Original Article

Incontinentia pigmenti diagnostic criteria update


In 1993 diagnostic criteria for incontinentia pigmenti (IP), a genodermatosis in which skin changes are usually combined with anomalies of other organs, were established. Approximately a decade ago, IKBKG gene mutation was discovered as a cause for IP. This finding has not been included in IP diagnosis so far. In addition, literature data pointed out a few other clinical findings as possible IP diagnostic criteria. Literature facts concerning IP diagnosis were analyzed. Different organ anomalies, their frequency and severity, were analyzed in the context of applicability as IP diagnostic criteria. Taking into account analyzed data from the literature, the proposal of updated IP diagnostic criteria was presented. We propose as major criteria one of the stages of IP skin lesions. As updated IP minor criteria in our proposal we included: dental, ocular; central nervous system (CNS), hair, nail, palate, breast and nipple anomalies; multiple male miscarriages, and IP pathohistological findings. In the diagnosis of IP, the presence of IKBKG mutation typical for IP, and existence of family relatives with diagnosed IP are taken into account.

Conflict of interest
None.

Incontinentia pigmenti [IP (OMIM 308300), Bloch–Sulzberger syndrome] is a rare X-linked genodermatosis with an estimated prevalence of 0.2/100,000 (1) in which changes of skin that are always present are usually combined with anomalies in skin appendages and in other organs (2). IP appears almost exclusively in females and is usually lethal in males (3). The total number of IP patients registered in the literature for the 1906–2012 period was 2291 (91.83% females, 5.85% males, and 2.32% with unspecified sex) (4). IKBKG (Inhibitor of Kappa B Kinase Gamma, previously NEMO; OMIM 300248) is the only gene known to be associated with IP (2). Mutations of the IKBKG gene, localized on the X-chromosome, locus Xq28, are responsible for IP (5). The IKBKG gene product NEMO/IKKγ is required for the activation of the nuclear factor-kappa B (NF-κB) transcription factor. As a consequence of IKBKG mutation in IP cells, its accurate gene product does not arise and NF-κB activation does not occur (5). At the skin level, NF-κB appears to have a dual role in cell growth and apoptosis (6).

The phenotypic expression of IKBKG mutation is highly variable, even among related patients with the same mutation (5). In contrast, patients with different IKBKG mutations may have the same clinical phenotype (5). This variability is likely to be the result of skewed X-chromosome inactivation and caused by the pleiotropic role of the IKBKG gene product (7, 8). It is hypothetically possible that a few different mutations (including IKBKG) are responsible for the complete phenotypic characteristics of IP (4, 7).

In routine practice from 1993, established diagnostic criteria for IP are Landy and Donnai’s (3) (Table 1). Anomalies are classified in the diagnostic criteria according to their frequency and severity. Besides dermatological findings, IP criteria included dental and retinal anomalies and multiple male miscarriages (3).
### Table 1. Proposal for updates to Landy and Donnai’s IP criteria (3)

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria (supportive evidence)</th>
<th>Conditions for establishing IP diagnosis</th>
</tr>
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<tbody>
<tr>
<td>Typical IP skin stages distributed along Blaschko’s lines:</td>
<td>Dental anomalies</td>
<td>No evidence of IP in a first-degree female relative:</td>
</tr>
<tr>
<td>Vesiculo-bullous stage</td>
<td>Ocular anomalies&lt;sup&gt;a&lt;/sup&gt;</td>
<td>If lacking genetic IKBKG mutation data, at least two or more major criteria or one major and one or more minor criteria are necessary to make a diagnosis of sporadic IP</td>
</tr>
<tr>
<td>Verrucous stage</td>
<td>CNS anomalies&lt;sup&gt;b&lt;/sup&gt;</td>
<td>In the case of confirmed IKBKG mutation typical for IP any single major or minor criterion is satisfactory for IP diagnosis</td>
</tr>
<tr>
<td>Hyperpigmented stage</td>
<td>Alopecia</td>
<td>Evidence of IP in a first-degree female relative:</td>
</tr>
<tr>
<td>Atrophic/hypopigmented stage</td>
<td>Abnormal hair (sparse hair, wooly hair, anomalies of eyebrows and eyelashes)</td>
<td>Any single major or at least two minor criteria</td>
</tr>
<tr>
<td></td>
<td>Abnormal nails</td>
<td>In all cases eosinophilia and skewed X-chromosome inactivation supports diagnosis&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Palate anomalies&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nipple and breast anomalies&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple male miscarriages</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Typical skin pathohistological findings&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> According to the authors.
<sup>b</sup> According to Minić et al. (4).
<sup>c</sup> According to Minić et al. (7, 9).
<sup>d</sup> According to Hadj-Rabia et al. (10).
<sup>e</sup> According to Parish et al. (44) and Donnai (11).

