J Hum Genet (2000) 45:323–326

MINIREVIEW

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Recent progress in the genetics of incontinentia pigmenti (Bloch-Sulzberger syndrome)

Received: August 15, 2000 / Accepted: August 30, 2000

Abstract Incontinentia pigmenti (IP) is a rare disorder which affects organs and tissues of ectodermal and mesodermal origin. It is characterized by swirled patterns of hyperpigmentation. In some cases, the condition is also associated with malformations of the teeth, nails, skeleton, hair, eyes, and the central nervous system. The disorder is inherited as an X-linked dominant trait and mostly affects females. However, there have been several cases of IP in males that survived to birth. While IP in females could be caused by a skewed pattern of X-inactivation, three mechanisms: namely, the half-chromatid hypothesis, unstable premutation, and a higher rate of de-novo germline mutations, have been proposed to explain the survival of affected male patients. Cytogenetic studies in several sporadic cases with signs similar to IP exhibited an X/autosomal translocation involving a breakpoint at Xp11, suggesting a gene locus on Xp11 (IP1). Linkage analysis of familial IP, on the other hand, has identified a second locus, in the Xq28 region (IP2). Molecular genetic analysis of two candidate genes located at Xp11 and Xq28, as well as the human homologue of the murine *Str* gene, failed to reveal any disease-causing mutations. Although heterozygous female mice deficient for the *IKKγ / NEMO* gene exhibited dermatopathy similar to that in human IP, studies of the gene in human IP have not yet been available. In an effort to isolate the genes causing IP, cosmid clones containing the translocation breakpoint located at Xp11 and the transcriptional map of the Xq28 region were constructed. These maps could be invaluable tools in the identification of genes in the near future.

Key words X-Linked · Dominant · Linkage · Genes · Translocation

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Introduction

Incontinentia pigmenti (IP), also called Bloch-Sulzberger syndrome, is a rare skin disorder and was first reported in 1906 (Garrod 1906). The disease causes a congenital disturbance of skin pigmentation and is also often associated with malformations of the teeth, nails, skeleton, hair, and central nervous system abnormalities such as mental retardation (Landy and Donnai 1993). The genodermatosis usually affects girls and is characterized by erythematous blistering, mainly on the extremities and trunk. The disease appears in affected females at or soon after birth, and the skin lesions are later replaced by a swirled pattern of hyperpigmentation. The pathogenesis of the skin lesions progresses through four stages (Landy and Donnai 1993) and the skin lesions fade with aging, but the dental features persist throughout life. Strict diagnostic criteria should be used to differentiate between IP and hypomelanosis of Ito (Happle 1998) which is a heterogeneous group of disorders, manifesting Blaschko's lines and mental retardation. In approximately one-third of IP patients, it is associated with unilateral visual impairment which may progress to severe visual loss (Goldberg and Cutis 1993; Spallone 1987). Ocular abnormalities in IP include persistent hyperplastic primary vitreous (Fard and Goldberg 1998); retinal abnormalities (Goldberg and Cutis 1993; Carney 1976); optic nerve neovascularization (Shah et al. 1997); corneal abnormalities (Ferreira et al. 1997); strabismus, exudative chorioretinitis, vascular retinal lesions, cataract, and nystagmus (Smith and Bedrossian 1984). However, more than 90% of patients have normal vision.

Cytogenetic and linkage studies

Although concern has been raised about the nomenclature of IP (Sybert 1994), there are two distinct IP loci, based on cytogenetic and linkage analysis. These loci are called type I (sporadic) and type II (familial) (IP1, MIM 308300; IP2,

Table 1. Chromosomal abnormalities in incontinentia pigmenti type 1 (IP1)

Abnormality	Chromosome	Reference
Translocation	t(X; 5)(p11.2; q35.2)	Bitoun et al. 1992
	t(X; 9)(p11.2; q33.2)	Hodgson et al. 1985
	t(X; 9)(p11.21; q34)	Gilgenkrantz et al. 1985
	t(X; 10)(p11; q22)	Cannizzarro and Hecht 1987
	t(X; 12)(p11.2; p13.3)	Jewett et al. 1997
	t(X; 13)(p11.21; q12.3)	Kajii et al. 1985
	t(X; 15)(unknown)	Bernstein et al. 1979
	t(X; 17)(p11.2; p11.2)	Hodgson et al. 1985
Ring chromosome	r(X)	deGrouchy et al. 1985

