Unraveling incontinentia pigmenti: A comparison of phenotype and genotype variants

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Background: Incontinentia pigmenti (IP) is a rare X-linked dominant genodermatosis that affects multiple systems with highly variable phenotypic expressivity. Although most affected individuals carry a common pathogenic variant on the *IKBKG* gene, approximately 20% have no identifiable mutation.

Objective: To describe clinical characteristics and genotype of IP patients and compare clinical differences between *IKBKG* pathogenic variant positive and negative cohorts.

Methods: Retrospective cohort study conducted at a large tertiary pediatric center from 1990 to 2017, for children with a clinical diagnosis of IP.

Results: Forty-two children with IP were identified, including 33 of 42 (79%) females. Most presented with cutaneous stage I findings (31 of 42; 74%). Extracutaneous involvements were common: dental (50%), ocular (31%), hair (31%), nail (15%), and neurodevelopmental (26%). An *IKBKG* pathogenic variant was detected in 20 of 34 (59%) patients. Compared with these, 14 of 34 (41%) patients who tested negative were significantly more likely ($P < .05$) to be male, have no family history of IP, and have lower incidences of dental and hair anomalies.

Limitations: Retrospective methodology limits clear determination of the temporality of symptoms.

Conclusion: Clinical differences between *IKBKG* pathogenic variant positive and negative IP cohorts support the prognostic utility of molecular genetic evaluation. (J Am Acad Dermatol 2019;81:1142-9.)

Key words: clinical genetics; genodermatosis; incontinentia pigmenti; pediatric dermatology.

Incontinentia pigmenti (IP, also known as Bloch-Sulzberger syndrome; OMIM 308300) is a rare genodermatosis with an estimated birth prevalence of 1 in 143,000.[1,2] This X-linked dominant condition occurs primarily in female individuals, with occasional reports of affected male individuals.[3,4] IP classically manifests with an erythematous, linear, vesicular rash that appears at or shortly after birth. Cutaneous findings are accompanied by variable neuroectodermal manifestations affecting the eyes, nails, hair, teeth, and central nervous system (CNS).

At present, the only known gene associated with IP is *IKBKG* (inhibitor of kappa B kinase gamma; previously identified as *NEMO*), located in Xq28.[5] The *IKBKG* gene product is responsible for activation of nuclear factor-kappaB (NF-kB), which is a regulatory protein with multiple roles in inflammatory reactions, immune response, and protection against cell apoptosis.[6] Genetic testing

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for IP usually begins with peripheral blood sample and targeted analysis performed on the *IKBKG* gene to identify the common exon 4-10 deletion present in approximately 70% of patients.[5] If the common deletion is not found, the *IKBKG* gene can be further analyzed via sequencing and deletion/duplication analysis to identify point mutations and other genetic aberrations, which increases the diagnostic yield by approximately 12%.[2] For those with an uninformative result based on lymphocyte DNA analysis, DNA testing from an affected skin tissue may identify somatic mosaicism of *IKBKG*.[7] It is estimated that 80% to 90% of patients with IP will carry a pathogenic variant of the *IKBKG* gene.[8] There remains a lack of observational data about the cohort of 10% to 20% of patients who present clinically with IP but have no identifiable *IKBKG* pathogenic variant.

CAPSULE SUMMARY

- Although most patients with incontinentia pigmenti carry an *IKBKG* gene pathogenic variant, some will have no identifiable mutation.
- Clinicians caring for children with incontinentia pigmenti should recognize that those with no identifiable mutation may be more likely to be male and have a milder clinical phenotype.

IP is clinically diagnosed based on the presence of characteristic lesions that occur in 4 successive and overlapping stages, as described by Landy and Donnai.[9] Stage I can be seen at birth, or shortly after, with an inflammatory vesicular rash in a linear distribution, following lines of Blaschko.[9] Complete blood count may reveal peripheral eosinophilia and histopathology shows eosinophilic spongiosis with focal dyskeratosis.[10,11] This is followed by verrucous lesions (stage II) in infancy, swirling macular hyperpigmentation (stage III) during childhood, and linear hypopigmentation (stage IV) that develops in young adulthood.[9] In some cases, presentation at birth with more advanced stages may be seen, presumably because of earlier stages occurring in utero.[12] In addition to cutaneous criteria for the diagnosis of IP, a variety of extracutaneous anomalies have been proposed as minor criteria (Table I).[13] The phenotypic expression of IP is highly variable and can range from minor findings, such as hair whorl and mild nail dystrophy, to severe presentations, including optic nerve atrophy, seizures, and global developmental delay.[9]

The primary objective of this study was to describe the clinical phenotype and genotype of a cohort of pediatric patients with IP. Secondarily, we aimed to explore variations in the phenotypic expression of patients with and without an *IKBKG* disease-inducing variant.

