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ORIGINAL ARTICLE

Incontinentia pigmenti in adults

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Abstract

Incontinentia Pigmenti (IP; MIM 308300) is an X-linked dominant genodermatosis caused by pathogenic variant in *IKBKG*. The phenotype in adults is poorly described compared to that in children. Questionnaire survey of 99 affected women showed an age at diagnosis from newborn to 41 years, with 53 diagnosed by 6 months of age and 30 as adults. Stage I, II, and III lesions persisted in 16%, 17%, and 71%, respectively, of those who had ever had them. IP is allelic to two forms of ectodermal dysplasia. Many survey respondents reported hypohidrosis and/or heat intolerance and most had Stage IV findings. This suggests that "Stage IV" may be congenitally dysplastic skin that becomes more noticeable with maturity. Fifty-one had dentures or implants with 26 having more invasive jaw or dental surgery. Half had wiry or uncombable hair. Seventy-three reported abnormal nails with 27 having long-term problems. Cataracts and retinal detachment were the reported causes of vision loss. Four had microphthalmia. Respondents without genetic confirmation of IP volunteered information suggesting more involved phenotype or possibly misassigned diagnosis. Ascertainment bias likely accounts for the low prevalence of neurocognitive problems in the respondents.

KEYWORDS
adult, ectodermal dysplasia, *IKBKG*, Incontinentia Pigmenti, phenotype

1 | INTRODUCTION

Incontinentia Pigmenti (IP; MIM 308300) is an X-linked dominant genodermatosis probably first described by Garrod in 1906 (Garrod, 1906). The name comes from histologic findings of loose melanin in the dermis: the cells are incontinent of their pigment. Landy and Donnai provided tighter delineation of the phenotype in 1993 (Landy & Donnai, 1993) and the associated gene was identified by the International IP Consortium in 2000 as *IKBKG* (previously known as *NEMO*) located at Xq28. (International Incontinentia Pigmenti Consortium, 2000). Germline mutations causing IP are an embryonic lethal in males. There are allelic conditions that affect primarily males: Ectodermal dysplasia with immune deficiency (EDAID1; MIM 300291), Anhidrotic Ectodermal Dysplasia with Immunodeficiency, Osteopetrosis, and Lymphedema (MIM 300301), and isolated immune deficiencies. Genotype/phenotype correlation is limited but full loss-of-function mutations typically cause IP while partial loss-of-function leads to the other conditions (Fusco et al., 2015).

The classic striking phenotype in IP consists of skin lesions that are described as evolving over four defined stages: Stage I: bullous; Stage II: verrucous; Stage III: hyperpigmented; and Stage IV: atrophic. Because it is X-linked, the lesions in affected females follow Blaschko's lines. It is the patterned pigmentation that tends to drive diagnosis. As such, it is likely that at some patients described prior to gene identification had other conditions such as chromosomal mosaicism, other single gene conditions, or teratogenic exposures such as varicella. As might be expected, the other commonly affected tissues are the ectodermal derivatives: hair, teeth, and nails. The more serious abnormalities involve the central nervous system and eyes: there can be congenital microphthalmia, and microvascular anomalies can precipitate stroke and retinal detachment.

IKBKG or IKK-gamma is active in the Nuclear Factor Kappa B (NF-kB) pathway (Aradhya et al., 2001; Hayden & Ghosh, 2004). It is

produced early in embryogenesis and is expressed ubiquitously (Aradhya et al., 2001; Hayden & Ghosh, 2004). There are three IKK proteins—alpha, beta, and gamma—forming a complex. The normal complex is stimulated by cytokines such as Tumor Necrosis Factor alpha or lymphocyte coreceptors like CD30 and CD40. When stimulated, the IKK complex activates the NF-kB complex by phosphorylating the I-kappa-B inhibitor protein. This splits off the inhibitor and it is degraded. Removal of the inhibitor activates the NF-kB complex. It has been shown that active NF-kB protects against the apoptosis induced by the signaling proteins (Bonizzi & Karin, 2004; Hayden & Ghosh, 2004; Jost & Ruland, 2007). When IKK-gamma is abnormal or absent, normal NF-kB activation cannot happen, and the mechanism that protects the cells from apoptosis does not proceed. Cells become sensitive to apoptosis from the various signaling proteins (Bonizzi & Karin, 2004; Jost & Ruland, 2007). This accounts for the embryonic death in males and extremely skewed X inactivation in the females with IP.

The phenotype is clearly defined in children, but discussions of the condition in adults has been limited to talking about the Stage IV lesions, sequelae of the childhood problems, and the high male spontaneous abortion rate. There is, otherwise, limited information. This study proposes to present a broader picture of the adult IP phenotype.

