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REVIEW

Dental and oral anomalies in incontinentia pigmenti: a systematic review

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Abstract
Objectives Incontinentia pigmenti (IP) is an X-linked genodermatosis caused by a mutation of the *IKBKG* gene. The objective of this study was to present a systematic review of the dental and oral types of anomalies, to determine the total number and sex distribution of the anomalies, and to analyze possible therapies.
Materials and methods We analyzed the literature data from 1,286 IP cases from the period 1993–2010.
Results Dental and/or oral anomalies were diagnosed for 54.38% of the investigated IP patients. Most of the anomaly types were dental, and the most frequent of these were dental shape anomalies, hypodontia, and delayed dentition. The most frequent oral anomaly types were cleft palate and high arched palate. *IKBKG* exon 4–10 deletion was present in 86.36% of genetically confirmed IP patients.
Conclusions According to the frequency, dental and/or oral anomalies represent the most frequent and important IP minor criteria. The most frequent mutation was *IKBKG* exon 4–10 deletion. The majority of dental anomalies and some of the oral anomalies could be corrected.
Clinical relevance Because of the presence of cleft palate and high arched palate in IP patients, these two anomalies may be considered as diagnostic IP minor criteria as well.

Keywords Incontinentia pigmenti · *IKBKG* gene · Dental anomalies · Oral anomalies · Palate anomalies · Systematic review

Abbreviations

IP	Incontinentia pigmenti
IKBKG	Inhibitor of kappa B kinase gamma
NEMO	NF-κB essential modulator
NF-κB	Nuclear factor-kappa B

Introduction

Incontinentia pigmenti [IP (OMIM 308300)], also known as Bloch–Sulzberger syndrome, is a rare X-linked genodermatosis in which skin changes are usually combined with anomalies of other organs. It appears almost exclusively in females and is usually lethal in males [1]. The estimated prevalence for IP is 0.2 of 100,000 [2]. Mutations of the *IKBKG* (inhibitor of kappa B kinase gamma, previously *NEMO*) gene, localized on the Xq28 chromosomal region, are responsible for IP [3]. The *IKBKG* gene produces nuclear factor-kappa B (NF-κB), which is involved in a

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multicomponent signaling pathway that regulates the expression of hundreds of genes involved in diverse and key cellular processes, including cell proliferation, cell survival, cell death, immunity, and inflammation [4, 5]. The misregulation of *IKBKG* is involved in many diseases [4], but failure to identify the *IKBKG* mutation does not rule out the diagnosis of IP [6]. It was found that the *IKBKG* exon 4–10 deletion causes the majority of registered mutations [3]. The lack of *IKBKG* mutations in the remaining 20–30% of IP cases was probably due to the detection system [7]. The phenotypic expression of *IKBKG* mutation is highly variable, even among related patients with the same mutation [3]. Because an extensive skewing of X-chromosome inactivation has commonly been observed in the blood cells and fibroblasts of IP patients [7], IP phenotype variability is likely to be a result of X-chromosome inactivation [8].

The proposed criteria for IP were those by Landy and Donnai [9] and have been in routine practice since 1993. The presence of symptoms other than skin changes is important if skin changes are subtle. Non-skin changes can be of great prognostic and diagnostic value because they may be present throughout the patient's whole life, whereas skin changes usually fade [10]. The prognosis of IP is generally good and depends on extracutaneous manifestations that may also affect patients' quality of life. In accordance with Landy and Donnai's [9] criteria, skin lesions (erythema; hyperpigmented streaks and whorls; and pale, hairless, atrophic linear streaks or patches) were classified as IP major criteria, whereas dental, hair, nail, and retinal anomalies were classified as IP minor criteria. Hadj-Rabia et al. [11] considered the histological features of affected skin and nipple anomalies as IP minor criteria too.