METHODS

Study design

This was a single-center, retrospective study conducted at the Hospital for Sick Children, a large tertiary pediatric center in Toronto, Canada. Ethics approval was obtained from the hospital's Research Ethics Board prior to initiation.

Patients with a clinical and/or genetic diagnosis of IP seen between January 1, 1990, and June 31, 2017, were identified from dermatology, genetics, and ophthalmology databases. Patients were included in the study if they were younger than 18 years of age at the time of diagnosis, met Landy and Donnai criteria,[9] and had sufficient clinical information to complete the data collection form. Records with insufficient clinical information or with investigations confirming an alternate diagnosis were excluded from the study.

Baseline demographic information, family history, cutaneous and extracutaneous presentation, and laboratory data were extracted. Dermatologic manifestations were confirmed by review of medical records, histories, physical examination notes, and photographs, if available. Eye and teeth anomalies were ascertained from ophthalmology and dentistry records, respectively. CNS manifestations were reviewed from neurology and magnetic resonance imaging reports and grouped under the term of neurodevelopmental disorders. Genetic testing reports available from as early as 2001 were extracted to identify whether the patient had a classic exon 4-10 *IKBKG* deletion, another *IKBKG* pathogenic variant, or no identifiable *IKBKG* pathogenic variant in peripheral blood samples. All individuals who initially tested negative for the common *IKBKG* deletion were subsequently re-evaluated by sequence analysis and targeted deletion/duplication analysis once these became available.

Statistical analysis

Descriptive analysis was conducted for the study's primary objective to analyze the phenotype and genotype findings of all patients with IP. Patients who had undergone molecular genetic testing were divided into 2 cohorts: those with a positive test result (identifiable *IKBKG* pathogenic variant) and those with a negative test result (no identifiable

Abbreviations used:

IP: incontinentia pigmenti
CNS: central nervous system

IKBKG pathogenic variant). Chi-square and regression analyses were conducted to compare the prevalence of phenotypic differences between positive and negative *IKBKG* pathogenic variant cohorts. The significance level was set at 5%. Statistical analysis was done using STATA version 14 (StataCorp, College Station, TX).

RESULTS

A total of 42 children with IP were identified and met the inclusion criteria. In baseline demographics (Table II), most patients were female (33 of 42; 79%) and of white (non-Hispanic) ethnicity (27 of 42; 64%). A family history of IP was noted in 10 of 42 (24%) patients. Maternal history of spontaneous abortion was reported in 14 of 42 (33%) cases. Median age at first dermatology or genetics consult was 6 weeks (interquartile range 2-12). The mean age of all patients at the time of chart review was 7.6 years (standard deviation [SD] 4.8)—specifically, 8.5 years (SD 5.6) in the positive genetics cohort and 6.5 years (SD 3.6) in the negative genetics cohort. All cases met the updated diagnostic criteria for IP by Minic et al.[13]

Skin manifestations of IP

Most patients presented with cutaneous stage I findings (31 of 42; 74%). A skin biopsy was performed in 24 of 42 (57%) patients and was confirmatory in 22 of 24 (92%), with predominant findings of spongiotic lesion with eosinophilic infiltrates. One of the 2 patients with skin biopsy findings that were not characteristic of IP was found to have a novel *IKBKG* pathogenic variant. The other had classic stage I and III cutaneous manifestations, skin biopsy findings of subcorneal pustules containing neutrophils and eosinophils, and no identifiable *IKBKG* pathogenic variant. Clinical manifestations pertinent for each stage are shown in Table III. In follow-up, 26 of 42 (62%) patients developed stage III rash, and only 9 of 42 (21%) patients reached stage IV at last follow-up.

