Clinical Study of 40 Cases of Incontinentia Pigmenti

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Objective: To analyze the distribution of manifestations in a pediatric cohort and define guidelines for follow-up of incontinentia pigmenti (IP).

Design: Retrospective study of 47 children referred to the Department of Pediatric Dermatology with a diagnosis of IP between 1986 and 1999.

Setting: The private or institutional practice of participating dermatologists and pediatricians.

Main Outcome Measures: Evaluation of IP clinical diagnosis using the Landy and Donnai criteria.

Results: Because hyperpigmentation following the Blaschko lines may be observed in several pigmented disorders, 7 patients were found misdiagnosed. During the neonatal period, erythema, vesicles, and hyperkeratotic lesions were rarely absent in the patients with IP. Ocular and neurological abnormalities were frequent (20% and 30%, respectively) but rarely severe (8% and 7.5%, respectively).

Conclusions: Clinical diagnosis is the first main step for a correct phenotype/genotype correlation, which remains indispensable to better understand the pathological mechanisms of IP and develop new therapies. In doubtful cases, molecular analysis is helpful but characteristic histological features must be added as major criteria for IP diagnosis. Multidisciplinary follow-up is needed, particularly during the first year of life, to detect possible ophthalmologic and neurological complications. Neuroimaging ought to be performed in the case of abnormal neurological examination results or when vascular retinopathy is detected.

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INCONTINENTIA PIGMENTI (IP), or Bloch-Sulzberger syndrome, is a rare X-linked dominant genodermatosis that affects mostly female patients and is usually lethal for males in utero. It is a multisystem disorder, primarily of ectodermal origin, accompanied by dental, ocular, and central nervous system disorders such as seizures, spastic paralysis, microcephaly, and mental retardation.1,2 The typical phenotype results from a functional mosaicism, itself a consequence of lyonization (the random inactivation of one of the two X chromosomes in women).3

For editorial comment see page 1206

The identification of nuclear factor–kappa B (NF-κB) essential modulator (NEMO) as the disease-causing gene, and the skewing of the X chromosome inactivation, are powerful new tools that have made the diagnosis of unusual forms of IP easier.4 Nevertheless, the diagnosis of IP is based on clinical examination. The skin lesions may occur in 4 classically successive diagnostic stages: erythema, then vesicles and pustules (stage 1); verrucous lesions (stage 2); linear hyperpigmentation (stage 3); and pallor and scarring (stage 4). Stages, however, may overlap or not occur at all in a same patient.5 A linear hyperpigmentation that follows the Blaschko lines leads to IP (a disease with a highly evocative name). However, Blaschko linear hyperpigmentation can be observed in a heterogeneous group of mosaic conditions, eg, hypomelanosis of Ito (HI). Thus, IP clearly appears to have been overdiagnosed in the past.6,7 For this reason, the frequency of the clinical features associated with the highly diagnostic cutaneous manifestations are discussed in the literature. Landy and Donnai5 classified IP criteria into 2 groups, negative family history and first-degree family history (Table 1). These criteria remain essential for distinguishing such disorders and their clinical and genetic implications.3

The aim of our study was to evaluate with the Landy and Donnai criteria a series of 47 patients previously diagnosed as having IP. We also analyzed the distribution of clinical manifestations and compared our findings with the data in the literature, thereby demonstrating the importance of attentive clinical examination.
METHODS

We reviewed the clinical records of pediatric patients diagnosed as having IP and referred to the Department of Pediatric Dermatology at Hô pital Necker–Enfants-Malades, Paris, France, between 1986 and 1999. The medical records of all affected patients, which included neonatal data as well as inpatient and outpatient records, were reviewed by 2 experienced dermatologists (D.F. and C.B.). They used a standardized form to collect clinical information (mostly regarding cutaneous, ocular, dental, and neurological manifestations as well as family history) and investigation results. When necessary, obstetric and pediatric medical records were consulted, as well as specialists from other disciplines who followed up the patients. The clinical data were analyzed according to the criteria set by Landy and Donnai (Table 1).

Skin biopsy samples obtained from 28 patients were examined by the same pediatric dermatopathologist (S.F.). Eosinophilic count in peripheral blood analysis was performed in 26 patients and skeletal radiographs in 20.