Since 1906, when the disease was described for the first time [12], there were numerous reports of dental and other oral anomalies in IP. In 1976, Carney [13] reviewed 653 case reports of IP from 464 references published between 1906 and 1975 and analyzed IP symptomatology in that period. A systematic review of a large series of IP patients, including extensive statistic evaluation, has been rarely done. Reported data concerning the number of diagnosed patients and a description of anomalies were often unreliable because of highly specialized approaches. Some papers dealing with genetic issues of IP [14] lacked complete clinical findings concerning analyzed patients. According to reports with larger series of IP patients [8, 11, 15–18], different percentages of dental and/or oral anomalies, from 30.86% [8] to 92% [11], as well as different numbers of dental and/or oral anomalies per patient, from 1.48 [16] to 2.48 [11], were found.

We made a systematic review to obtain an overview of relevant aspects of dental and oral findings. Our review covered data in the available literature of IP cases published from 1993, when Landy and Donnai [9] proposed the IP criteria, until 2010. The aim of our study was to find out whether there were any differences in the number and type of anomalies according to sex, to investigate the influence of anomalies on the quality of life of IP patients, and to discuss possibilities for their correction. We analyzed IP literature published before 1993, divided into two periods, 1906–1975 and 1976–1992, and we compared results from different periods. Because of the genetic background of IP and a lack of causative therapy, there was no influence on phenotype expression. The only cause for the possible differences among these three periods was varying diagnostic criteria. In addition, the discovery of *IKBKG* as the IP causative gene [3] enabled the molecular genetic confirmation of IP. We investigated the correlation of genetic data (when available) and the clinical phenotype, with the main focus on dental and oral findings.

Methods

We analyzed available literature data concerning IP cases published between 1993 and 2010. We found 261 references from the literature with acceptable data for this systematic review. We analyzed studies that covered the pan-ethnic IP patients' populations in Europe, Asia, Africa, Australia, North America, and South America. We list these references separately in "Additional references published in the period of 1993–2010" in Electronic supplementary material (ESM) 1. We took for granted and did not assess the validity of the analyzed articles. Whenever possible, we excluded multiplications of data, such as patients described in more than one reference. We collected references for the period of 1906–1993 in the same manner. We took the data of IP patients for the period between 1906 and 1975 from Carney's review [13]. We list these references in "Additional references published in the period of 1906–1993" in ESM 2. The collected data were mainly frequencies, and we present them in tables. We used a chi-square test to compare the observed frequencies with their expectations [19]. We performed all calculations in Microsoft Office Excel™ 2003.

We reviewed the data of 1,286 diagnosed IP patients who were presented in the available literature published during the period of 1993–2010. Of these, 513 patients provided enough information to evaluate possible dental and oral anomalies. Dentition usually begins at the end of the first year of life; thus, we analyzed only data from patients older than 1 year. In this analysis, we considered the following as dental anomalies: dental shape anomalies, hypodontia including anodontia and dental loss, delayed dentition, and dental anomalies registered in small number or unspecified dental anomalies. We counted the following as dental shape anomalies: cone- or peg-shaped teeth, teeth with accessory cusps, tulip-shaped teeth, impacted teeth, and microdontia. We counted the following as oral anomalies: palate anomalies and different oral anomalies registered in small number. Cleft palate and high

Table 1 Number of IP patients, dental and oral anomalies, and the number of anomaly types per patient by sex for the 1993–2010 period

Sex	No. of IP patients	No. of stomatologically investigated IP patients	No. of stomatologically investigated IP patients with dental and/or oral anomalies	Total no. of dental and oral anomalies	Total no. of dental and oral anomaly types per patient	Total no. of dental anomalies	No. of dental anomaly types per patient	Total no. of oral anomalies	No. of oral anomaly types per patient
Total	1,286[a]	513	279	465	1.67	442	1.58	23	0.08
Female	1,197	459	258	429	1.66	408	1.58	21	0.08
Male	83	54	21	36	1.71	34	1.62	2	0.10

[a] For six patients, data concerning sex were not available in the literature

arched (gothic) palate were included in palate anomalies. We counted the number of dental and oral anomaly types per patient by sex. Quite often, an individual patient had more than one type of dental and/or oral anomaly. To determine the effect of different *IKBKG* mutations on the clinical phenotype, we analyzed the dental and/or oral anomalies of IP patients with a proven *IKBKG* mutation separately.