Extracutaneous manifestations of IP

Extracutaneous involvements in IP were common (Table III and Fig 1). For skin appendage anomalies, hair anomalies were detected in 13 of 42 (31%) patients, with the most common findings being vertex alopecia and abnormal hair textures (thin and coarse). Six patients had mild nail ridging and pitting anomalies. One patient had a supernumerary nipple.

Eye anomalies were seen in 13 of 42 (32%) patients and included retinal findings such as avascularity, neovascularization, abnormal pigmentation, and hemorrhage. All patients were followed by ophthalmology for eye surveillance, and 3 patients had eye surgery because of complications from retinal detachment.

Dental anomalies were the most prevalent extracutaneous manifestation and found in 21 of 42 (50%) patients with IP. Dental findings included delayed dentition, conical teeth, and hypodontia. Three patients underwent dental surgery to correct these anomalies. One patient had oral cleft palate.

Neurodevelopmental disorders such as intellectual disability and seizures were present in 11 of 42 (26%) patients, with some individuals having multiple problems. One patient had hypoxic ischemic encephalopathy as a neonate, and another had a congenital Chiari malformation and subsequently developed hydrocephalus.

Table I. Updated diagnostic criteria for incontinentia pigmenti, according to Landy and Donnai[9] and updated by Minic et al[13]

Major criteria	Minor criteria	Condition for establishing IP diagnosis
Typical 4 skin stages of IP distributed along Blaschko lines: I Vesiculo-bullous II Verrucous III Hyperpigmented IV Hypopigmented or atrophic	Abnormal hair (sparse, woolly, alopecia) Abnormal nails CNS anomalies Dental anomalies Nipple and breast anomalies Ocular anomalies Palate anomalies History of multiple male miscarriages Typical skin pathohistological findings	If evidence of IP in a first-degree female relative: • Any single major criteria or at least 2 minor criteria If no evidence of IP in a first-degree female relative: • At least 2 or more major criteria or 1 major and 1 or more minor criteria • If confirmed *IKBKG* mutation typical for IP, any single major or minor criterion

CNS, Central nervous system; *IP*, incontinentia pigmenti.

Table II. Baseline demographics and investigation results for patients with incontinentia pigmenti

Characteristic	All IP patients (n = 42)	Positive genetic (n = 20)	Negative genetic (n = 14)	No genetic (n = 8)
Sex				
Female	33 (79)*	20 (100)	8 (57)	5 (62)
Male	9 (21)	0	6 (43)	3 (38)
Ethnicity				
White/non-Hispanic	27 (64)	15 (75)	8 (57)	4 (50)
White/Hispanic	1 (2)	0	1 (7)	0
Asian	9 (21)	4 (20)	4 (29)	1 (12)
Black	4 (10)	0	1 (7)	3 (38)
Other	1 (2)	1 (5)	0	0
Family history				
(+) for IP in 1 first-degree relative	8 (19)	6 (30)	0	2 (24)
(+) for IP in more than first degree relative or in other family members	2 (5)	1 (5)	0	1 (12)
(+) Maternal history of multiple male miscarriages	14 (33)	8 (40)	2 (14)	4(50)
Investigation and results				
(+) Skin biopsy	22/24 (92)	9/10 (90)	10/11 (91)	3/3 (100)
(+) Peripheral eosinophilia	5/20 (25)	2/9 (22)	2/6 (33)	1/5 (20)
Genetic testing and results				
Total completed	34/42 (81)	-	-	-
(+) Positive: common	16/34 (47)	16/20 (80)	-	-
(+) Positive: other	4/34 (12)	4/20 (20)	-	-
(−) Negative	14/34 (41)	-	14/14 (100)	-

IP, Incontinentia pigmenti.
*Data are presented as n (%), unless otherwise specified n/N (%).

Female patients were less likely to experience extracutaneous manifestations, although this finding did not reach statistical significance (odds ratio 2.78 [95% confidence interval 1.29-5.95] for females vs 3.5 [95% confidence interval 1.29-5.95] for males; $P = .07$).

