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CONGENITAL ERYTHROPOIETIC PORPHYRIA: MUTATION UPDATE AND CORRELATIONS BETWEEN GENOTYPE AND PHENOTYPE

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Abstract – High quality genotype/phenotype analysis is a difficult issue in rare genetic diseases such as congenital erythropoietic porphyria (CEP) or Günther's disease, a heme biosynthesis defect due to uroporphyrinogen III synthase deficiency. The historical background and the main phenotypic features of the disease are depicted together with an update of published mutants and genotype/phenotype correlations. General rules concerning the prediction of disease severity are drawn as a guide for patient management and therapeutic choices. The phenotypic heterogeneity of the disease is presented in relation with a likely influence of modifying factors, either genetic or acquired.

Key words: Porphyria, molecular diagnosis**,** UROS gene

INTRODUCTION

Congenital erythropoietic porphyria (CEP) is a rare autosomal recessive disorder of heme biosynthesis, one of the least common porphyrias. The disease results from markedly deficient uroporphyrinogen III synthase enzymatic activity (UROS, EC 4.2.1.75). The enzymatic defect causes specific overproduction and diffuse tissue accumulation of the non-physiological and pathogenic porphyrin isomers, uroporphyrin I and coproporphyrin I. The molecular study of the UROS gene in CEP patients has highlighted a variety of mutations in both coding and promoter sequences of the gene. Clinical features combine cutaneous photosensitivity and chronic hemolysis whose severity is mainly heterogeneous among patients. Bone marrow transplantation is the only curative treatment in potentially severe forms (2, 10, 11).

Abbreviations: CEP, congenital erythropoietic porphyria; **UROS**, uroporphyrinogen III synthase.

Gene based therapy is currently under investigation (28, 29). In cellular therapy as well as gene therapy protocols, the evaluation of a benefit/risk ratio before treatment is dependent on predictions drawn from genotype/phenotype correlation (9, 34).

CEP HISTORICAL BACKGROUND

Drawing phenotype/genotype correlations in CEP may rely on early descriptions of the disease (19). The first case of CEP was reported in 1874 by Schultz in a 33-year-old man who had suffered from skin photosensitivity since the age of 3 months; had an enlarged spleen, icteric conjunctivae and red urine containing a substance called hematoporphyrin by Hopple-Seyler. In 1898, McCall Anderson suggested a close connection between the cutaneous manifestations and the pigment in urine. Meyer-Betz confirmed the photosensitization properties of porphyrins in 1913. Hans Günther was the first to recognize congenital porphyrias as inborn

errors of metabolism; he proposed a classification of acute and chronic porphyrias between 1911 and 1922. Fisher's laboratory was a major contributor to porphyrin chemistry work, as exemplified by the Nobel price obtained in 1930.

The knowledge of the disease made a huge progress with the description of the enzyme defect (31): the deficiency of the enzyme uroporphyrinogen III synthase (also named cosynthetase) which catalyses the cyclisation of the linear tetrapyrrole hydroxymethylbilane (HMB) into uroporphyrinogen III. Enzymatic deficiency leads to a spontaneous cyclisation of HMB to form uroporphyrin and coproporphyrin type I isomers, which are in a metabolic dead-end, since these compounds are unable to contribute further to heme biosynthesis (figure 1). The accumulation of porphyrins, through a hyperactive heme pathway, is responsible for the cellular damage observed mainly in photo-exposed skin and in the erythroid lineage.

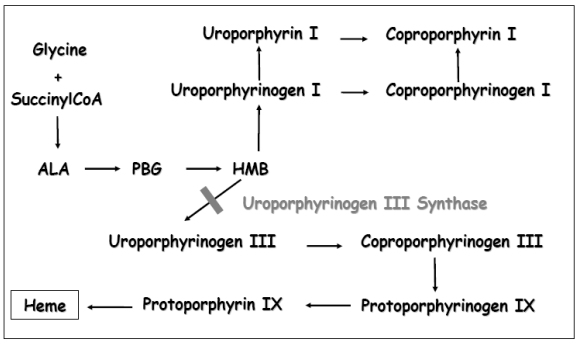

Figure 1. The heme biosynthetic pathway. Uroporphyrinogen III synthase deficiency is responsible for the accumulation of uroporphyrin I, coproporphyrin I and oxygen derivatives which are not substrates for heme synthesis and accumulate in tissues, urine, and faeces.