Results

We present the results of our systematic review of the period 1993–2010 in tables. In Table 1, we show the summarized data for IP patients, dental and oral anomalies, and the number of anomaly types per patient by sex. In Table 2, we show the structure in percentage of types of dental and oral anomalies in IP patients. In Table 3, we show data from IP patients with genetically confirmed *IKBKG* mutations and oral and/or dental anomalies. In Table 4, we list the *IKBKG* mutations, except exon 4–10 deletions, registered in investigated IP patients. In this investigation of 64 registered rare or unclassified dental anomalies, 44 were unclassified but frequent types of dental anomalies.

The total number of IP patients in the literature during the period 1993–2010 was 1,286 (93.08% females, 6.45% males, and 0.47% without adequate data regarding sex in literature). Of all analyzed IP patients, 39.89% were older than 1 year, and only those patients were further investigated for types of dental and oral anomalies. Among stomatologically investigated IP patients, dental and/or oral anomalies were observed in 54.38% of patients. There were in total 465 types of dental or oral anomalies registered in 279 patients (Table 1). The majority of anomalies (442, 95.05%) were dental; the rest (23, 4.95%) were oral. The most frequent types of dental anomalies were shape anomalies and hypodontia, which comprise 36.42% and 31.22%, respectively, of all observed dental anomalies. Delayed dentition was found in 17.87% of patients, and 14.48% of anomalies were unclassified (Table 2). We included caries as an unclassified anomaly type because of the small number of reported patients (only 3.84% of dental anomalies). Thus, 0.31% of IP patients had caries. Among 23 observed types of oral anomalies in IP patients, the most frequent were cleft palate and high arched palate. The total number of dental and oral types of anomaly per patient was 1.67. The results of our statistical analysis of data by sex showed that there was not a significant difference in the number of types of dental and oral anomalies per patient ($p=0.86>0.05$), in the number of types of dental anomalies per patient ($p=0.89>0.05$), or in the distribution of dental anomalies ($p=0.61>0.05$). We did not perform the chi-square test for oral anomalies because of the small expected frequencies for male oral anomalies.

IKBKG mutations were confirmed for 66 IP patients with dental and/or oral anomalies (Table 3). Patients positive for *IKBKG* mutations [6, 18–22] (86.36%) had the common exon 4–10 deletions, whereas 13.63% had different *IKBKG* mutations, as listed in Table 4. The total number of dental and/or oral types of anomalies per patient was 1.66 in IP

Table 2 Percentage of types of dental and oral anomalies by sex for the 1993–2010 period

Sex	Percentage distribution of dental anomaly types				Percentage distribution of oral anomaly types	
	Dental shape anomalies	Hypodontia	Delayed dentition	Rare or unclassified dental anomalies	Cleft and high arched palate	Rare/other oral anomalies
Total	36.42	31.22	17.87	14.48	30.43	69.56
Female	35.78	31.62	17.65	14.95	28.57	71.43
Male	44.11	26.47	20.59	8.82	50.00	50.00

Table 3 Number of IP patients with confirmed *IKBKG* mutations, dental and oral anomalies, and the number of anomaly types per patient for the 2001–2010 period