Laboratory and genetic results

Molecular genetic testing was performed in 34 of 42 patients (81%). In this cohort, 20 of 34 (59%) were found to have an *IKBKG* pathogenic variant, including 16 of 34 (47%) with the common exon 4-10 deletion. Other *IKBKG* pathogenic variants were found in 4 of 34 (12%) patients including novel nonsense mutation (p.R324.X:c.970C>T), frameshift mutation (p.Prp369ArgfsX26), and 2 novel exon deletions producing junction *Hind*III fragments of 9.2kb and 9.8kb as per Southern hybridization assay probes. These individuals presented with similar phenotype compared to those who had the common *IKBKG* deletion. No molecular diagnosis could be found in 14 of 34 (41%) patients. All male patients had karyotype testing that ruled out other chromosomal anomalies. Under complete blood count, peripheral eosinophilia was found in 5 of 20 (25%) infants who were tested.

Comparison of positive and negative IKBKG pathogenic variant

Compared with those with an *IKBKG* pathogenic variant, patients with negative genetic testing results were more likely to be male (6 of 14 vs 0 of 20; $P = .001$) and less likely to have a positive family history (0 of 14 vs 7 of 20; $P = .024$). Individuals with negative genetic testing were also significantly less likely to have extracutaneous manifestations, specifically dental (3 of 14 vs 14 of 20; $P = .002$) and hair (2 of 14 vs 10 of 20; $P = .03$) abnormalities.

DISCUSSION

To our knowledge, this is the first study in literature to report a large cohort of pediatric patients with a clinical diagnosis of IP, analyze genotype and phenotype variants, and present a cohort of 14 IP patients with no identifiable *IKBKG* mutation. Patients clinically diagnosed with IP who are negative for an *IKBKG* pathogenic variant are significantly more likely to be male and less likely to have a family

Table III. Cutaneous and extracutaneous manifestations of incontinentia pigmenti

Clinical manifestations	All IP patients n = 42	Positive genetic n = 20	Negative genetic n = 14	No genetic n = 8
Cutaneous manifestations				
At initial presentation				
Stage I	31 (74)*	14 (70)	12 (86)	5 (63)
Stage II	7 (17)	4 (20)	1 (7)	2 (25)
Stage III	4 (9)	2 (10)	1 (7)	1 (12)
At follow-up				
Stage I	2 (5)	0	2 (14)	0
Stage II	5 (12)	3 (15)	1 (7)	1 (12)
Stage III	26 (62)	11 (55)	9 (64)	6 (75)
Stage IV	9 (21)	6 (30)	2 (14)	1 (12)
Extracutaneous manifestations				
Hair				
Total	13 (31)	10 (50)	2 (14)	1 (12)
Vertex alopecia	11 (26)	8 (40)	2 (14)	1 (12)
Thin hair	5 (12)	4 (20)	0	1 (12)
Wiry hair	2 (5)	2 (10)	0	0
Coarse	1 (2)	1 (5)	0	0
Nail				
Total mild ridging/pitting	6 (14)	2 (10)	2 (14)	2 (25)
Dental				
Total	21 (50)	14 (70)	3 (21)	4 (50)
Delayed dentition	14 (33)	10 (50)	3 (21)	2 (25)
Conical teeth	11 (26)	9 (45)	0	2 (25)
Hypodontia	3 (7)	3 (15)	0	0
Palate				
Total	1 (2)	0	1 (7)	0
Ocular				
Total	13 (31)	9 (45)	4 (29)	0
Retinal anomaly	10 (24)	6 (30)	4 (29)	-
Retinal detachment	3 (7)	2 (10)	1 (7)	-
Strabismus	3 (7)	3 (15)	0	-
Cataracts	2 (5)	2 (10)	0	-
Astigmatism	2 (5)	1 (5)	1 (7)	-
Neuro-developmental				
Total	11 (26)	4 (20)	5 (36)	2 (25)
Seizure(s)	4 (9)	2 (10)	1 (7)	1 (12)
Intellectual disability	5 (12)	4 (20)	0	1 (12)
Speech delay	4 (9)	1 (5)	2 (14)	1 (12)
Autism spectrum disorder	2 (5)	1 (5)	0	1 (12)
Motor delay	1 (2)	0	1 (7)	0
Congenital malformation	1 (2)	0	1 (7)	0
Breast				
Total	1 (2)	1 (5)	0	0

IP, Incontinentia pigmenti.
*Data are presented as n (%) and n.

history of IP or present with hair and dental anomalies.