Original IP criteria did not include non-dental oral anomalies, non-retinal ocular anomalies, CNS anomalies, nipple anomalies, or pathohistological findings (3). Because the causative gene and type of mutation were not known yet, Landy and Donnai (3) could not consider the possibility of confirming IP diagnosis by detecting IKBKG gene mutation using molecular genetic testing. On the basis of several articles (4, 7–12) that considered some modifications of the existing criteria (3), we discussed the available literature, analyzed the diagnostic criteria, and here propose their updating.

### Phenotypic expression of disease

To obtain consistent and comparable data on the frequency of hair and ocular anomalies in the IP literature for the period 1993–2012, we carried out the meta-analysis of these anomalies in a manner similar to that used in systematic reviews of central nervous system (CNS), dental, and oral anomalies (4, 7). The meta-analysis included IP patients from the period 1993–2012 after IP diagnostic criteria were established (3). Details of analyses are presented in Appendix S1: meta-analysis of hair, nail, and ocular anomalies in the incontinentia pigmenti literature, Tables S1–S7.

### Skin manifestations

Skin changes in IP represent IP major criteria (3). They typically occur at birth or during the first weeks of life to adulthood along Blaschko lines (2). Skin abnormalities are consistent IP features and usually occur in four stages that evolve sequentially (2). The onset, duration, and overlapping of IP stages vary among patients, and not all patients experience all four stages; stage 4 does not occur in all individuals (2). Each clinical stage has characteristic pathohistological findings (10, 13). We present details of the clinical skin changes for each stage, onset, and pathohistological findings in Table 2. Because of the important diagnostic value of pathohistological findings in IP, Hadj-Rabia et al. (10) proposed them as IP minor criteria.

### Anomalies of hair

Hair anomalies were classified as IP minor criteria (3). Almost 50% of IP patients have had or do have minor abnormal hair features (3, 15). In a recent study of 198 IP patients, 66% reported hair abnormalities (16). Alopecia is a common hair anomaly in IP, especially at the vertex and often after blistering or verrucous lesions at the site (11). Most commonly, alopecia is mild and unnoticed (15). Besides the scalp, alopecia may occur also on the trunk and extremities (2). Hair is often described as sparse early in childhood and as lusterless, wiry, or coarse later (11). Sparse eyelashes and eyebrows were also reported in 76% of 25 adult patients (10). According to our investigation (Appendix S1, Tables S2 and S3), 24.83% (22.78% females and 2.05% males) of 733 IP patients with investigated hair presented different hair anomalies. All types of alopecia were registered in 20.33% of investigated IP patients, and other non-alopecia hair anomalies were registered in 4.50%. Non-vertex alopecia was found in 12.14% of investigated IP patients, and non-vertex alopecia was found in 8.18%. Non-alopecia hair anomalies included sparse hair, wooly hair, and anomalies of eyebrows and eyelashes.