Type of *IKBKG* mutation	Total number of			Percentage of genetically diagnosed IP patients with				
	Genetically diagnosed IP patients with dental and/or oral anomalies	Dental and/or oral anomaly types in genetically diagnosed IP patients	Types of dental and/or oral anomalies per patient	Dental shape anomalies	Hypodontia	Delayed dentition	Rare or unclassified dental anomalies	Oral anomalies
All mutations	66	107	1.62	21.50	17.76	11.21	48.60	0.93
IKBKG exon 4–10 deletions	57	95	1.66	22.10	18.95	10.53	47.37	1.05
Other than *IKBKG* exon 4–10 deletions	9	12	1.33	16.67	8.33	16.67	58.33	0

patients with common exon 4–10 deletions and 1.33 in IP patients with other types of *IKBKG* mutations. Although the number of dental and/or oral types of anomalies was higher for common *IKBKG* exon 4–10 deletions, the difference was not significant ($p=0.44>0.05$).

Besides the presented results during the period 1993–2010, our analyses of all reported data (for the whole period of 1906–2010 and by three periods of investigation: 1906–1975, 1976–1992, and 1993–2010) are available in Additional Tables 1 and 2 in ESM 3. For the three investigated periods, we found no significant difference in the total number of dental and oral types of anomalies per patient ($p=0.98>0.05$) and in the total number of dental types of anomalies per patient ($p=0.14>0.05$). We found a significant difference in the distribution of dental anomalies for the three investigated periods ($p=0.00002<0.05$).

Discussion

Incontinentia pigmenti is a hereditary X-linked disease with skin, dental, ophthalmologic, and neurologic manifestations, lethal for most but not all male embryos. IP is easily diagnosed in neonates with obvious skin manifestations and anamnestic

Table 4 List of *IKBKG* mutations except *IKBKG* exon 4–10 deletions for the 2001–2010 period

Reference	Type of *IKBKG* gene mutation	Sex	Type of anomalies	Diagnosis
Mansour et al. 2001 [20]	Missense mutation c.1259A>G (p.Term420Trp)	F	Hypodontia and conical teeth	IP
Mansour et al. 2001 [20]	Missense mutation c.1259A>G (p.Term420Trp)	M	Delayed dentition	IP + HED-ID
Dupuis-Girod et al. 2002 [21]	Missense mutation c.1259A>G (p.Term420Trp)	F	Delayed dentition	IP
Rola et al. 2004 [22]	Nonsense mutation c.397C>T (p.Gln133Term)	F	Delayed dentition	IP
Fusco et al. 2004 [8]	Frameshift mutation c.943dupG (p.Glu315GlyfsX80)	F	1 unspecified anomaly[b]	IP
Fusco et al. 2004 [8]	Frameshift mutation c.1078delC (p.His360MetfsX91)	F	1 unspecified anomaly[b]	IP
Fusco et al. 2004 [8]	Frameshift mutation c.1116delT (p.Gly373ProfsX78)	F	3 unspecified anomalies[b]	IP
Martinez-Pomar et al. 2005 [41]	Frameshift mutation c.792dupA (p.Gln265ThrfsX19)	F	1 unspecified anomaly	IP + transient immunodeficiency
Zou and Zhao 2007 [23]	g.19545DelT[a]	F	1 unspecified anomaly (teeth irregularity)	IP

F female, *M* male, *IP* incontinentia pigmenti, *HED-ID* hypohidrotic ectodermal dysplasia and immunodeficiency

[a] Mutation annotation inconsistence with genomic reference sequence

[b] Some frequent anomalies: dental shape anomalies, hypodontia, delayed dentition

heredity data for IP. The constellation of skin manifestations, and possible dental, neurologic, and eye abnormalities, assists in the diagnosis [10] in older children and adults.

The results of our investigation present the distribution of IP patients by sex similar to the results of other studies [6, 13]. In this systematic review, dental and oral anomalies were present in 54.38% of stomatologically investigated IP patients. In most of the other published results of IP patient series with dental anomalies, the proportion of stomatologically investigated IP patients with dental and oral anomalies was much higher: 92% [11], 88.89% [15], 84.6% [17], 80% [16], and 80% [23]. However, Hadj-Rabia et al. [18] found 58.83%, and in the Fusco et al. [8] study, dental and oral anomalies were present in only 30.86% of stomatologically investigated IP patients. These discrepancies could be explained by the differences in the IP patients' cohort.