RESULTS

Forty-seven patients believed to have IP (43 girls and 4 boys) were referred to us during this period with relevant medical records. However, we considered that only 40 of them (37 girls and 3 boys) had been rightly diagnosed. Age at diagnosis was unknown for 7 of the children who had IP; for the remainder, median age was 6 months 9 days (range, birth to 12 years). Among the 7 patients with a questionable IP diagnosis, 3 were finally diagnosed with HI, 1 with orofacial-digital syndrome, and diagnosis is still uncertain in the last 3 cases (Table 2).

SKIN MANIFESTATIONS

Information was available for all 40 patients. Dermatological manifestations were present as early as the first day after birth in 27 (68%) of them, during the neonatal period in 9 (22%), and after the age of 3 months in 4
skin lesions were present before the second week of life in 36 (90%). Data are reported in Table 3 and manifestations shown in Figure 1.

Erythema and vesicles (stage 1) were the first manifestations in 37 (92%) of the 40 patients, but stage 1 was absent in 3 (8%), and 2 had late recurrences of stage 1 lesions: 7 episodes of blisters occurred during the first year in one of them, and several episodes until the age of 3 years in the other.

Typical stage 2 hyperkeratotic lesions were noted in 32 (80%) patients but were absent in 6 (15%), and information was not available for 2 (5%). For 1 patient, stage 1 skin manifestations were absent and skin disease began with hyperkeratotic lesions. Frequently diffuse, stage 2 lesions were limited to the scalp (1 case) or the extremities (2 cases).

Linear hyperpigmented stage 3 lesions were present in 36 (90%) patients, but absent in 4 (10%) who were referred before the age of 2 months. Hyperpigmented lesions initiated skin manifestations in 2 patients and were present at birth in 1.

Finally, stage 4 manifestations were recorded in 12 (30%) patients but absent in 20 (50%), and information was not available for 8 (20%) patients. Linear, reticulate, or macular atrophic lesions were described in 9 (75%) of the 12 patients; lesions were present before the second week of life in 4, and after 1 year in 2. Linear hypopigmentation was noted in 4 (10%) of the 40 patients with IP. Information on the evolution of pigmentation anomalies was not available because there was no long-term follow-up.

Alopecia of the vertex was observed in 11 (28%) of the 40 patients, was absent in 24 (60%), and information was not available for 8 (20%) patients.

Table 3. Skin Manifestations of the 40 Patients With Incontinentia Pigmenti and Their Topography

<table>
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<tr>
<th>Lesion Stage</th>
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<td>4</td>
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*Data are given as number (percentage) of patients for each lesion stage. Diagnosis was performed before 1 month of life for 36 patients and before 1 year for all 40 patients.

Figure 1. Skin features of incontinentia pigmenti. A, Erythema and vesicles following Blaschko lines (stage 1); B, hyperkeratotic and verrucous lesions (stage 2); C, linear hyperpigmentation (stage 3); and D, pale, atrophic, hairless linear lesions (arrow) (stage 4).
tion was not available for 5 (12%). Alopecia was present in 7 patients younger than 6 months and in 4 older than 6 years.

Nail dystrophy was present in only 3 (10%) of the 30 patients for whom this information was noted. Nails were striated and thick in a 4-month-old girl, while onycholysis and hyperkeratosis of the 10 fingernails were present in another severely affected 10-year-old girl. Trachyonychia was noted at birth in 1 girl and supernumerary nipples were noted in 2.

NEUROLOGICAL INVOLVEMENT AND NEUROIMAGING

Clinical neurological manifestations were observed in 13 (32%) of the 40 patients (Table 4, patients 1-13). Neurological manifestations occurred within the first weeks, even within the first day of life, in the 5 (38%) children in this group cared for since birth in our department. Seizures were the prominent feature in 10 (77%) of the 13 patients with neurological involvement. Grand mal seizures occurred in 2 patients (patients 8 and 9) and led to death due to vascular cerebral damage: thalamic hemorrhage in one and ischemia and necrosis of both hemispheres in the other. These 2 individuals presented with early and extensive skin manifestations. Delayed psychomotor development was noted in 7 (54%) of the 13 patients, while mental retardation was reported in 3 (23%), and a spastic hemiplegia sequela was reported in 2 (15%).