2 | METHODS

The IP Genetic Biobank (http://igb.cnr.it) is a DNA repository at the Human Genetics Laboratory at the Institute of Genetics and Biophysics-Adriano Buzzati-Traverso (IGB-ABT) in Naples, Italy. As part of sample submission there is a detailed questionnaire. Using that as a model, a RedCap survey was created. Permission was obtained from the Institutional Review Board of the University of Texas Southwestern Medical Center for distribution of the anonymous survey.

The survey was designed with questions for adults 18 and over (Supporting Information). Moderators of the IP Family Support Facebook group were contacted and gave permission for posting of an introduction and link to the survey. This group at the time of the survey had 1,070 members. All respondents were proficient in English or had translation services through Facebook and had internet access.

3 | RESULTS

There were 103 completed surveys of which one was a duplicate and three were incorrectly filled out for minor children. There remained 99 completed, evaluable surveys for analysis. All participants were female ranging in age from 18 to 74. Most lived in the United States or the United Kingdom. With 99 surveys, the raw numbers and centiles for the group are the same. Centiles are noted only when the numbers refer to a subset of the survey responses.

Reported age at diagnosis ranged from newborn to 41 years. Forty-three were diagnosed within the first month of life and 53 total by 6 months of age. Thirty were diagnosed as adults, some after the birth of an affected child. The reported method of diagnosis confirmation varied only slightly in the childhood age ranges. Those diagnosed as adults were more likely to have had genetic testing or diagnosis by clinical exam (Figure 1).

For each stage of the skin lesion, the majority stated that it had been present at some point. Stages I–IV affected 87, 52, 71, and 79 respondents, respectively. Of those reporting ever having had each stage, a significant number had persistence of one or more stages. For the Stage I lesions, of the 87 who reported ever having them, 14 people, or 16% of the 87, still had Stage I lesions. For Stage II it was 9 (17%), Stage III 51 (71%), and Stage IV 78 (99%).

There was expected involvement of skin appendages (Table 1) with most reporting a dental abnormality. Twenty-six, or about a quarter, had had some sort of dental or jaw surgery separate from dentures or implants, which were reported by 51. Forty-nine reported wiry or uncombable hair. Nail problems were mostly transient: 73 reported abnormal nails with 27 having long-term problems. Twelve respondents reported previous or current problems with

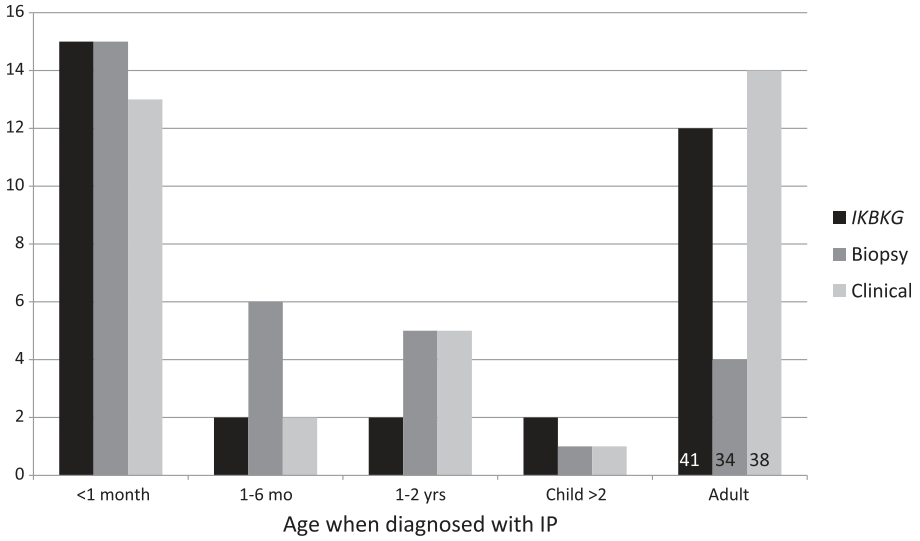

FIGURE 1 Self-reported age at diagnosis by reported type of testing confirming diagnosis: *IKBKG* gene testing, skin biopsy, or clinical evaluation. Forty three total were diagnosed in the first month of life and 53 by 6 months of age. All patients in the sample were adults prior to *IKBKG* gene discovery. It is most likely those diagnosed as children had genetic testing in adulthood and not at the time of diagnosis. The numbers in the bars on the far right represent the oldest age of diagnosis for each group

TABLE 1 Abnormalities of skin appendages were common throughout. These prevalences may be higher than previously reported because the study population was limited to adults

