Congenital abnormalities reported in Pelger-Huet homozygosity as compared to Greenberg/HEM dysplasia: highly variable expression of allelic phenotypes
Oosterwijk, J.C.; Mansour, S.; van Noort, G.; Waterham, H.R.; Hall, C.M.; Hennekam, R.C.M.

Published in:
Journal of Medical Genetics

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)
Congenital abnormalities reported in Pelger-Huët homozygosity as compared to Greenberg/HEM dysplasia: highly variable expression of allelic phenotypes

J C Oosterwijk, S Mansour, G van Noort, H R Waterham, C M Hall and R C M Hennekam

doi:10.1136/jmg.40.12.937

Updated information and services can be found at:
http://jmg.bmjjournals.com/cgi/content/full/40/12/937

These include:

References
This article cites 33 articles, 4 of which can be accessed free at:
http://jmg.bmjjournals.com/cgi/content/full/40/12/937#BIBL

Rapid responses
You can respond to this article at:
http://jmg.bmjjournals.com/cgi/eletter-submit/40/12/937

Email alerting service
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Notes

To order reprints of this article go to:
http://www.bmjjournals.com/cgi/reprintform

To subscribe to Journal of Medical Genetics go to:
http://www.bmjjournals.com/subscriptions/
Congenital abnormalities reported in Pelger-Huët homozygosity as compared to Greenberg/HEM dysplasia: highly variable expression of allelic phenotypes

J C Oosterwijk, S Mansour, G van Noort, H R Waterham, C M Hall, R C M Hennekam

LETTER TO JMG

In 1928 the Dutch physician Pelger described two patients with a morphological abnormality of leukocytes that consisted of hypolobulation of the nuclei: there were two lobes instead of the usual five or more and the chromatin structure was coarse and denser. This was subsequently shown to be a genetic trait by paediatrician Huët. In the following years many families with Pelger-Huët anomaly (PHA) from different countries were reported and autosomal dominant inheritance was firmly established. Bilobulated PHA nuclei (“spectacle” or “pince-nez” cells) can also be a transient symptom in the presence of underlying disease — for example, infection, myeloid leukaemia or medication — as part of a “shift to the left” (pseudo PHA), but constitutional PHA is a constant, genetic, and harmless nucleomorphic variant. The frequency of PHA ranges from 0.01–0.1%, with documented clustering in the region of Gelenau, Germany, where 1% of the population has PHA.

Homozygosity for PHA was first detected in rabbits before it was described in man. Ever since, PHA homozygosity has been associated with (skelatal) abnormalities and early lethality, though mainly based on animal data. In 2002, through positional cloning, mutations in the lamin B receptor gene (LBR) on 1q42 were found to cause PHA. One single founder mutation was detected in 10 Gelenau families, as well as seven other mutations in 10 families from elsewhere. Homozygosity for the founder mutation was detected in one patient that was previously reported with mild congenital abnormalities and homozygous PHA on haematological investigations.

At about the same time, investigations in autosomal recessive Greenberg/HEM (hydrops, ectopic calcifications, moth-eaten) dysplasia had led to the same gene from quite a different angle. Greenberg/HEM dysplasia is a rare, early (in utero) lethal skeletal dysplasia, characterised by severe hydrops, short limbed dwarfism and marked disorganisation of chondro-osseous calcification (with a moth-eaten aspect). Polydactyly and other malformations may be present. An accumulation of cholesta-8,14-dien-3β-ol was detected in fibroblasts of an affected fetus, due to deficiency of 3β-hydroxysterol Δ14-reductase. This was caused by a homozygous 7-base pair substitution in exon 13 of LBR, leading to a stop codon. In the patient’s mother, more than 60% of granulocytes appeared to have PHA (the father could not be tested). Since this finding, mutations have been detected in both alleles of LBR in three additional HEM cases (H Waterham, personal communication). Moreover, the relation between PHA and Greenberg/HEM was recently confirmed in a patient of Offiah et al where PHA was demonstrated in >95% of maternal granulocytes, but not in those of the father (S Mansour, personal communication).

The finding that PHA (homozygosity) and Greenberg/HEM skeletal dysplasia are allelic disorders sheds new light on the presumed congenital skeletal abnormalities in PHA homozygosity reported in the literature. We therefore critically examined these reports.