Neuroimaging performed in 12 of the 13 patients revealed neurological manifestations in 10, and 2 had normal results (Table 4, patients 14 and 15). Transfontanellar ultrasonography was performed in 3 (25%) of these 12 patients; a computed tomographic scan in 5 (42%), all of whom had neurological symptoms; and magnetic resonance imaging (MRI) in 6 (50%). Cerebral atrophy and local or extensive hemorrhagic necrosis were the prominent features in the 5 patients who had a computed tomographic scan. Porencephalia was reported in 3 (25%) of the 12 patients, enlargement of lateral ventricles also in 3 (25%), and hypoplasia of the corpus callosum in 2 (17%). Leukodystrophy was detected in patient 15, who presented with severe retinal detachment.

DENTAL ABNORMALITIES

At evaluation, 23 (58%) of the 40 patients with a verified IP diagnosis were younger than 1 year and teeth examination was impractical, but information was available for 17 (42%) patients. Among these 17 patients, 10 (59%) presented with tooth abnormalities: 7 (70%) with partial anodontia of deciduous or permanent teeth, and 5 (50%) with conical teeth; this was an isolated condition in only 2 (20%). Microdontia and delayed eruption of permanent teeth were reported in only 1 patient. Two sisters and their mother had isolated cleft palate.

EYE ABNORMALITIES

Information concerning a detailed ophthalmologic examination was available for 34 (85%) of the 40 patients studied and anomalies were noted in 7 (20%) of them. The association of ocular and neurological manifestations is reported in Table 4. Strabismus was noted in 4 patients (12%); the condition was isolated in 3 (9%) and was associated with ophthalmoplegia of the sixth cranial nerve as a complication of cerebral hemorrhage in the fourth. Unilateral microphthalmia was reported in 2 patients (6%); it was associated with retinal detachment in one and with retinal detachment, aneurysm, hemorrhage, cataract, early seizures, and monococular blindness as a sequela in the other. Each of the following features was reported in only 1 patient: unilateral retinal pigmentation, coloboma, and occlusion of the central retinal artery.

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Abbreviations: A, abnormal; D, death; N, normal; +, present; −, absent.

*Neurological manifestations occurred before 3 weeks of life in patients 2, 3, 4, 8, and 9. Age of onset is unknown for the others. Patients 14 and 15 had normal neurological examination results. Patients 3 and 13 are males. Patients 7 and 15 had retinal detachment and patient 11 had occlusion of the central retinal artery.
Our series included 3 boys (8%) with a sporadic form of IP. One presented with stage 4 skin manifestations only. His karyotype was normal (46,XY). The second presented with skin manifestations, and with such neurological abnormalities as hemiparesia of the left arm and porencephalia of the left globus pallidus on computed tomographic scan. The third presented with skin manifestations, strabismus, and seizures, and MRI showed ischemic lesions of the frontal lobes (Table 4). His karyotype was normal (46,XY).

ASSOCIATED DISORDERS

One patient had associated Down syndrome. It was diagnosed by chromosomal analysis (47,XX+21) and probably related to maternal age. Each of the following was reported in this patient only: exudative enteropathy, megalourether, port-wine stains on the superior lip and scalp, laryngomalacia, tumor of the vertebral lumbar canal, and recurrent pulmonary infections.

FAMILY HISTORY

On examination, 11 (28%) of the 40 patients studied had a family history of IP involving at least the mother. Clinically, IP was considered sporadic in 25 patients (62%). All affected boys were diagnosed as having a sporadic form. Information was not available for 4 (10%) of the patients.

HISTOLOGICAL FEATURES

A skin biopsy sample was obtained for 26 of the 40 patients, and skin lesion stage was known for 21 of the samples. There were 11 with histological analysis of stage 1 lesions, 8 of stage 2 lesions, and 2 of stage 3 lesions. The results are reported in Table 5 and shown in Figure 2.

EOSINOPHILIA AND SKELETAL RADIOGRAPHIC FINDINGS

Eosinophilia was present in 23 of the 26 patients tested. Absolute eosinophil counts ranged between 550/µL and 15400/µL. Skeletal radiographs showed normal bones in the 20 patients tested.