	N = 99
Bald patches scalp	65
Wiry/Uncombable hair	49
Missing teeth	85
Extra teeth	7
Abnormal shape teeth	81
Orthodontics	75
Dentures/implants	51
Dental/jaw surgery	26
Abnormal shape nails ever	73
Persistent nail problems	27
Absent breast and nipple	3
Absent nipple alone	3
Supernumerary nipple	12
Hypohidrosis	12
Heat intolerance	49

TABLE 2 Highest educational diploma or degree received. In the United States, an associate degree is a formal 2-year college degree (14 years total) and Bachelor's degree is a formal 4-year college degree (16 years total). Four reported difficulty with schooling because of poor eyesight. Of the 69 with paid employment, jobs reported included many in health care, education at all levels, arts and sciences, and general business

	N = 99
Graduated high school (12 years)	17
Associate degree (14 years)	9
Bachelor's degree (16 years)	23
Graduate or professional degree	21
Total	70
Special education needed	7
Repeated a grade	6
Visual impairment complication	4
Paid employment	69

decreased sweating and half reported heat intolerance, although this is without further definition.

Assessment of vision loss was problematic and not all answers were clearly interpretable. Two had total blindness. One responded that she had total blindness but "not both eyes" which might be interpreted as partial blindness. Of the 16 who reported partial blindness and provided more information, causes were retinal detachment or cataract. Four reported microphthalmia.

Central neurologic problems were unusual in this group with only one person reporting significant disability due to spasticity. That person also volunteered that she had unilateral brain atrophy and limb asymmetry. She had been diagnosed based only on clinical exam—no biopsy or genetic testing. The majority had completed some defined level of schooling (Table 2). Slightly more than half completed a degree past high school. Seven reported needing special education and six repeated a grade. Four had schooling problems related to visual impairment. Asked about type of work, 69 had paid employment. Jobs included many in health care, education, general business, and professionals in the arts and sciences.

The last item on the survey was an open text box with the question "Is there anything else you would like to share about how IP affects you as an adult?" Fifty-eight gave some response. Overall, those diagnosed before a year of age reported more abnormal clinical features. Of those who were diagnosed based on skin biopsy or clinical exam only, there were more comments about disability and medical problems that seem to fall outside the current understanding of IP. This included leg tumors, carotid dissection, body asymmetry, multiple sclerosis, and descriptions that could be interpreted as hyperkeratosis. One woman reported subungual keratocanthomata leading to surgical digit amputation. There can be nail bed tumors in IP, but whether they are true keratocanthomata remains undetermined (Mahmoud, Zembowicz, & Fisher, 2014).

4 | DISCUSSION

The pediatric phenotype of IP is well defined (Landy & Donnai, 1993; Scheuerle & Ursini, 1999), but the phenotype in adults has largely been inferred rather than observed. Adult reports are included in larger case studies with children (Meuwissen & Mancini, 2012; Pizzamiglio et al., 2014) and there are numerous individual case reports of largely unconfirmed older cases. Investigation of historic and current status of IP-affected adults challenges the conventional wisdom about the condition.

The Stage I (bullous) rash is frequently present at or soon after birth and can recur in crops for years, usually with febrile illness. Stage II (verrucous) is said to occur up to 2 years of age. Based on results of this survey, it appears that the early stage skin lesions do not universally recede and can persist into adulthood. Stages I and II continued in significant minorities of affected women with one woman, age 24 years, stating that her Stage I lesions would still come in breakouts during times of illness. The Stage III (hyperpigmented) skin finding is said to occur from 4 to 16 years with fading adulthood; however, the hyperpigmentation was still present in almost three quarters of women who had ever had this manifestation.

Conventionally, IP is not discussed as an ectodermal dysplasia, but it is allelic to two so-named conditions that are X-linked recessive with residual partial gene function and do not have male lethality: Ectodermal dysplasia and Immunodeficiency 1 (MIM 300291) and Anhidrotic Ectodermal Dysplasia with Immunodeficiency, Osteopetrosis, and Lymphedema (MIM 300301). IP is included as a covered condition of the National Foundation for Ectodermal Dysplasias (National Foundation). The IP phenotype includes features common to ectodermal dysplasias. Alopecia of the scalp can be extensive. The hair can be wooly or

uncombable. Hypodontia and/or oligodontia can be seen with both the deciduous and the permanent teeth. There is older information in the dermatology literature, including an article by Vilanova and Aguade (1959) that calls IP a perspiratory disorder and Rott (1984) in which he counted sweat pores in palm prints of IP patients and noted decreased or absent sweat pores in 5 of 8 cases. More recent literature identifies IP as a condition with altered sweating (Wataya-Kaneda, 2016).