### Anomalies of nails

The age of onset of nail anomalies ranges from 3 to 45 years of age, usually after puberty (17). The mean
Table 2. Stages of skin changes evolution in IP: clinical findings (2, 3), stage onset (2, 3), pathohistological findings (10, 13) and differential diagnosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical skin changes</th>
<th>Stage onset</th>
<th>Pathohistological skin findings</th>
<th>Differential diagnosis</th>
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<tbody>
<tr>
<td>Stage 1 vesiculo-bullous stage</td>
<td>Erythema and blistering</td>
<td>Within the first few weeks of life; generally disappears by age 18 months</td>
<td>Eosinophilic spongiosis and intraepidermal vesicle containing eosinophils. Many apoptotic keratinocytes in the epidermis</td>
<td>Dermatoses with blistering in early infancy such as different types of epidermolysis bullosa and bullous bacterial infection</td>
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<tr>
<td>Stage 2 verrucous stage</td>
<td>Hypertrophic rash</td>
<td>Within the first few months of life; usually lasts for a few months</td>
<td>Papillomatosis, hyperkeratosis, and acanthosis of the epidermis. Many apoptotic cells in the epidermis forming squamous eddies. Major melanin incontinence</td>
<td>Verrucae vulgares (simple warts) Nevus verrucosus Molluscum contagiosum X-linked-dominant chondrodysplasia punctata Linear epidermal nevi</td>
</tr>
<tr>
<td>Stage 3 hyperpigmented stage</td>
<td>Hyperpigmentation</td>
<td>Usually begins as stage 2 starts to resolve; persists into adulthood</td>
<td>Marked melanin incontinence with numerous melanophages in the dermis. No more epidermal hyperplasia. Scattered apoptotic cells in the epidermis</td>
<td>Hypomelanosis of Ito Naegeli syndrome Pigment mosaicism</td>
</tr>
<tr>
<td>Stage 4 atrophic/ hypopigmented stage</td>
<td>Hypopigmentation and alopecia</td>
<td>The hyperpigmentation usually begins to fade in the teens and early twenties; does not occur in all patients</td>
<td>An atrophic epidermis; massive reduction of melanin in the basal layer; the persistence of apoptotic bodies in the epidermis or papillary dermis; the complete absence of pilosebaceous units and eccrine glands</td>
<td>Vitiligo with localized alopecia Different types of ectodermal dysplasia</td>
</tr>
</tbody>
</table>

age is 26.88 years of age (17). The reason for such late onset of nail anomalies is still unknown. Nail changes may involve all or most of the fingernails and toenails. The changes typically affect fingers more than toes (15), but the most common are on the first three digits of the hands (17). Nail changes were included in IP minor criteria (3). In several reported series of IP patients, 7.1–48% of them had nail anomalies (3, 12, 16, 18). According to our investigation (Appendix S1, Table S4), 8.7% (8.9% females, 7% males) of 723 IP patients with investigated nails had different nail anomalies. Their manifestations ranged from mild ridging or pitting to severe nail dystrophy (11) or subungual or periungual tumors (3, 16). Biopsies and X-ray examination of the digits provide identification and diagnosis of such subungual tumors (17). The pathohistology of these tumors corresponds closely to that seen in the verrucous cutaneous lesions of stage 2. These lesions can be associated with bony deformities of the underlying phalanges (3).

Anomalies of the breast and nipples
Abnormalities of the breast and nipples in IP have been reported inconsistently in the literature (3). They were not mentioned in Carney’s review (18). According to Landy and Donnai (3), the incidence of nipples and breast anomalies was at least 10 times greater than the incidence in the general population. In order of frequency predominate supernumerary nipples, nipple hypoplasia, breast hypoplasia, and aplasia (3). Besides Landy and Donnai (3), exceptions were studies of Badgwell et al. (16) and Hadj-Rabia et al. (10), where 11% and 30% of IP patients, respectively, with breast and nipple anomalies were presented. A possible reason for the discrepancy in the frequency of anomalies is the fact that in the literature IP patients were usually presented as neonates or prepubescent children, whereas Hadj-Rabia et al. (10) presented 25 adult IP patients. The prevalence of supernumerary nipples in the general population was 0.2–5% (19), lower than in IP patients. Differences in clinical phenotype of breast and nipple
anomalies between prepubescent children and adults arose from the fact that only after puberty are breasts completely developed. Generally, before puberty it is possible to notice only nipple numerical anomalies.