Key points

- Pelger-Huët anomaly (PHA) is a benign, autosomal dominant haematological trait characterised by hypolobulation of granulocyte nuclei. PHA homozygosity, however, is associated with skeletal abnormalities and early lethality on the basis of animal studies and case reports. In 2002 PHA was found to be due to heterozygous mutations in the lamin B receptor gene (LBR), and a homozygous LBR mutation was detected in a boy with mild congenital abnormalities. Homozygous mutations in LBR cause the ic/ic phenotype in mice.

- Recently it was shown that Greenberg/HEM skeletal dysplasia, an in utero lethal disorder, is caused by a 3β-hydroxysterol Δ14-reductase deficiency, also due to homozygosity for mutations in the LBR. Moreover, in two Greenberg/HEM cases, PHA was detected in relatives, indicating that PHA and Greenberg/HEM dysplasia are indeed related disorders. To assess the phenotypes and possible clinical overlap, all published cases of PHA homozygosity and of Greenberg/HEM were reviewed.

- In 11 people reported as PHA homozygotes, congenital abnormalities were rarely seen, there was no obvious skeletal dysplasia, nor were there indications for skin abnormalities or early lethality. PHA homozygosity causes increased intrauterine lethality, perinatal death and severe chondrodystrophy with limb defects in rabbits. In Lbr/-/- mice there is increased intrauterine lethality, severe ichthyosis and sometimes congenital hydrocephaly and mild syndactyly. Phenotypic similarities to Greenberg/HEM dysplasia are indeed related disorders. To assess the phenotypes and possible clinical overlap, all published cases of PHA homozygosity and of Greenberg/HEM were reviewed.

- The results suggest that in human beings, PHA homozygosity is phenotypically distinct from Greenberg/HEM dysplasia. This might be due to allelic heterogeneity, on the basis of the nature and localisation of the LBR mutations involved. However, since the phenotypes may be the extremes of one clinical spectrum, which is also suggested on the basis of animal data, the existence of intermediate phenotypes cannot be ruled out yet.

Abbreviations: HEM, hydrops, ectopic calcifications, moth-eaten; LBR, lamin B receptor gene; PHA, Pelger-Huët anomaly.
reviewed all published cases of PHA homozygosity, to assess a possible clinical overlap which might be relevant for genetic counselling and that could help understand the phenotypic variability of homozygous LBR defects.

**REVIEW OF REPORTED CASES**

A Medline literature search was used to collect all articles on PHA homozygosity. Of these, all references were checked for additional reports. A total of 11 patients were found with the diagnosis PHA homozygosity.6-11,14,20-21

**Pelger-Huët homozygosity in human beings**

In 1952 Haverkamp Begeman et al were the first to describe PHA homozygosity in a Dutch girl.8 She had convulsions (which ran in the family) and mild psychomotor delay. Apart from mild short stature there were no abnormalities and the skeletal survey was normal. Haematological examination showed round, coarse nuclei in 94% of the neutrophil granulocytes with clumped chromatin structure, strikingly similar to that in the homozygous PHA rabbit.9 Three other siblings had died in the first years of life due to diphtheria, diarrhoea, and convulsions respectively, and the mother had had two miscarriages. It was concluded that, although the haematological picture in humans and rabbits is the same, the disorder is not necessarily lethal in humans and does not always lead to skeletal abnormalities.9