Almost all of the women in this study reported having the Stage IV findings and there were many reports of abnormal sweating and/or heat intolerance. Given the association between *IKBKG* pathogenic variants and ectodermal dysplasia, it is possible that the designation of "Stage IV" is a misnomer. If IP is defined as a true ectodermal dysplasia, a condition in which tissue organization of the skin is abnormal, then the dysplasia should be present in some form from the time of skin formation, Thus, the atrophic skin with absent dermal appendages may be present from birth, not becoming visible until growth of adult-type hair on or tanning of the adjacent normal skin. Studies of sweat gland number, form, and/or function do not appear to have been done in infants or children with IP.

Abnormalities of hair, teeth, and nails were reported at higher rates than in the large European IP central data repository (Fusco et al., 2014). This may result from the current study's being purposely limited to adults and incidentally including only females. Fusco et al. (2014) report data from two subsets of patients, those who submit information to their repository along with a DNA sample (registry) and those for whom there is only clinical data (clinical). There were hair defects in 26.6% of the registry and alopecia in 9.7% of the clinical data. The study reported here indicates that 65 of 99 respondents had scalp alopecia. Seventy-three survey respondents had abnormal nails compared with 14.6% and 64% in the IP registry and clinical populations, respectively. Dental defects also were more commonly reported in this survey than in either of the IP registry or clinical data subsets.

The potentially most serious aspects of IP are those involving the eye and brain. There can be primary microphthalmia, though this is uncommon (Fusco et al., 2014). In the eye, the concerning feature involves the retina. It is presented as hypervascularization, but may actually be a response to initial undervascularization and ischemia (Moreira Neto, Ramos Moreira, & Moreira, 2014; Müller, Courtois, Ursini, & Schwaninger, 2017). There can also be microvascular abnormalities in the brain leading to stroke and abnormalities of the blood brain barrier (Müller et al., 2017; Ridder et al., 2015). It is the sequelae of these abnormalities that cause the severe neurologic phenotype in IP including spastic paresis, seizures, and severe neurocognitive impairments. Of the survey respondents, four reported microphthalmia and 19 reported total or partial blindness with retinal detachment being the primary reported cause of vision loss. These numbers are comparable to those reported from the IP data registry, which shows vision defects in 17% of cases with microphthalmia in 6.4% (Fusco et al., 2014).

The current estimate is that 25–30% of persons with IP have intellectual disability of some degree, mostly mild (Pizzamiglio et al., 2014; Pizzamiglio et al., 2017). There was some report in this survey group of school problems, but it was small. No respondent volunteered frank intellectual difficulty. Only one reported significant neurologically based physical impairment. The relatively low prevalence of neurocognitive impairments is probably a sample ascertainment bias due to the recruitment method.

Of the 99 respondents in this study, roughly one-third each had been diagnosed or had the diagnosis confirmed by *IKBKG* testing, by skin biopsy without gene testing, or based on clinical features alone. The gene was identified in 2000 and not available for clinical testing until 2002. The youngest study participant was 18 years old in early 2018. Thus, those who had *IKBKG* testing had it as an adult. There were 21 respondents who reported being diagnosed as children who also reported having had *IKBKG* testing. It is possible that they misunderstood or incorrectly remembered what testing they underwent, or that they had testing once it became available, having previously been clinically diagnosed. The survey did not ask what year genetic testing was done if the respondent had had it.

An attempt was made to understand about infertility and pregnancy loss, but the results were not interpretable. Three respondents, for example, reported nine or more pregnancy losses, but without the ability to review medical records this could not be confirmed. There were a few who reported using artificial reproductive technologies, including preimplantation genetic diagnosis, and donor eggs. This area would be better served with a separate, focused questionnaire.

The strengths of these data were the high number of well-engaged participants. The participation level far exceeded that expected. The primary limitation was the self-selection and self-reporting. Medical records were not reviewed and there was no way to confirm the diagnosis in those who had not had genetic testing. The participants were all English-proficient and had access to the internet in general and Facebook specifically.

5 | CONCLUSION

It appears that, contrary to current counseling, the early skin lesions often do not fade off and can persist into adulthood, particularly Stage III (hyperpigmented). The findings currently called Stage IV may actually be manifestations of mosaic congenital skin dysplasia that appear to manifest in adulthood simply because they do not become obvious until after puberty and growth of adult body hair. This congenital dysplasia would also account for the reported heat intolerance and the altered sweating. This should be investigated further. Unsurprisingly, persons diagnosed by a year of age tend to have a more medically involved phenotype. Also, persons without genetic confirmation should be re-evaluated for possible alternate diagnoses.

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Study data were collected and managed using REDCap electronic data capture tools hosted at University of Texas Southwestern Medical Center (Harris et al., 2009). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Internally funded, no associated grant.

CONFLICT OF INTEREST

The author has no potential sources of conflict relevant to this work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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