophy (TTD) have brittle, sulphur deficient hair, and retardation of physical and mental development. Some patients with TTD have ichthyosis, and a few are photosensitive, but there is no increase in skin cancers. We do not yet know what protects TTD patients from the potentially malignant effects of the ERCC2 mutation.[16]

Chromosome 20 and the McCune–Albright syndrome

McCune–Albright syndrome is a condition of excess: it is characterised by various endocrine overactivities, particularly precocious puberty, and by patches of increased pigmentation in the skin. It is due to mutations in the GNAS1 gene at 20q12-q13.5, which encodes a protein which stimulates the adenylate cyclase 'second messenger' system.[17] Unlike most of the mutations discussed so far, this defect produces 'constitutive activation' of the gene, that is resistance to normal inhibitory controls, hence the endocrine and pigmentary overactivity.

Chromosome 21 and Down's syndrome

Although Down's syndrome may involve trisomy of the whole of chromosome 21, the same clinical picture is produced by triplication of a minimal, critical segment at the end of the long arm. In this region, 21q22.3, lie genes for collagen type 6,[18] which may be responsible for the unusual skin texture, joint hypermobility, and tendency to perforating collagenoses in Down's syndrome.

X chromosome

Several rare genodermatoses are X-linked. The best known is hypohidrotic ectodermal dysplasia, mapped to Xq12-q13.1. Steroid sulphatase deficiency due to deletions at Xp22.32 produces a characteristic ichthyosis in affected boys. This condition may in future be correctable by gene therapy. Already the missing gene has been replaced in cultured keratinocytes from a patient with X-linked ichthyosis,[19] heralding a new era in dermatology.

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SKIN AND THE PSYCHE*

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Emotional and psychological disturbances underlie many problems in dermatological practice. Patients may be divided into four groups.

1. Those with delusions of parasitosis, depression and body image disturbances, obsessional neuroses, dermatitis artefacta and trichotillomania.

2. Dermatological conditions which may be initiated or exacerbated by stress, eg urticaria, atopic eczema, acne vulgaris, rosacea and alopecia areata. Others which may occur in association with emotional or psychiatric disturbances, eg neurodermatitis, pruritus ani, pruritus vulvae, hyperhidrosis and generalised pruritus.

3. Reactive depression and/or anxiety associated wtih their skin disease.

4. Skin disease induced by psychotropic drugs, eg lithium induced acne or psoriasis.

This short review concentrates on patients in the first group.

BODY IMAGE AND ITS DISTURBANCES

A major component of the perceived body image is cutaneous, and some areas are more important than others; the face, especially the nose, the hair and genital are all crucial in body image perception. What is desirable is continuously changing. Thus, the voluptuous woman painted as the role model by artists of the 17th, 18th and 19th centuries has been replaced in the latter part of this century by the Barbi doll. The sophisticated women in the 1990s is expected to have plenty of hair on her head, but virtually none in secondary sexual areas, such as the axillae. The pubic hair must be as inconspicuous as possible, and no hair is permissible on the arms, legs, face or chest. Breasts are expected to be relatively inconspicuous, and the ideal distribution of fat is conceptualised as prepubertal. Indeed, the body structure of a Barbi doll, if attained by an adult female, would be incompatible with normal menstruation. In addition to this almost complete negation of secondary sexual characteristics in adult women, the skin itself is expected to be like that of a baby and should therefore be wrinkle, spot and grease free. Without such a skin, many women become unhappy and their self-esteem and confidence falls, resulting in secondary depression.

The personality most vulnerable in this regard is found in those females who have never communicated well with their fellows, men or women, and in addition show narcissistic, ruminant, obsessional and perfectionist traits which render them incapable of accepting anything less than perfection. Many such individuals have a borderline personality disorder.

It should be remembered that, whilst a thin, cachectic woman may be perceived as desirable in the Western world, in societies elsewhere more traditional values prevail. Indeed, some societies see an excessively thin woman as

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