Table 2. Examples of X-linked dominant disorders with possible lethal trait in hemizygous males

McKusick (1994) catalogue number	Disease
302,300	Cataract, congenital with microcornea
302,960	Chondrodysplasia punctata
304,050	Aicardi syndrome
305,600	Focal dermal hypoplasia
308,050	Ichthyosiform erythroderma, unilateral, with ipsilateral malformations
308,310	Incontinentia pigmenti
309,801	Microophthalmia with linear skin defects
311,200	Oral-facial-digital type I
312,750	Rett syndrome
314,600	Cervico-oculo-acoustic

MIM 308310). Several sporadic cases (IP1) exhibit X/autosomal translocation (Table 1) involving a breakpoint and ring chromosome located at Xp11 (Gilgenkrantz et al. 1985; Hodgson et al. 1985; Kajii et al. 1985; Cannizzaro and Hecht 1987; Jewett et al. 1997; Bernstein et al. 1979; Bitoun et al. 1992; deGrouchy et al. 1985) suggesting that genes in Xp11 are responsible for IP1. A yeast artificial chromosome (YAC) containing 1.2Mb DNA, spanning the X-chromosomal breakpoint, was constructed to map and isolate the gene responsible for IP1 (Gorski et al. 1996). Meanwhile, analysis of a candidate gene (Norrie disease gene), which is also located in this region of the X-chromosome, failed to reveal mutations in one familial case of IP (Shastry and Trese 2000), indicating a different gene in the pathogenesis of familial IP (IP2).

Familial IP (IP2) is inherited as an X-linked dominant trait, with lethality in males (Carney 1976; Hecht et al. 1982). This mode of inheritance is supported by the high female: male ratio, the increased incidence of miscarriages and stillbirths (Devriendt et al. 1998), and female-to-female transmission. The disease, in general, is transmitted from mother to daughter, but some cases of mother to son (Hecht et al. 1982) and father to daughter (Sommer and Liu 1984) have also been reported. A large genetic linkage analysis of a series of familial IP excluded the locus in Xp11 and mapped the gene to the distal part of Xq28 (Sefiani et al. 1989; 1991; Smahi et al. 1994; Jouet et al. 1997). Although the gene responsible for IP2 has not been isolated to date, transcriptional analysis of the candidate region in Xq28 has identified a large number of genes (Rogner et al. 1996). Because the disease dyskeratosis congenita (DKC) is also localized to Xq28 and shows phenotypic similarity to IP, it was hypothesized that this gene may serve as a candidate gene for IP2. However, mutational analysis failed to identify disease-causing mutations, implying that IP2 is non-allelic to DKC (Heiss et al. 1999).

Animal models

Because the X-chromosome breakpoint is known to contain the lined gene (*Li*) locus in the mouse, the *Li* mutation (Blair et al. 1994), the murine X-linked dominant male lethal *Str* (striated) mutation (Erickson 1990), and the streaked hairlessness mutation in cattle (Eldridge and Atkeson 1953) have been proposed as animal models of human IP. However, mutational analysis of the human homologue of the murine *Str* gene failed to identify any disease-causing alterations (Swaroop et al. 2000). On the other hand, heterozygous female mice deficient for the *IKKγ / NEMO* gene, which codes for the *IKKγ / NEMO* regulatory subunit, exhibited a dermatopathy similar to that in human IP (Makris et al. 2000). Because the *IKKγ / NEMO* gene is located at the Xq28 region, and undergoes random X-inactivation, and because mutant males die in utero and show complete absence of *IKKγ / NEMO* expression, while female mice transmit the disease and female patients with IP also exhibit defective *IKKγ / NEMO* expression, it is likely that human IP is caused by mutations in the *IKKγ / NEMO* gene. Because of the striking similarities between human IP and *IKKγ / NEMO* mutant mice, this model may further provide insight into the pathogenesis of human IP. However, mutational analysis is needed to confirm the involvement of the *IKKγ / NEMO* gene in human IP. It is also interesting to note that the above transgenic mice did not exhibit the ocular and dental abnormalities which have often been found to be associated with human IP. Analysis of genes involved in other models may also prove to be invaluable in understanding the human disorder.