Ten other patients have subsequently been described: one each from Morocco,7 and Romania,10 three each from Gelenau, Germany,4,11,14 and Italy,20,21 and two from Spain.12,13,22 The clinical data of all patients are summarised in table 1. Two patients had congenital skeletal abnormalities. Aznar and Vaya12 described a girl with postaxial polydactyly of one hand and of both feet, but no other abnormalities on X-ray. Otherwise she was healthy. As 30% of neutrophil granulocytes had a round nucleus and 66% an indented nucleus, homozygous PHA was diagnosed and both parents appeared to be PHA heterozygous. However, hexadactyly of all limbs was also observed in the proband’s sister (without PHA) and in a cousin of the maternal grandmother (PHA status unknown). Considering the skeletal abnormalities in homozygous PHA rabbits, the authors speculate on a relation between polydactyly and PHA homozygosity in human beings. However, the absence of cosegregation in this family makes a correlation unlikely. Von Siegert et al14 describe a 20 month old boy, with a systolic heart murmur and psychomotor retardation. He also had macrocephaly, a bell shaped thorax, hepatomegaly and muscular hypotonia. Typical PHA homozygous nuclei were found in 96% of neutrophils and both parents had heterozygous PHA. When he was 16 years old there was a ventricular septum defect (VSD), normal muscle tone, mildly disturbed motor co-ordination and debilities. An aetiologic relation with PHA homozygosity was considered unlikely. This patient appeared to have the homozygous founder mutation in LBR affecting mRNA splicing.9 A photograph of the boy’s hands shows shortened 3rd and 5th metacarpals on the left hand and shortened 3rd to 5th metacarpals of the right hand. This case still had some expression of wild type protein, probably from a trace amount of normally spliced mRNA. No steroid data are available on this case to date.

**Pelger-Huët homozygosity in animals**

Undritz was the first to describe Pelger-Huët anomaly in rabbits, both in the heterozygous and in the homozygous state.3 Later Klein15 and Nachtshēim14 extensively reported on the phenotypic effects of PHA homozygosity in these rabbits. In the heterozygous state, the haematological phenotype is almost identical to that in human beings, the disorder is benign and the mode of transmission is autosomal dominant. However, when PHA rabbits were mated, not the expected 223 but only 39 homozygous rabbits were counted of which 27 died perinatally and 10 died within the first months of life. Prenatal lethality occurred in more than 80% in homozygous PHA rabbits, and only 1 homozygous PHA rabbit survived to adulthood and fathered heterozygous offspring.6,7

Homozygous PHA rabbits showed granulocytes with round or oval nuclei and clumped chromatin. Moreover, they had phocomelia with extremely shortened, curved tubular bones and reduction defects, shortened ribs, and a fixation of the thorax leading to respiratory failure. Hydrops is not mentioned. Histology revealed chondrodystrophy with widened epiphyses and reduced and arrested enchondral ossification,4 comparable to that seen in Greenberg/HEM dysplasia. No metabolic or molecular investigations in these rabbits are available to confirm the clinical data.

Lattimer et al described the occurrence of PHA in cats,23 and subsequently the phenotype of PHA homozygosity in cats.24 The latter was the result of a brother-sister mating of two PHA cats. A litter of five kittens was produced of which three were stillborn. One of the stillborn kittens was assumed homozygous for PHA on haematological investigation and also had severe chondrodystrophy—that is, short devi-

---

**Table 1** Summary of clinical findings in 11 reported PHA homozygotes from the literature

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Mental retardation</th>
<th>Macrocephaly</th>
<th>Seizures</th>
<th>Congenital skeletal defects</th>
<th>Additional findings</th>
<th>Reason for investigation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>f f</td>
<td>2.5</td>
<td>+ (mild)</td>
<td>+ (familial)</td>
<td></td>
<td>mild short stature</td>
<td>retardation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>m m</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>fever and flu</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>f f</td>
<td>46</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>climactenic complaints</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>m m</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>bronchitis</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>m m</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
<td>arthrosis</td>
<td></td>
<td>pneumonia</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>f f</td>
<td>10</td>
<td>+ (mild)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>acute meningitis</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>f f</td>
<td>1.5</td>
<td></td>
<td>+ (familial)</td>
<td>post-axial polydactyly of one hand and both feet</td>
<td></td>
<td></td>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td>8</td>
<td>f m</td>
<td>82</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cardiac complaints</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>m m</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>mild short stature</td>
<td></td>
<td>brother of patient no 8</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>m m</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td>mild short stature, slightly short arms, dyshidrosis, dyshidrosis, hyperkyphosis, hypotonia, VSD, poor co-ordination</td>
<td></td>
<td></td>
<td>Fuuij-0ever</td>
</tr>
<tr>
<td>11</td>
<td>m m</td>
<td>16</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+ (short metacarpal)</td>
<td>+</td>
<td>Retardation</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td></td>
<td>1.5-82</td>
<td>3/11</td>
<td>2/11</td>
<td>2/11</td>
<td>2/11 variable</td>
<td>2/11: short stature</td>
<td>4/11: infection</td>
<td></td>
</tr>
</tbody>
</table>

f, female; m, male; +, reported to be present; −, not reported to be present; absent.
Pelger-Huet homozygosity and Greenberg/HEM dysplasia