In the male cohort of IP patients, 6 of 9 had molecular genetic evaluation. This builds on previous literature of 47 male IP patients who underwent testing of the *IKBKG* gene,[3,4,7,14-16] and includes 1 patient overlap with a published case series from our institution.[3] Almost half of the prior reported male IP patients tested positive for the common *IKBKG* pathogenic variant[7] compared with none in this present cohort. Several studies also found that male patients with IP either had Klinefelter syndrome (47,XXY karyotype) or somatic mosaicism for the *IKBKG* gene.[14,15] All male patients in our study had a normal (46,XY) karyotype; none had genetic testing of affected tissue, which can potentially increase

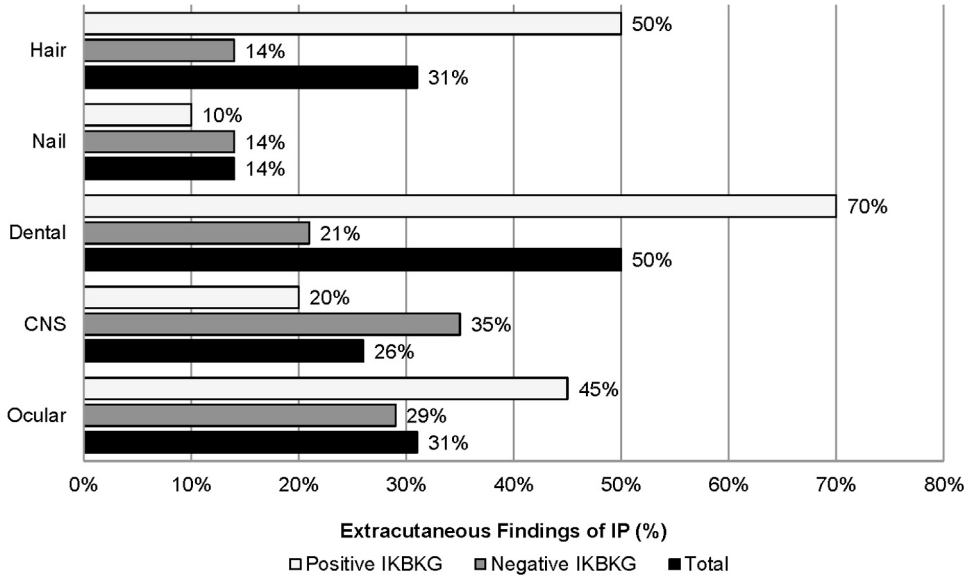

Fig 1. Incontinentia pigmenti. Frequencies of extracutaneous findings for each genetic variant cohort: total (n = 42), positive *IKBKG* pathogenic variant (n = 20), and negative *IKBKG* pathogenic variant (n = 14). This figure does not include 8 IP patients with no genetic testing. *CNS*, Central nervous system; *IP*, incontinentia pigmenti.

diagnostic yield in patients with postzygotic mosaicism.[7] Peripheral blood sample testing may be negative in male IP patients because of selective apoptosis of leukocytes carrying an *IKBKG* pathogenic variant.[15] Of note, in both our study and prior studies, male and female IP patients had similar frequencies of cutaneous and extracutaneous manifestations.[3,17] These findings support the argument that the significant variations in clinical phenotypes observed between positive and negative *IKBKG* pathogenic variant cohorts cannot simply be explained by sex differences alone.

Significantly, there was no family history of IP in all 14 patients who tested negative for an *IKBKG* pathogenic variant. This finding correlates with prior literature that found most occurrences (65%) of IP to be sporadic.[1] A recent report by Fusco et al[18] on father-to-daughter transmissions of IP suggests that mosaicism should also be considered as a possible inheritance pattern. Further, these affected individuals and their family members could potentially have a pathogenic variant on another region of the *IKBKG* gene such as regulatory, deep intronic, or noncoding regions that warrants whole-genome evaluation.