We found no significant difference in the number of dental and oral types of anomalies per patient by sex during the period 1993–2010. A nearly equal number of anomalies per patient was found in the different periods because there was no treatment to prevent dental and/or oral anomalies in IP. The majority of anomalies were dental, and the most frequent dental anomalies were shape anomalies and hypodontia. Dental shape anomalies in IP patients (36.42%) were much more prevalent than in the general population of children (0.92%) [24]. The prevalence of hypodontia in the analyzed IP patients (31.22%) was much higher than the prevalence of hypodontia in different ethnic groups, both males and females (2.7–7.7%) [25]. The distributions of observed types of dental anomalies in female and male patients did not differ significantly. There was a significant difference in the distribution of dental anomalies for the three investigated periods. It is most likely that these differences in the proportion of dental anomalies were a consequence of the different methods used for diagnosing anomalies.

A low registered percentage (0.31%) of caries in IP patients could be a result of neglecting this type of anomaly as an IP finding. Some authors noted subtle alterations of enamel and dentin structure that may precede caries besides IP typical dental anomalies [26–28]. Because dental caries, diagnosed with visual examination [29], are still a major oral health problem in most industrialized countries, affecting 60–90% of school children and the vast majority of adults [30], there is no doubt that IP patients had caries. One of the highest frequencies of IP patients with dental and/or oral anomalies in our previously published study (88.89%) included caries as an indicative anomaly in IP patients [15]. Recently, Hadj-Rabia et al. [11] reported a series of 25 adult patients with an IP diagnosis confirmed using molecular genetic testing of *NF-κB* and skin biopsies pathohistology. All patients reported increased decay development in spite of early dental care [11]. Because saliva is important in preventing caries, we suppose that the finding of Holmström et al. [17] of decreased stimulated saliva secretion in 10 of 25 IP patients was also interesting in the context of caries pathogenesis in IP. Bearing in mind that *IKBKG* mutations produce severe cellular disorders in skin and other affected tissues, mostly of ectodermal origin that include salivary glands, it is reasonable to consider a relation between *IKBKG* mutations and possible teeth and other oral tissue alterations that may favor the occurrence of caries. Wang et al. [31] demonstrated the heritability of dental caries traits and provided evidence that different genes, or genes with differential effect sizes, are involved in tooth decay in primary and permanent dentitions. *IKBKG* is neither identified nor excluded as a gene involved in pathogenesis of dental caries. The most frequent oral anomalies were cleft palate and high arched palate.

The task of counting and identifying anomalies in some references was challenging [8] because there was only a list of observed anomalies with no exact number. These lists included frequent types of anomalies such as dental shape anomalies and hypodontia. These anomalies were classified as unspecified anomalies together with different anomalies presented in small numbers. Because of these difficulties, the exact number of frequent types of dental anomalies like dental shape anomalies, hypodontia, and delayed dentition was actually higher than that presented in tables. Another problem in performing a systematic review was the lack of direct confirmation of Carney's results [13] because the list of references that he used was not available and, perhaps, some of the patients were misdiagnosed with IP [18]. However, when establishing IP criteria, Landy and Donnai [9] used Carney's article [13] as one of the major references.

During the period 1906–2010, 52 oral anomalies were registered in IP patients. The most frequent types of anomalies were cleft palate and high arched palate. Some oral anomalies like high arched palate were not registered before 1982 [32]. We suppose that oral anomalies had not been recognized as IP-associated anomalies and were not included in case reports. Approximately one third of the oral anomalies were palate anomalies. During the period 1993–2010, 1.55% of IP patients with cleft palate were recorded. Clefts of the lip and palate arise in approximately 0.17 per 100 in general population liveborn babies, with ethnic and geographic variations [33]. Clefts of the lip and palate were approximately ten times more frequent in IP patients than in the general population. This finding indicates that it would be useful for diagnostic purposes to consider cleft palate and high arched palate as IP minor criteria, especially because they are visible at birth, not like dental anomalies which are detectable after 1 year of age.