Incontinentia pigmenti in males

There are several known X-linked dominant disorders with sex-limited expression (Wettke-Schafer and Kantner 1983; Table 2). Although male cases of IP are rare, 49 male patients with apparent IP have been reproted (Schenerle 1998). The existence of karyotypically normal males with IP contradicts the proposal of male lethality (Prendiville et al. 1989), and therefore some explanations are needed for the survival of male IP patients. The presence of an extra X chromosome found in some male patients with IP may be one of the explanations for male survival, but this issue may confuse the diagnosis with Klinefelter syndrome. As far as females are concerned, X-inactivation studies have shown a skewed pattern of X-inactivation (Wieacker et al. 1985;

Migeon et al. 1989; Moss and Goodship 1991; Parrish et al. 1996). This results in two functionally different cell populations which contribute to the disease (Happle 1985).

In order to explain the survival of some male patients with IP, three mechanisms have been proposed. The first one is the half-chromatid hypothesis. According to this model, one chromatid of the X chromosome contains mutations and the other chromatid is normal. This will result in two cell lines, similar to what occurs in female IP patients (Lenz 1975; Gartler and Francke 1975; Langenbeck 1982). However, two known cases of female-to-female transmission contradict this mechanism, although reversion, as suggested by others, is a possibility (Hecht et al. 1982; Kurczynski et al. 1982). The second mechanism proposed to explain mosaic disease expression in males is unstable pre-mutation (Traupe and Vehring 1994). In this model, the pre-mutation normally remains silent during embryogenesis in males, but occasionally this silencing becomes incomplete and, hence, produces a clinical phenotype. This mechanism may explain mother-to-son transmission in some cases of IP. The mother may carry the pre-mutation and transmit it to her son; the pre-mutation then becomes fully expanded, producing the phenotype in males. However, the report of gonadal mosaicism in the father of two affected half-sisters (Kirchman et al. 1995) and the association of IP with Klinefelter mosaicism in two cases of female-to-male transmission (Hecht et al. 1982; Kurczynski et al. 1982) suggest that this mechanism is not applicable to IP. The third proposal put forward to explain the low incidence of affected males in X-linked dominant disorders is the higher rate of de-novo germline mutations in males (Thomas 1996). According to this theory, the highly mutated gene is inherited from the father rather than from the mother. Because the male child inherits the maternal X chromosome, and the affected heterozygous female does not transmit the mutant gene, because of the genetic lethality, the highly mutated paternal X chromosome may explain the exclusive occurrence of X-linked dominant disorders in females. In support of this hypothesis is the observation that there is a striking difference in mutation rates between males and females (Shimmin et al. 1993; Vogel 1977; Vogel and Rothenberg 1975). However, a recent report (Roberts et al. 1998) suggests that IP in a newborn male infant is maternally transmitted, which, again, contradicts the above de-novo germline mutation theory.

Summary and conclusion

IP is a rare ectodermal disorder that occurs almost exclusively in females (Landy and Donnai 1993). Although pedigree studies have shown an increased number of presumed male abortuses, which could be due to a high rate of aneuploidy (Munne et al. 1996), several male cases of IP in fetuses that survived to birth have been described (Schenerle 1998). In female patients, the disorder could be due to a skewed X-inactivation (Wieacker et al. 1985; Migeon et al. 1989). Three mechanisms have been proposed to explain the occurrence of IP in male patients. However, these mechanisms are not enough to explain mother-to-son transmission, or the gonadal mosaicism in the father of the two affected half-sisters referred to earlier. Whatever the mechanisms of IP pathogenesis in males, the survival of several male patients with IP indicates that the previously held view that IP was lethal in utero in males should be revisited before patients are counseled. The availability of cosmid clones containing the breakpoint and the transcriptional map of the Xq28 region should provide the necessary tools for the identification and isolation of the *IP1* and *IP2* genes. This will enhance our understanding of this devastating disorder at the molecular level, and will ultimately, provide a gene-based therapeutic approach for its prevention or cure.

Note added in proof While this paper was in press, Swaroop et al. (Swaroop et al. 2000. Am J Med Genet 94:79–84) reported that, filamin, plexin, major palmitoylated protein p55, and von-Hippel Lindau binding proteins are not candidate genes for IPZ.

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