Dental and oral anomalies

Dental anomalies could be seen only after reaching the first year of life when tooth eruption starts, whereas oral anomalies can be detected immediately after birth. According to the reports with larger series of IP patients (9, 10, 12, 20–22), different percentages of IP patients with dental and oral anomalies, from 30.86% (20) to 92% (10), as well as different numbers of dental and oral anomaly types per patient, from 1.48 (21) to 2.48 (10), were found. In a systematic review in the period 1993–2012 dental and/or oral anomalies were observed in 54.38% of 513 stomatologically investigated IP patients (7). According to the frequency, dental and/or oral anomalies represent the most frequent and important IP minor diagnostic criteria (7). Of all registered anomalies, 95.05% were dental, and 4.95% were oral. The most frequent dental anomalies were dental shape anomalies, hypodontia, and delayed dentition (36.42%, 31.22%, and 17.87%, respectively). Cleft and highly arched palate were the most frequently registered oral anomalies (7, 9). Although the absolute number of palate anomalies is relatively small, the number is 25 times higher in IP patients than in the general population (7). This fact indicates that it would be useful for diagnostic purposes to consider oral anomalies, especially cleft and highly arched palate, as IP minor criteria because they are visible at birth, unlike dental anomalies, which are detectable only after 1 year of age (7).

Ocular anomalies

Retinal anomalies were included in a list of IP diagnostic criteria (3). It was also concluded that despite all reported anomalies more than 90% of IP patients have normal vision (3). Ocular anomalies occur from the neonatal period through the early infantile period (2). In IP patients ocular anomalies may be serious and may lead to vision-threatening manifestations or even blindness caused by retinal disease (23). Ophthalmologic findings of IP patients were published in several retrospective studies with different results of IP patients with ocular anomalies, from 16% to 77% (12, 18, 21, 24–27). The majority of retinal anomalies in IP represented vascular anomalies that included telangiectasia, ectasia, hemorrhage, arteriovenous anastomoses, neovascularization, and avascularity of retina (28). They lead to a sequence of events, ending with retinal detachment (23). Occasionally, the process can stop at any time and spontaneously regress, leaving various sequelae (29, 30).

According to our investigation 37.24% of 831 IP patients had different ocular anomalies (Appendix S1, Tables S5–S7). Retinal and non-retinal anomalies were present in approximately the same ratio, 53.00% and 47.00%, respectively. Vitreous anomalies and lens anomalies represented 3.38% and 2.61% of all anomalies. Microphthalmia and amaurotic eyes represented 2.30% and 6.91%, respectively. The total number of ocular types of anomalies per patient was 2.11. A single IP patient had different combinations of ocular anomalies: only retinal, only non-retinal, or a combination of both types of anomalies. Serious vision-threatening anomalies represented 69.89% of all ocular anomalies.

Some of the aforementioned non-retinal, but serious, vision-threatening anomalies registered in IP patients were present in the general population in much smaller numbers than in IP patients. Congenital cataracts were present in 0.3% (31) and microphthalmia in 0.02% of the general population (32). However, according to the etiologic classification of infantile and developmental cataracts in dermatologic diseases, cataracts were classified as an IP feature (33). Although retinal anomalies are one of the IP diagnostic criteria (3), we found non-retinal ocular anomalies in approximately half of IP patients registered (Appendix S1, Tables S6 and S7). Some of the non-retinal anomalies were not included in actual IP diagnostic criteria (3). This was why we suggested modification of ‘retinal diseases’ in the ‘ocular anomalies’ criterion that covers both retinal and non-retinal anomalies.

Central nervous system anomalies

CNS anomalies constitute the most serious complications of IP (23). Similar to skin changes in IP, CNS anomalies occur from the neonatal period through the early infantile period (4). CNS abnormalities that emerge in adulthood IP patients are unlikely to be a consequence of IP. According to the several reports with series of IP patients, 13–35% of the patients had CNS anomalies (18, 20, 25). Landy and Donnai (3) omitted CNS anomalies as an IP criterion although a high percentage of registered CNS anomalies that the authors stated (under 10%) for their unpublished series of 111 IP patients. Differences in findings are very likely to originate from different sample sizes, and, because of the larger sample size, the results of the recent study were more reliable (4). In a systematic review of CNS anomalies in IP during the period 1993–2012, CNS anomalies were observed in 30.44% of 795 neurologically investigated IP patients (4). The most frequent types of CNS anomalies were seizures, motor impairment, and mental retardation, which comprise 41.98%, 25.70%, and 20.36%, respectively, of all observed CNS anomaly types. Microcephaly was registered in 4.07% of IP patients (4). The majority of neurologically investigated IP patients with CNS anomalies (18.86%) suffered from severe CNS anomalies (4). Moreover, IKBKG gene mutation involvement in mental retardation is generally recognized, and the gene was added to the list of mental retardation genes (34). Although limitations such as heterogeneity, different definitions, and criteria for their diagnosis, frequencies of seizures, motor impairment, mental retardation,
and microcephaly were generally higher than in the
corresponding general population. For example,
microcephaly for live births for the 2005–2009 period was
1.67 per 10,000 births (35). In the general population,
the prevalence of epilepsy was 0.005–0.01% (36), and
the prevalence of mental retardation was 1–3% (37).