Although the vast majority of IP patients are females, the number of types of dental and oral anomalies per patient among females and males was nearly equal. It was interesting that the number of types of dental and oral anomalies per patient in all analyzed periods was almost the same, 1.67–

1.69. In some studies, the results were similar: Fusco et al. [8] and Zou and Zao [23] found 1.73 and 1.62 types of dental and/or oral anomalies, respectively. In several studies, authors found higher values of types of dental and/or oral anomalies per patient. Holmström et al. [18] found 1.95, Minić et al. [15] 2.06, and Hadj-Rabia et al. [11] found 2.48; Phan et al. [16] found a lower value, 1.48, of anomaly types per patient. Different values could be attributed to the small number of IP patients in all reports and various study approaches. There was a difference in the distribution of diverse types of dental anomalies in females and males, but it was not statistically relevant. We did not perform such a comparison for oral anomalies because of the small sample size.

In our systematic review of eye anomalies in IP patients, we found 36.5% (449/1,227) IP patients with diagnosed eye anomalies [34]. It is obvious that dental and/or oral anomalies (59.64%) were more frequently observed than eye anomalies (36.5%). Dental and oral anomalies affected patients' quality of life and had important diagnostic value. According to frequency among IP patients, dental and oral anomalies represent the most important diagnostic IP minor criteria.

Finally, 66 IP patients with dental and/or oral anomalies who tested positive for *IKBKG* mutations were independently analyzed. They represent 11.52% of the total number of analyzed IP patients with dental and/or oral anomalies. In this group of IP patients, 86.36% had the common exon 4–10 deletions, whereas 13.63% had different *IKBKG* mutations. This finding is similar to the statement by Smahi and the International Incontinentia Pigmenti Consortium [3] that *IKBKG* exon 4–10 deletions cause 80% of new mutations. The total number of dental and/or oral anomaly types per patient was 1.66 in IP patients with the common exon 4–10 deletions and 1.33 in IP patients with other types of *IKBKG* mutations. Although the number of dental and/or oral anomaly types was higher for the common exon 4–10 deletions, their difference was insignificant. However, besides the fact that *IKBKG* gene mutations were considered as the only cause of IP phenotypical characteristics [6], we must consider that other possibilities for their origin exist. To date, more than 300 genes have been found to be associated with the patterning and morphogenesis of teeth [35]. There are no facts that exclude the possibility that some other gene mutations exist in IP patients besides *IKBKG* [7]. There are a number of genes whose mutations are responsible for different anomalies, including some anomalies found in IP such as anodontia (*MSX1*, *PAX9*, *AXIN2*) [36] and cleft palate (*FGF8*, *FGFR1*, *MSX1*, *TBX2*) [37]. Thus, it is hypothetically possible that cutaneous manifestations in IP originate from *IKBKG* mutation, whereas extracutaneous anomalies in IP patients originate from some gene mutation other than *IKBKG*. According to this hypothesis, there is an option that the combination of mutations of *IKBKG* and some other gene(s) are responsible for final IP phenotype expression—skin changes and associated anomalies of different organs. In the available literature, there are no facts to confirm or reject such a hypothesis.

It is known that the degree of NF-κB function impairment depends on the location of the *IKBKG* mutation [8]. A mutation located in the N-terminal domain of NF-κB reduces but does not abolish its function, whereas mutations that disrupt the C-terminal domain showed lower or no NF-κB activity [8]. According to our results, as well as the results of other authors [8], the IP phenotypic expression and its severity in IP patients with the same *IKBKG* exon 4–10 deletions were highly variable. This variability is probably the result of skewed X-chromosome inactivation [8]. It is currently believed that the highly heterogeneous and often severe clinical presentation of IP might be due to the pleiotropic role of *NEMO*/IKKγ [7].