MOLECULAR INVESTIGATIONS

Karyotype screening performed in 7 (18%) of the 40 patients (3 with familial forms, 3 with sporadic forms, and 1 with an undetermined form of IP) showed an abnormal result only in the girl with Down syndrome.

Samples of DNA were available for only 12 patients (1 with familial and 11 with sporadic forms of IP). Inactivation of an X chromosome and NEMO deletion were tested in all of them. The skewing of chromosome X inactivation was constant; it concerned the maternal X chro-
mosome in 4 patients (in 3 with sporadic forms and in
the patient with the familial form of IP) and the paternal
X chromosome in the 8 remaining patients. The NEMO
rearrangement (deletion of exons 4 through 10) was pre-
sent in 9 of the 12 patients (4 with sporadic and 5 with
familial forms).

**COMMENT**

Between 1986 and 1999, 47 children diagnosed as hav-
ing IP in the Department of Pediatric Dermatology were
reevaluated using the Landy and Donnai criteria, and 7
were found misdiagnosed. Hypomelanosis of Ito had been
mistaken for IP in 3 patients, 2 girls and 1 boy. Since birth,
these 3 children had had linear hyperpigmentation fol-
lowing the Blaschko lines, with indistinct edges to the
hyperpigmented or hypopigmented areas, and no re-
corded episodes of vesicular or verrucous lesions. They
had no family history of HI and no psychomotor de-
velopmental delay, which is more frequent in the excep-
tional cases of familial HI.11-15 Genetic counseling is dif-
ferent in the case of HI as, unlike IP, it is frequently related
to chromosomal anomalies.11 Orofacial-digital syn-
drome was diagnosed in a girl who presented with lin-
er hyperpigmentation and hypopigmentation, micro-
cephaly, cleft palate, ear abnormalities, coloboma of the
optic nerve, and interventricular communication.12 Di-
agnosis is still uncertain for the 3 remaining girls who
had nonfading linear hyperpigmentation at birth (Table
2). No episodes of vesicular or verrucous lesions were
recorded for these children. Follow-up lasts up to 5 years.
The absence of histological IP features, the random na-
ture of X chromosome inactivation, and the absence of
NEMO gene rearrangement permitted to exclude IP for
all the misdiagnosed children. The association of inflam-
atory colitis, bipolar aphtosis, and linear hyperpigmen-
tion previously reported as Behçet disease with IP did
not satisfy the Landy criteria.13 Nevertheless, such an
association may provide a key for understanding the mo-
lecular basis of IP and should to be further explored.

According to the Landy and Donnai criteria, 40 pa-
ients had been rightly diagnosed as having IP (Table 1).
All 4 classic stages of IP skin lesions were found (Table
3 and Figure 1). Several stages may overlap, making di-
agnosis difficult. However, the first 2 stages are rarely ab-
sent during the neonatal period, and the features of the
last 2 stages are helpful for diagnosing IP in adulthood.

Stages 1 lesions frequently occur, and were noted in
92% of our cases. They are characteristic of IP and no
differential diagnosis may be evoked regarding vesicles
following the Blaschko lines and preceded by erythema
scattered over the face (Figure 1A). As previously re-
ported,14 stage 1 lesions appear before the second week
of life in 90% of cases and clear within the first 4 months.
In our series, recurrence of stage 1 lesions was noted in
2 patients and reported elsewhere.15 The frequency of such
late recurrences, sometimes several years after the neo-
natal period, remains unknown.16-18 Thus, a diagnosis of
IP could be considered in the case of a child presenting
with recurrent inflammatory lesions of unknown origin
along the Blaschko lines. The frequency of stage 2 ver-
rucous and keratotic lesions in our series was consistent
with published data (80% vs 70%, Figure 1B), as well as the
lesions’ time of appearance (within the first 2 months
of life) and duration (they cleared within 6 months).3,14
Verrucous lesions may be localized (Table 3), and are
highly evocative on the scalp. Late onset of focal verru-
cous lesions has been reported.20 In our series, stage 3
linear hyperpigmentation began at 2 weeks of life, ear-
ier than previously reported (Table 3 and Figure 1C).
On the trunk, the spontaneous occurrence and nonscar-
ring resolution of Blaschko linear hyperpigmentation are
major characteristics of IP.5 Such isolated hyperpig-
mented lesions during adulthood may be confused with
other pigmented disorders. Interestingly, 1 of 2 biopsy
results of stage 3 lesions showed free dermal melanin
associated with focal dyskeratosis. Pale, stage 4 macular
and reticulat atrophic lesions were observed in only 9 (22%)
of the 40 patients in our series. These lesions occurred
before 1 year of age in 78% of cases (Table 3 and Figure
1D). Classically, stage 4 begins later than the other stages;
and because it persists in adulthood, it is helpful in the
tardive diagnosis of IP in women.3,14