There was significantly lower incidence of hair anomalies in the negative *IKBKG* pathogenic variant cohort. Overall, hair anomalies were found in 13 of 42 (31%) patients, which is slightly higher than the rate of 24% as reported by Minic et al.[13] Vertex alopecia was the most common hair finding in both genetic cohorts and is consistent with prior literature.[13] Specifically, abnormal hair textures were found in 7 patients who tested positive but none who tested negative. Evolution of hair texture in IP has also been previously described to progress from thin and sparse in childhood to coarse and wiry in adulthood.[19] Thus, phenotypic variations in hair anomalies could potentially be attributed to a younger mean age (6 vs 8.5 years) in the negative *IKBKG* pathogenic variant cohort.

Those who tested negative for an *IKBKG* pathogenic variant had significantly lower rates of dental anomalies. In contrast, dental anomaly was the most common extracutaneous manifestation overall, affecting 50% of the total cohort, and comparable to prior systemic review (54%).[20] Although it is hypothesized that the IKBKG protein may play a role in the pathway for the formation of ectodermal tissues including teeth, the exact mechanism remains unclear.[21] Further molecular understanding of the role of *IKBKG* in dental development can help to clarify the phenotypic variations. Given the significant difference in dental anomalies observed between positive and negative *IKBKG* pathogenic variant cohorts, it is plausible that those who tested negative could have an underlying pathogenic mutation in a different gene that has less downstream impact on dental morphogenesis.

The overall frequencies of cutaneous, eye, and nail manifestations were comparable to past literature.[11,22,23] Although only 1 individual in this cohort had a breast anomaly, breast manifestations have

generally been inconsistently reported, ranging from 11% to 30%.[11,24] This difference is likely attributed to the prepubescent age of this pediatric cohort, where breast tissues may not be fully developed.

CNS manifestations remain the most serious clinical sequelae of IP and usually begin early in the neonatal or infantile period.[25] The neurologic phenotype is highly variable, with frequencies ranging from 13% to 46% of patients affected.[17,25] In the present cohort, 11 of 42 (26%) patients were found to have a neurodevelopmental disorder. Seizures remain the most common presentation[25]—in our sample 2 patients had a single seizure episode and 2 developed epilepsy. The involvement of the *IKBKG* gene in intellectual disability has been recognized[26] and affected 5 patients in this cohort. Early neurologic involvement, magnetic resonance imaging screening, and developmental surveillance should be considered for all patients with IP.

To our knowledge, this is the largest study of pediatric patients with IP published to date. Strengths of the study include generalizability of the data as they were collected from a heterogeneous patient population in an ethnically diverse, large tertiary referral center. This study was limited by the retrospective methodology: because there was no follow-up, we could not establish clear temporality and progression of the symptoms over time.

Future large-cohort investigations into patients with IP who test negative for an *IKBKG* pathogenic variant in both pediatric and adult populations are needed to better understand this unusual cohort. Molecular studies on the structure of the *IKBKG* gene and role of *IKBKG* gene products in dental, ocular, and CNS morphogenesis can help to better elucidate the underlying reason for the phenotypic variabilities. Considering that a subset of IP patients has a different clinical phenotype and no identifiable *IKBKG* pathogenic variant, investigation into other potential genetic etiologies for IP should be considered.

Conclusion

Given the uncommon cutaneous findings of IP, early consultation of dermatology and genetic subspecialists is critical in helping to make the diagnosis and beginning the initial workup in the neonatal period. With variable incidence of potentially severe extracutaneous manifestations affecting the eyes, teeth, and CNS, the clinical approach to IP should be multidisciplinary with the involvement of ophthalmology, dentistry, and neurology. Findings of clinical variations between positive and negative *IKBKG* pathogenic variant cohorts suggests the need for in-depth evaluations into key phenotypic and genotypic differences between these groups. Male patients with suspected IP should undergo molecular genetic testing of affected skin as well as peripheral blood sampling, with consideration of whole exome or genome sequencing in those without an identifiable *IKBKG* pathogenic variant. Further understanding of the genotype-phenotype correlation of IP will support clinicians to direct investigations and better provide counseling to patients and affected families regarding prognosis and inheritance in the future.

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