Analysis of clinical data in the investigation of anomalies in IP patients with genetically confirmed *IKBKG* exon 4–10 deletions was problematic because of the large number (41 of 95) of unclassified anomalies. Thirty-nine frequent dental types of anomalies were found in a large cohort of IP patients with confirmed *IKBKG* mutations [8]. These included dental shape anomalies, hypodontia, and delayed dentition. Precise distribution according to anomaly type was lacking. We encountered a similar problem with data from IP patients with confirmed mutation other than *IKBKG* exons 4–10; 7 of 12 types of anomalies were unclassified. Because of this lack of data, the exact number of frequent dental anomaly types like dental shape anomalies, hypodontia, and delayed dentition was actually higher than presented.

Unlike anomalies of other organ systems in IP, such as the skin, eyes, and central nervous system, which have very few therapeutic possibilities, the most frequent types of dental anomalies (71.48%) could be successfully corrected. Dental and oral anomalies are seldom life-threatening, but they influence the quality of life of IP patients. Some of these anomalies may cause feeding problems (hypodontia, cleft lip, and cleft palate), and others could cause serious psychological problems for IP patients with visible signs of congenital anomaly. Urgent interventions are usually not necessary, with the exception of cleft lip and cleft palate. Besides surgical intervention, stem cell technology combined with tissue engineering could provide solutions for improvements in the treatment of oral clefts in children [37]. When a dentist diagnoses IP in a patient, he takes on an advisory role in addition to handling the patient's dental and oral problems. Patients should receive genetic counseling as well. Restoration of most frequent dental anomalies (dental shape anomalies, hypodontia) depends on individual clinical findings and technical facilities [38]. There are different possibilities for the correction of dental shape anomalies that differ from patient to patient. Hypodontia may be corrected by different fixed or removable prostheses [38] or, in

some cases, by teeth autotransplantation [39]. Although they are often neglected as an IP finding, caries are present in IP patients and can be cured [38]. Cleft lip and cleft palate can be fixed with surgery, and high arched palate does not require treatment [40].

Conclusion

The total number of IP patients found in the literature and analyzed during the period of 1993–2010 was 1,286. Dental and/or oral anomalies were registered in 54.38% stomatologically investigated patients older than 1 year. The number of types of dental and oral anomalies per patient in all analyzed periods for both sexes was almost the same. According to frequency, dental and/or oral anomalies represent the most important IP minor criteria. Because of the high frequency of cleft palate and high arched palate in IP patients, they may be considered as diagnostic IP minor criteria. In the group of genetically tested IP patients, 86.36% had *IKBKG* exon 4–10 deletions. The total number of dental and/or oral anomaly types per patient was higher, although not statistically significant, in IP patients with *IKBKG* exon 4–10 deletions than in IP patients with other types of *IKBKG* mutations. Dental and oral anomalies often influence the quality of life of IP patients. Unlike other clinical findings in IP, the majority of dental and some oral anomalies could be corrected. A dentist who diagnoses IP in a patient has therapeutic and advisory roles within the patient's family.

In the future, for IP patients with associated extracutaneous anomalies, it would be useful to make corresponding molecular genetic analyses of *IKBKG* mutations and mutations of the genes known to cause such anomalies (e.g., anodontia, cleft palate). Thus, it would be possible to determine whether these anomalies were independent of *IKBKG* mutation. In future IP studies, it would be useful to include analysis of caries as a potential indicative anomaly in IP patients. It would be advisable to investigate possible direct (on teeth) or indirect (on other oral tissue like salivary glands) involvement of *IKBKG* in caries pathogenesis

Conflict of interest The authors declare that they have no conflict of interest.

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