On the basis of the collected and analyzed data, it is
obvious that percentages of IP patients with CNS
(30.44%) (4) and ocular anomalies (37.24%) (Appendix
S1, Table S7) were high. Taking into account the fact that retinal anomalies were already recognized as
IP minor criteria (3), the similar frequency of CNS
(30.44%) (4) and retinal anomalies (23.58% according
to our study, Appendix S1, Table S7), and the fact that CNS anomalies represent the most important threat to
the normal lifespan of IP patients (14), CNS anomalies
should be recognized as IP minor criteria (4).

Non-ectodermal IP manifestations

Under the influence of eotaxin expression in IP-affected
keratinocytes (38) leukocytosis with eosinophilia may
occur, particularly in stages 1 and 2 (2). In IP diagnostic
criteria (3), eosinophilia was classified as a major
criterion. As eosinophilia is not pathognomonic for IP it
may only support IP diagnosis. Some unusual features
in IP, such as ultrastructurally disordered leukocytes,
were also observed (39).

Combination of different organ anomalies in IP

The relationship of the simultaneous occurrence of the
most frequent IP extracutaneous anomalies: CNS, ocular, and dental and/or oral anomalies were investigat-
gated (4). According to this analysis of the literature
data, 54.30% of IP patients with CNS anomalies had
associated ocular anomalies. Dental and/or oral anomalies were present in 69.56% of IP patients with CNS
anomalies. CNS, ocular, and dental and/or oral anomalies occurred in 36.93% of IP patients simultaneously.
Different combinations of associated extracutaneous
anomalies in IP are likely to be the result of skewed X-
chromosome inactivation and caused by the pleiotropic
role of IKBKG gene product (20, 40).

Miscarriages

A history of multiple male miscarriages is one of the
IP diagnostic criteria (3). Affected women have an
increased risk of miscarriage, most likely represent-
ing affected male conceptions (11) that typically fail
to survive past the second trimester (15). It is advis-
able to perform careful skin evaluation in women with
recurrent miscarriages and to perform IKBKG molecu-
lar genetic testing (10).

IP in males

Although IP has been identified as a disease lethal
for males, approximately 120 males who meet the
diagnostic criteria for IP have been reported (7).
Survival in a male is most often mediated through
somatic mosaicism (41, 42). In some cases it is
mediated through the 47,XXY karyotype (Klinefelter
syndrome) (41, 42).

Timetable of different organ anomalies appearance in IP

In establishing the diagnosis of IP, it is very important
to take into account the age at onset of some changes
and age of the examinees. Usually skin changes appear
first at birth (15), followed immediately by CNS (4)
and eye (2) anomalies. Oral (not dental) anomalies
are visible at birth also (11). Hair anomalies are
detectable somewhat later, when the hair begins to
grow. Dental anomalies can be seen only after reaching
the first year of life when tooth eruption starts (11).
Numeric anomalies of the nipple are present at birth,
and other breast anomalies develop after puberty (12).
Nail anomalies occur usually after puberty (17).

Molecular genetic testing

Detecting IKBKG gene mutation responsible for IP (5),
because of its high prevalence in IP, indicates that
the mutation detection has a high diagnostic relevance (43).
Besides IP, several other phenotypes can be expressed
that are caused by different types of IKBKG gene
mutations (2).