Hair, nail, dental, and nipple involvements are mi-
nor but useful criteria for IP diagnosis in adults.3 The
frequency of alopecia of the vertex was less (28%) in our
retrospective study than previously reported in the lit-
erature (38%).5,14 Wooly hair has been reported but hair
shaft is usually found normal on microscopic examina-
tion.24 Nail involvement ranges from mild pitting to ony-
chogryphosis.22 The low frequency of nail anomalies in
our study (8% vs 40% elsewhere5) may be related to our
recording only severe forms. In 1 case, subungual hy-
perkeratosis of all fingernails was painful and neither topi-
cal treatment with salicylic acid nor retinoic acid given
orally was efficient.23 Unfortunately, follow-up was not
possible. Supernumerary nipples were noted in 2 girls.
As it is 10 times more frequent in patients with IP than in
the general population,5 breast involvement may be
added as a minor criterion for IP diagnosis. The early age
of our patients may explain the low frequency (25%) of
dental involvement, which is usually common in IP.5,7,14
The deciduous and/or permanent dentitions may be af-
fected. Partial anodontia (lateral incisors and premo-
lars) and conical teeth (incisors and canines) are com-
mon in IP5 and were noted in in 70% of our patients; how-
ever, these tooth abnormalities are frequent in the
pediatric population (6% and 0.33% for partial anodon-
tia and conical teeth, respectively24). Microdontia, enamel
dysplasia, delayed eruption, or caries have also been re-
ported in IP.23 During the neonatal period, panoramic ra-
diography is not necessary. Cleft palate has been de-
scribed in 1.1% of patients with IP, vs 0.28% in the general
population.25

The severity of IP is related to ocular and neuro-
ological impairment.5,7 In our series, ocular involvement
was less frequent (20%) than that reported (approximate
ly 40%)3,16 because we chose not to record myopia
and astigmatism, which are common in the general popu-
lation.25 Ophthalmologic manifestations are divided into
retinal (retinal detachment, visual loss) and nonretinal
(strabismus, cataract, pigmentation of the conjunctiva).29
The incidence of strabismus is significantly higher in IP
than the 3.7% found in the general population.30 Mi-
crophthalmia, which occurred in 6% of our patients, has also been reported in IP. The frequency of only severe ocular impairment, ie, retinal detachment or visual loss, was similar to that reported in previous studies and close to 8%. Retinal detachment is a consequence of neovascularization following retinal ischemia caused by abnormal peripheral retinal vessels. The entire process may occur slowly over several years or quickly within the first month of life. Thus, careful and regular ophthalmologic follow-up is required during the first year so that specific therapy for retinal detachment, such as laser treatment, may be implemented. Since vascular abnormalities may explain severe ocular and neurological involvement, neuroradiological explorations must be performed if any vascular retinopathy is identified. Leukodystrophy was detected by MRI in a 9-year-old girl who presented with severe retinal detachment and normal neuroradiological examination, and MRI or computed tomography scan may detect microphthalmia and retinal detachment. In IP, vascular retinopathy constitutes a predictive risk factor for cerebral involvement.