Dactyly of both hands 15 17 19 and one case was described with disturbed ossification (‘moth eaten’) and some extreme micromelia and short ribs dominate the clinical characteristics are summarised in table 2. Gross hydrops, dystrophy may well have been unrelated to PHA homozygosity and due to inbreeding of laboratory animals.¹⁴ No metabolic or molecular data on these cats have been published so far.

Recently, Shultz et al²⁵ demonstrated that mutations in both alleles of the mouse homologue Lbr cause autosomal recessive ichthyosis in mice, a disorder in which nuclear morphology is very similar to that in PHA homozygosity. Twenty one ic/ic mice were bred and all displayed a thick scaly skin. Moreover, three had soft tissue syndactyly or proximal symphalangism of one or more limbs and three had gross hydrocephaly. Segregation analysis showed that approximately half the homozygous mice died in utero. Three independent deleterious mutations were detected and for one of these, immunohistochemistry revealed complete loss of LBR protein.²⁶ The authors hypothesise that the effect on sterol metabolism may cause the ichthyosis. This study demonstrates a relation between abnormal nuclear morphology (—that is, PHA homozygosity), increased in utero lethality, ichthyosis and homozygous mutations in Lbr. It also underscores the highly variable phenotypic expression in mice with respect to limb and brain abnormalities.

Greenberg/HEM skeletal dysplasia in humans

To date eight cases of Greenberg/HEM dysplasia have been described, all diagnosed prenatally by ultrasound. The characteristics are summarised in table 2. Gross hydrops, extreme micromelia and short ribs dominate the clinical picture, and disturbed ossification (‘moth eaten’) and sometimes fractures of the long bones are seen on X-rays, together with severe platyspondyly and skull hypomineralisation.¹⁵–¹⁹ Three cases were reported to have post-axial polydactyly of both hands²⁶ ²⁸ ²⁹ and one case was described with additional abnormalities— that is, omphalocle, intestinal malrotation and lung hypoplasia.¹⁸ Hydrocephaly or ichthyosis are not reported. The histological picture is dominated by severe disorganisation of cartilage— that is, absence of column formation, defective enchondral ossification and ectopic calcification of cartilage. Although there is some phenotypic variability among the reported cases, all have severe hydrops and show an early (in utero) lethal skeletal dysplasia.

Unfortunately, no data are available on neutrophil granulocytes in Greenberg/HEM cases, to confirm that nuclear morphology is similar to that in PHA homozygosity. We are not aware of possible Greenberg/HEM cases with milder (—that is, non-lethal) skeletal dysplasia, but this may be due to ascertainment bias. Unless defects in cholesterol biosynthesis are detected in milder cases of skeletal dysplasia, it remains unlikely that the spectrum of homozygous 3β-hydroxysterol Δ14-reductase deficiency can also include only polydactyly or only shortened metacarpals.

**DISCUSSION**

The phenotypic spectrum of PHA homozygosity in human beings, as compared to Greenberg/HEM dysplasia

Among the 11 published descriptions of patients diagnosed with PHA homozygosity (table 1), we found no convincing case of skeletal dysplasia or other congenital malformations comparable to that described in cases with Greenberg/HEM dysplasia. The fact that three patients were mildly mentally retarded, two patients had convulsions, two patients had macrocephaly and two patients had—dissimilar—hand abnormalities does not permit the delineation of a clear PHA homozygosity “syndrome”.