IKBKG exons 4–10 deletion is common in individu-
als with IP and is found in nearly 70–80% of IP patients
(5, 8, 40). To date, 53 different (missense, frameshift,
non-sense, and splice-site) mutations of IKBKG have
been reported in IP patients (40). The rate of de novo
mutations is approximately 65% (40). These mutations
originate from different molecular mechanisms at the
IKBKG locus (8).

When other IP major criteria are absent, detection of
positive IKBKG gene mutation typical for IP in
the presence of a single IP minor criterion would
be acceptable for making a diagnosis among female
first-degree relatives. Analytical methods for IKBKG
mutation screening were discussed in detail recently by
Fusco et al. (8). In male patients with clinical signs of
IP, a diagnostic algorithm is proposed (42).

Although skewed X-chromosome inactivation is not
unique for IP (2), some authors recommend adding
evidence of skewed X-chromosome inactivation results
to IP criteria (11, 44). Results of X-chromosome
inactivation studies are only supportive and need to
be carefully interpreted in the context of clinical
findings and/or family history (2). Sometimes (e.g.
when Klinefelter syndrome is suspected) karyotype
analysis may be useful.

Identification of an IKBKG mutation allows carriers
to make informed reproductive decisions, which takes
into account the risk of having an IP-affected child. A
women with a mutation may decrease her risk of having
an IP-affected child by taking advantage of prenatal
diagnosis (8). Preimplantation genetic diagnosis is also
possible (8).
Differential diagnosis

Any condition with skin manifestations in Blaschko’s lines may be confused with IP (11). The age of the patient and the onset of changes are important. Differential diagnosis in the context of skin changes depends on the IP stage. Numerous skin diseases could be considered (14) and are summarized in Table 2. If there are no visible skin changes, differential diagnosis is far more difficult especially if no other family members have been diagnosed with IP.

Conclusion

Clinical features of IP are variable and are difficult to diagnose in cases with mild manifestations. Taking into account all previously discussed aspects of clinical and laboratory IP diagnostics, we present the proposal of updated IP diagnostic criteria.

Our proposal for updated IP major criteria includes any of four IP skin stages. For updated IP minor criteria, because of their frequency in IP compared with the frequency in the general population and potential severity, included the following: dental anomalies, ocular (instead of retinal) anomalies, CNS anomalies, alopecia and abnormal hair, abnormal nails, palate, breast and nipple abnormalities, multiple male miscarriages, and IP pathohistological findings. Eosinophilia and the evidence of skewed X-chromosome inactivation studies may be carefully considered as conditions that support the diagnosis of IP.

Besides IP major and minor criteria in establishing IP diagnosis presence of \( IKBKG \) mutation typical for IP, and existence of family relatives with diagnosed IP are taken into account. If there is no evidence of IP in a first-degree female relative and genetic \( IKBKG \) mutation data are lacking, at least two or more major criteria or one major criterion and one or more minor criteria are necessary to make a diagnosis of sporadic IP. If there is no evidence of IP in a first-degree female relative and the case is confirmed for \( IKBKG \) mutation typical for IP, any single major or minor criterion is satisfactory for IP diagnosis. If there is evidence of IP in a first-degree female relative, single major criterion or at least two minor criteria are satisfactory for IP diagnosis.

Supporting Information

The following Supporting information is available for this article:

Appendix S1. Meta-analysis of hair, nail, and ocular anomalies in the incontinentia pigmenti literature.

Table S1. Number and percentage of IP patients according to sex in the period 1993–2012.

Table S2. Number of IP patients according to sex with investigated hair and presence of hair anomalies in the period 1993–2012.

Table S3. Number of different hair anomaly types and their percentage in IP patients investigated for presence of hair anomalies according to sex in the period 1993–2012.

Table S4. Number of IP patients according to sex, investigated presence of nail anomalies and presence of nail anomalies in the period 1993–2012.

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Table S5. Number of IP patients according to sex, ophthalmological investigation and presence of eye anomalies in the period 1993–2012.

Table S6. Number and percentage of single mild and serious vision threatening nonretinal anomaly types according to sex in the period 1993–2012.

Table S7. Number and percentage of retinal, nonretinal, serious vision threatening anomaly types with and without included retinal anomalies in IP patients according to sex in the period 1993–2012.

Additional Supporting information may be found in the online version of this article.

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References


