Short Report

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Monique Jouet[a], Helen Stewart[b]
Sara Landy[b], John Yates[c, d]
Siu Li Yong[h], Ann Harris[e]
Christine Garret[f], Eli Hatchwell[g]
Andrew Read[b], Di Donnai[b]
Sue Kenwrick[a]

[a] Cambridge University Department of
Medicine, Addenbrooke's Hospital,
Cambridge,
[b] Department of Medical Genetics,
St. Mary's Hospital, Manchester,
[c] Department of Clinical Genetics,
Addenbrooke's Hospital and
[d] Cambridge University Department of
Pathology, Cambridge,
[e] Paediatric Molecular Genetics, Institute of
Molecular Medicine, Oxford,
[f] North West Thames Regional Genetics
Service, Northwick Park Hospital, Harrow,
and
[g] Wessex Clinical Genetics Service, Level G,
Princess Anne Hospital, Southampton, UK;
[h] Department of Medical Genetics,
University Hospital, Vancouver, Canada

Linkage Analysis in 16 Families with Incontinentia pigmenti

Abstract

A locus for the X-linked dominant genodermatosis incontinentia pigmenti (IP) has been linked to markers in Xq28. Here we report high lod scores for markers spanning the interval DXS52-DXYS154 using 16 families, providing further evidence for a single major X-linked IP locus.

Introduction

Incontinentia pigmenti (IP) or Bloch-Sulzberger syndrome (McKusick No. 308300) is an X-linked dominant genodermatosis that predominantly affects females. The spontaneous abortion rate as well as the female:male offspring ratio for carriers is consistent with lethality in males. Characteristically, newborn affected females present with erythematous blistering that evolves into verruccous lesions followed by streaks and whorls of hyperpigmentation. These hyperpigmented lesions are prominent in the axillae and groin and eventually fade leaving superficially scarred, hairless, pale tissue as the only dermatological sign in adulthood. IP is often associated with developmental abnormalities of the teeth, eyes, hair and the central nervous system [1, 2]. The most obvious clinical signs present in adulthood are the dental abnormalities, affecting 80% of cases. They include hypodontia, delayed eruption and malformed crowns.

Reports of several isolated females with clinical signs similar to IP and Xp11/autosome translocations lead to the hypothesis that a gene in Xp11 was responsible for IP. However, genetic linkage analysis in families with classical X-linked transmission of IP has excluded this region [3, 4] and provided evidence for a locus in Xq28. Genetic linkage to markers in distal Xq28 (DXS52-Xqter) has been established with a few recombinant chromosomes providing proximal boundaries to the gene location [5–7].

Here we present results of further genetic linkage analysis aimed at localising the gene for IP in distal Xq28 using 16 families with X-linked dominant disease.

Materials and Methods

Families

All cases were ascertained by SL or SLY using criteria described by Landy and Donnai [2]. Clinical manifestations were highly variable but all families contained at least one female with skin lesions typical of IP from the newborn period onwards. IP was considered familial if female relatives showed more than one of the following: characteristic skin manifestations, abnormal dentition, retinal dis-
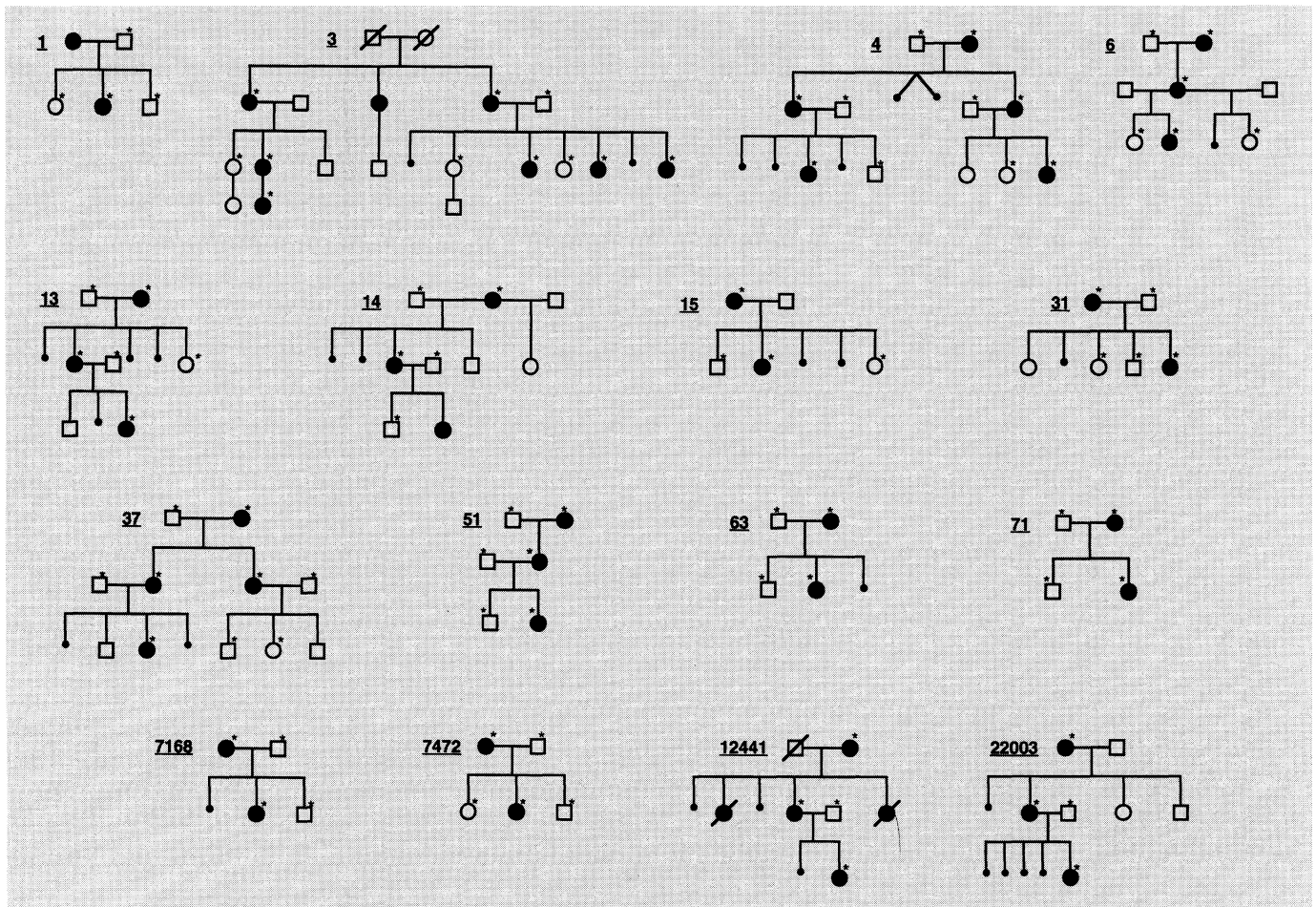
Sue Kenwrick
Cambridge University Department of Medicine, Addenbrooke's Hospital
Hills Road
Cambridge CB2 2QQ (UK)
Tel. (1223) 336868, Fax (1223) 336846; E-Mail SJK12@mole.bio.cam.ac.uk