There can be several reasons for the lack of congenital defects in reported cases. First, a mistaken diagnosis can be made. Vaya et al²⁸ reported that in cases of familial PHA, infectious disease can induce nuclear morphology identical to that found in homozygous PHA,—that is “pseudo homozygous PHA’. With the exception of von Siegert’s patient, which was confirmed molecularly, all patients were diagnosed only haematologically,—that is, on blood smears—and proof of PHA in both parents was only available in five patients.¹¹ ¹² ¹³ Without thorough family study or molecular confirmation, this phenocopy of PHA homozygosity is possible in at least half of the cases. Molecular analysis of newly diagnosed homozygous PHA cases will help elucidate this issue. Secondly, ascertainment bias is likely: the reasons for investigating the published cases were varied, and PHA detection was usually a chance occurrence. Moreover, although PHA is a diagnosis that is not easily overlooked, we are not aware of a systemic haematological analysis in (parents of) patients with skeletal dysplasia, and especially not in (very) early lethal cases, such as Greenberg/HEM dysplasia. Thirdly, most cases were described in haematological literature, which may have led to an underreporting of non-haematological findings, such as skeletal defects. Fourthly, there is confusion in the literature on the relation between skeletal defects and PHA: even PHA heterozygosity

---

**Table 2** Summary of findings in eight reported cases of Greenberg/HEM skeletal dysplasia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at diagnosis (weeks gestation)</th>
<th>Hydrops</th>
<th>Calcifications</th>
<th>Ectopic platyspondyly</th>
<th>Micromelia</th>
<th>Malformations</th>
<th>Other congenital short ribs</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>post-axial polydactyly in both hands</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>post-axial polydactyly in both hands</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>post-axial polydactyly in both hands</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>post-axial polydactyly in both hands</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>post-axial polydactyly in both hands</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>post-axial polydactyly in both hands</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>17</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>post-axial polydactyly in both hands</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>post-axial polydactyly in both hands</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>(14–30)</td>
<td>8/8</td>
<td>8/8</td>
<td>8/8</td>
<td>8/8</td>
<td>3/8 post-axial polydactyly</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+, reported to be present; –, not reported to be present; absent.
The phenotypic spectrum PHA homozygosity in animals as compared to Greenberg/HEM dysplasia

The skeletal defects in PHA homozygous rabbits are very similar to those described in Greenberg/HEM dysplasia, both clinically and histologically, although hydrocephalus (obligate in Greenberg/HEM) is lacking in animals. The case of chondrodysplasia in cats shows similarities as well, as does the histology. However, the chondrodystrophy and PHA homozygosity does not cosegregate in a littermate, making a syndromal entity less likely. Only a small fraction of affected ic/ic mice have discrete limb abnormalities (syndactyly), whereas X-rays do not show signs of chondrodysplasia. Thus, skeletal findings in human beings are most similar to those in rabbits homozygous for PHA.

In mice the clinical picture is dominated by ichthyosis, which is not reported in cats, or in rabbits. Although ichthyosiform skin lesions are not uncommon in cholesterolopathies, this is not reported in Greenberg/HEM dysplasia or in any of the human PHA homozygotes. Schultz et al explained this discrepancy by the fact that ic/ic mice show complete loss of Lbr, whereas the reported human PHA homozygote still expressed some detectable LBR protein. Alternatively, the ichthyosis in Greenberg/HEM dysplasia may not yet have developed at the age of diagnosis (14–30 wks gestational age), or could be concealed by maceration.

Survival in PHA homozygosity in animals and in human beings

In rabbits and mice, there is a striking increase of prenatal and perinatal death in PHA homozygosity, with survival rates of <20% and <50% respectively. In human beings such data are lacking. The mothers of patients 1 and 10 had both had two unexplained abortions. In the first family, death in the first years of life of three other children was ascribed to specific diagnoses, and no congenital malformations are reported. We assume that these findings are a chance occurrence and a link with early lethality seems premature. Detection of a distorted segregation in human beings, however, will be very difficult. In the village of Gelenau, with a carrier frequency of 1 in 100, the chance of homozygosity would be 1 in 40,000 births. Given the fact that homozygosity of the Gelenau founder mutation is clearly non-lethal in at least one case, it would take a lot of carrier couples to approach the problem of possible increased (in utero) lethality in humans.