In 1976, Carney stressed the frequency of neurological manifestations, which he reported occurring in 30.5% of his 653 patients. Landy and Donnai, however, consider that Carney overestimated this frequency because of misdiagnosed cases and found neurological manifestations in 18% of their own 111 patients. Even when considering the Landy and Donnai criteria, neurological impairment was found to be frequent (32%) and severe—causing death in 2 cases (Table 4). Mental retardation, found in about 8% of patients with IP, could be a consequence of early and frequent convulsive episodes, mostly within the first year of life. Thus, the child should be watched carefully during this period. Limited data concerning central nervous system imaging have been published. In our series, MRI and computed tomographic scan results confirmed the findings of clinical examination. Cerebral atrophy, porencephalia, hemorrhage, and hypoplasia of the corpus callosum (2 cases in this study) have been also reported elsewhere. The IP-induced pathogenesis of the central nervous system is still unknown, but developmental inflammatory mechanisms, occlusive phenomena in small vessels, or both, have been suggested. Developmental malformations such as spina bifida seem to be fortuitous in IP. We observed 1 case, with isolated megalourethra; this led to excluding the diagnoses of mammo-renal or acromammo-renal syndromes, in which urinary malformations are associated with abnormal nipples.

Few paraclinical explorations are required for IP diagnosis. According to Landy and Donnai, eosinophilia is a major criterion during the neonatal period. Eosinophilia then decreases slowly to normal values and is usually not complicated by visceral disorders. Histological analysis may be helpful for diagnosis. Stage 1 lesions are characterized by eosinophilic spongiosis of the epidermis (100% of patients in our series), which disappears at the beginning of stage 2 lesions. Focal dyskeratosis occurs very early, persists until the onset of stage 4 lesions (Table 3 and Figure 2), and was clearly determined to be related to keratinocyte apoptosis. During the neonatal period, association of both apoptosis and eosinophilic spongiosis characterize IP. With stage 3 lesions or, later, with residual linear hyperpigmentation in adults, the association of both apoptosis and free melanin is highly suggestive of IP. Although their absence cannot exclude a positive diagnosis, the detection of such histological features should be considered a major criterion for IP diagnosis. Intensity of skin manifestations and eosinophil count are not related to more severe visceral involvement and have no prognostic value.

Careful and systematic examination of first-degree relatives allowed the detection of minor manifestations in the relatives of 11 of our 40 patients. In 2000, IP was shown to be caused by mutations of the NEMO gene. In 9 (80%) of our 12 patients for whom DNA samples were available, the disease-causing mutation was a large-scale deletion of exons 4 to 10, which produces an unstable protein. The NF-κB pathway is involved in local inflammatory response and in the control of keratinocyte apoptosis, which explains the clinical and histological features of apoptosis in IP. The severity of the clinical manifestations of the disease are not related to the type of mutation. Skewed X inactivation is detected in over 98% of female patients with IP and in our series, it was detected in all 12 tested girls. Testing X inactivation is helpful for diagnosing mild forms of IP or identifying the paternal origin of the mutated X chromosome in sporadic cases. Germline mutations in the father's gonads explains over 80% of sporadic IP cases. As indicated earlier, the mutated X chromosome was of paternal origin in 8 of the 11 sporadic cases in our series, revealing the occurrence of paternal-germline mosaicism. Usually, affected male fetuses die in utero at the end of the first trimester. As the diagnosis is not systematically established, the frequency of IP in boys is probably underestimated; in this study, 3 boys with normal karyotype fulfill the criteria. In boys, the disease may occur with a broad spectrum of phenotypic manifestations, from isolated skin involvement to severe neurological impairment. Genetically, such cases may be explained by the presence of the Klenefelter syndrome (47,XXY) or early somatic mutations of the NEMO gene. Interestingly, NEMO mutations have also been reported in anhidrotic ectodermal dysplasia with immune deficiency. This emphasizes the strong relations between these 2 diseases affecting ectoderm-derived structures.

The diagnosis of IP is initially based on clinical criteria. Dermatologists and pediatricians are those first concerned. As, at birth, both eosinophilic spongiosis and apoptosis are characteristic of IP, histological features may be added as major criteria for diagnosis. The follow-up of patients with IP is based on multidisciplinary collaboration, and its primary goal is the detection of rare ophthalmologic and neurological involvement as early as possible in the first year of life. Neuroimaging is performed when abnormal findings on neurological examination, vascular retinopathy, or both, are detected. Genetic counseling must involve both patient and relatives. In doubtful cases, DNA studies are helpful to ascertain or rule out the diagnosis. Clinical diagnosis is the first main step toward a correct phenotype/genotype correlation, which remains indispensable for a better understanding of the
pathological mechanisms of IP and for developing new therapies.

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