The purification of human uroporphyrinogen III synthase from erythrocytes was achieved in 1987 (39). Further progress gained from molecular analyses which represented powerful tools for genotyping analyses: from 1990, cDNA cloning made possible a genetic diagnosis (12), then came the assignment to chromosome 10q25 (3), the description of the full UROS gene structure (1), and structure/function analyses from the crystallized protein (1, 23) or NMR studies (7).

GENOTYPE STUDIES IN CEP

So far, 39 disease-causing mutants have been published. The update, shown in table I, includes four unpublished mutants studied in our laboratory. Mutations are spread along the UROS gene in the promoter and the 9 coding exons (figure 2). All types of point mutations are observed (table I). The molecular lesions include promoter mutations responsible for decreased transcriptional activity (5/43) splicing defects resulting in exon deletion causing a truncated protein (6/43); missense mutations, the most frequently found (25/43), few nonsense (2/43), frameshift leading to an unstable truncated protein (3/43), or complex mutations (2/43); no large deletion has been described yet. A common missense mutation, p.Cys73Arg, is found in 30 to 40% Caucasian disease alleles; however, haplotype analyses did not demonstrate a founder effect (15). A relatively high prevalence of the mutation p.Pro248Asn has been observed in Spain (38). Of note, some mutations remain unknown in few patients, about 8 % of the published alleles. Moreover, it is interesting to note that CEP is no longer a monogenic disease since the recent description of CEP features due to a gene defect in GATA-1 erythroid specific transcription factor (27).

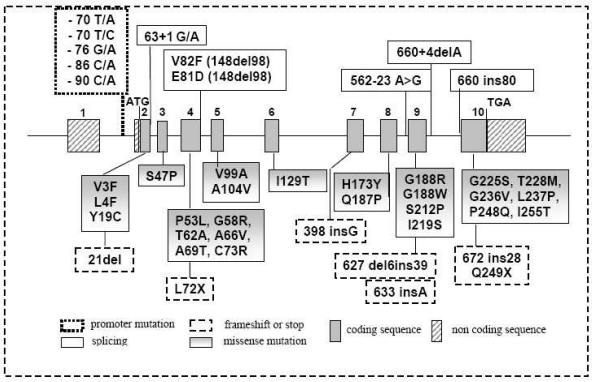

Figure 2. Location of mutations causing CEP on the UROS gene. For easier reading, missense and nonsense are shown using protein designation of mutants; promoter mutation, splicing defects and frameshifts using cDNA designation.

PHENOTYPE DESCRIPTIONS IN CEP

In classical forms, the phenotypic expression of the disease is dominated by skin photosensitivity, starting early in childhood, including abnormal skin fragility, bullae, erosions and scarring leading to severe deformities if sun protection is not adequate. Porphyrinuria is present from the first months of life, with typical red-wine urine deposits on diapers. Massive accumulation of uroporphyrin I isomer is evidenced in urine. Hematologic