Related phenotypes, extremes of one spectrum

On the basis of 11 reported cases so far, we conclude that, although suggested otherwise, PHA homozygosity in man is not associated with a well-defined syndrome of skeletal dysplasia, ichthyosis or congenital abnormalities, or with early lethality. Greenberg/HEM skeletal dysplasia at the same time, was invariably lethal in all eight reported cases. The phenotypes do not show overlap and are therefore distinct. There is however considerable overlap between Greenberg/HEM dysplasia and PHA homozygosity in rabbits, and to a lesser extend in mice and cats, with respect to radiology, histology and early lethality. This might imply that PHA homozygosity and Greenberg/HEM dysplasia are the extremes of one clinical spectrum, and that intermediate phenotypes may be discovered in the future — for example in cases of unexplained non-lethal skeletal dysplasia.

The LBR gene has two domains: a basic amino-terminal domain of approximately 200 amino acids, which binds to B-type lamins and is involved in retention of the inner nuclear membrane, and an approximately 400 amino acid carboxy-terminal domain, which shows strong sequence similarity to sterol reductases in several species. This may (partly) explain the pleiotropic phenomenon that both a “nuclear membrane” phenotype (abnormal nuclear morphology in both the PHA heterozygote and in PHA homozygosity) and a “cholesterolopathy” phenotype (Greenberg/HEM dysplasia in the homozygote) can be due to mutations in the same gene. Indeed in the Greenberg/HEM case, the mutation is in the C-terminal part of LBR. However, the eight different mutations (four splice site mutations, two nonsense mutations and two frame shift mutations) detected by Hoffmann et al are dispersed throughout LBR: six out of eight are located in the domain homologous to sterol reductases. This was also the case in the proven PHA homozygote. The fact that the ic/ic mouse has homoygous Lbr mutations that predominantly lead to disruption of the sterol reductase homologous domain and cause total absence of gene product, may explain the cutaneous phenotype. It does not, however, clarify the total lack of skin symptoms in the humans with either PHA homozygosity (one of whom still had some detectable protein) or Greenberg/HEM dysplasia. One could conclude that Greenberg/HEM dysplasia most probably represents the null phenotype of Lbr-related conditions in humans, whereas hypomorphic or neomorphic mutations in LBR in the homozygous state result in a milder PHA homozygosity phenotype without skeletal manifestations. In this respect the nature of the mutation seems to be more important than the localisation of the mutation within the gene, for determination of the ultimate phenotype.

Greenberg/HEM skeletal dysplasia has been added to the list of MCA syndromes that are caused by defects in sterol metabolism, including Smith-Lemli-Opitz syndrome, Conradi-Hünermann syndrome, CHILD syndrome, and desmosterolosis. Pelger-Huet anomaly has recently been added to the list of laminoopathies, such as Emery-Dreifuss muscular dystrophy, partial lipodystrophy, and mandibulocural dysplasia. With Greenberg/HEM skeletal dysplasia and Pelger-Huet anomaly respectively, these groups of disorders are now related through LBR. Further metabolic and molecular studies in both human beings and animals should help to elucidate the relationship between these phenotypes and so answer the question whether PHA may eventually be a marker of heterozygosity for a severe skeletal dysplasia.

ACKNOWLEDGEMENTS

Dr. A. Wischmeijer (Ravenna, Italy) for translating the Italian case reports and Dr. R. Pelger (Leiden, the Netherlands) for investigating historical sources.

Authors’ affiliations

J C Oosterwijk, Department of Clinical Genetics, Groningen University Hospital, Groningen, Netherlands
S Mansour, Department of Medical Genetics, St George’s Hospital Medical School, London, United Kingdom
G van Noort, Regional Pathology Laboratory, Enschede, Netherlands
H R Waterham, R C M Hennekam, Department of Paediatrics, Emma Children’s Hospital, Academic Medical Centre, Amsterdam, Netherlands
C M Hall, Department of Radiology, Great Ormond Street Hospital for Children, London, United Kingdom

Correspondence to: Dr J C Oosterwijk, Department of Clinical Genetics, University Hospital Groningen, P.O. Box 30.001, NL-9700 RB, Groningen, Netherlands; j.c.oosterwijk@medgen.azg.nl

REFERENCES

Pelger-Huet homozygosity and Greenberg/HEM dysplasia


Have your say

If you wish to comment on any article published in the Journal of Medical Genetics you can send an eLetter using the eLetters link at the beginning of each article. Your response will be posted on Journal of Medical Genetics online within a few days of receipt (subject to editorial screening).