Fig. 1. Pedigrees with IP females (large black circles). Small black circles indicate miscarriage. Asterisks indicate that DNA was available for linkage analysis.

ease, linear atrophic hairless regions of skin, more than one affected daughter, multiple male miscarriages. No male cases were found and there was no evidence of consanguinity. 15 of the families have not been previously described. Family 3 was described in Curtis et al. [8] and typed for F8C and DXS52. These and additional markers were used for the present study (fig. 1).

DNA Polymorphisms

Blood samples were collected with informed consent. Families were typed for DNA polymorphisms DXS52 (St14, VNTR), F8C (CA_n), RCP/GCP (colour vision DA_n), DXS1108 (CA_n) and DXYS154 (CA_n). CA repeats were all resolved on 1-mm-thick, 12% acrylamide gels [Accugel (Flowgen)] containing 7M urea and buffered with 1XTBE. Gels were silver-stained as described previously [9].

Linkage Analysis

Data were analysed by JY using the LIPED [10] computer programme for two-point analysis. Confidence intervals were obtained by taking values of the recombination fraction corresponding to a lod score one unit less than the maximum.

Results and Discussion

A total of 16 families representing samples from 52 affected females, 13 unaffected females and 36 healthy males were used for the present linkage analysis. Highly significant two-point lod scores were obtained for all markers used except for RCP/RGP which was rarely informative (table 1). No cross-overs were found either between marker loci or between the entire haplotype and IP.

Previous reports have provided strong evidence for a single major locus for X-linked IP in the distal portion of Xq28. Several cross-overs have indicated that the gene may lie in the telomeric portion of the chromosome and multipoint analysis strongly favours a location between F8C and the telomere ($3 \cdot 10^5$ times more likely than a more proximal location between DXS52 and F8C) [7].

Table 1. Two-point lod scores between the locus for IP and Xq28 markers

Locus	Lod score Z at recombination fraction θ							Zmax	θmax	Confidence interval for θ
	0	0.01	0.05	0.1	0.2	0.3	0.4			
DXS52	7.22	7.08	6.47	5.70	4.11	2.50	1.03	7.22	0.0	0–0.07
R/GCP	3.01	2.94	2.66	2.30	1.55	0.83	0.24	3.01	0.0	0–0.14
F8C	6.62	6.50	5.98	5.33	3.97	2.58	1.20	6.62	0.0	0–0.08
DXYS1108	8.73	8.56	7.87	6.98	5.15	3.27	1.47	8.73	0.0	0–0.06
DXYS154	7.83	7.69	7.12	6.38	4.84	3.2	1.53	7.83	0.0	0–0.07

Sefiani et al. [6] described three cross-overs in a healthy boy and two affected girls in a single family that placed the gene distal to DXS52, R/GCP and factor VIII, respectively. The latter cross-over suggests that the gene is within the terminal 1-Mb region of DNA by comparison with physical maps [11]. In all three cases more distal markers were found to segregate with the disease.

We have typed distal markers in 16 families. High lod scores obtained with all markers support the existence of a single major locus close to the factor VIII gene. No cross-overs were observed across the haplotype DXS52-DXS154 which represents about 3.7 Mb by comparison with physical maps. In view of the lack of recombination in the large cohort presented here further genetic analysis may have limited value in narrowing down the position of the disease locus. Direct screening of the many candidate genes now described for the region may therefore be a more fruitful approach.

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