Table 1. Description of UROS gene mutants

Location	Nucleotide change	Amino acid change	Protein defect	Reference 1st description
IVS 1	c.01-90 C>A	*CP 2 site	low expression	33
(erythroid	c.01-86 C>A	*CP 2 site	low expression	33
promoter)	c.01-76 G>A	*CP 2 site	low expression	33
	c.01-70 T>C	*GATA 1 site	low expression	33
	c.01-70 T>A	*GATA 1 site	unknown	unpublished
Exon 2	c.07 G>T	p.Val 03 Phe	missense	35
(first	c.10 C>T	p.Leu 04 Phe	missense	42
coding	c.21 del G	p.Asp 08 Met fsX16	frameshift/truncation	32
exon)	c.56 A>G	p.Tyr 19 Cys	missense	42
IVS 2	c.63+1 G>A	p.Met ?	**splicing	42
Exon 3	c.139 T>C	p.Ser 47 Pro	missense	18
Exon 4	c.158 C>T	p.Pro 53 Leu	missense	12
	c.172 G>A	p.Gly 58 Arg	missense	unpublished
	c.184 A>G	p.Thr 62 Ala	missense	40
	c.197 C>T	p.Ala 66 Val	missense	42
	c.205 G>A	p.Ala 69 Thr	missense	32
	c.215 T>A	p.Leu 72 X	nonsense	unpublished
	c.217 T>C	p.Cys 73 Arg	missense	12
	c.243 A>T 148 del 98	p.Glu 81 Asp/del 83-106	splicing/truncation	32
	c.244 G>T 148 del 98	p.Val 82 Phe/del 83-106	splicing/truncation	6, 42
Exon 5	c.296 T>C	p.Val 99Ala	missense	4
	c.311 C>T	p.Ala 104 Val	missense	42
Exon 6	c.386 T>C	p.Ile 129 Thr	missense	30
Exon 7	c.398 ins G	p.Glu 133Gly fsX64	frameshift/truncation	33
Exon 8	c.517 C>T	p.His 173 Tyr	missense	14
	c.560 A>C	p.Asn 187 Pro	missense	14
IVS 8	c.562-23 A>G	not tested	splicing	14
Exon 9	c.562 G>A	p.Gly 188 Arg	missense	37
	c.562 G>T	p.Gly 188 Trp	missense	32
	c.627 del 6 ins 39	p.del 211-212 ins 13	deletion/in frame insertion	32
	c.633 ins A	p.Ser 212 Ile fsX2	frameshift/truncation	4
	c.634 T>C	p.Ser 212 Pro	missense	36
	c.656 T>G	p.Ile 219 Ser	missense	32
IVS 9	c.660+4 del A	p.del 188-221	splicing/in frame deletion	42
Exon 10	c.660 ins 80	p.del/ins 188-265	splicing/in frame insertion	6
	c.672 ins 28	p.224ins90	insertion/elongation	32
	c.673 G>A	p.Gly 225 Ser	missense	42
	c.683 C>T	p.Thr 228 Met	missense	40
	c.707 G>T	p.Gly 236 Val	missense	41
	c.710 T>C	p.Leu 237 Pro	missense	41
	c.743 C>A	p.Pro 248 Asn	missense	14
	c.745 C>T	p.Asn 249 X	nonsense	42
	c.764 T>C	p.Ile 255 Thr	missense	unpublished

* indicates a promoter mutant with no amino acid change

** exon 2 deletion demonstrated by RNA analysis

Mutants are designated according to the HGV nomenclature.

Table 2. Predicted and observed severity of homoallelic mutants

Mutant allele	Common designation	Activity in E coli (%)	Phenotype	Affected families	References
p.Val 03 Phe	V3F	< 2	moderate to severe	1	35
p.Ser 47 Pro	S47P	3	mild to severe	1	18
p.Gly 58 Arg	G58R	1.5	mild	1	unpublished
p.Ala 69 Thr	A69T	1.4	? (graft)	1	13
p.Cys 73 Arg	C73R	< 1 - 2	severe	5	10, 12, 14, 40, 42
p.Ile 129 Thr	I129T	< 2	mild	1	30
p.His 173 Tyr	H173Y	< 1	moderate	1	14
p.Gly 188 Arg	G188R	4.3	severe (graft)	1	37
p.Ile 219 Ser	I219S	1.3	moderate to severe	1	32
p.del 188-221*	*IVS9+4 delA*	-	mild	1	42
p.Thr 228 Met	T228M	< 1 - 3	severe	1	44
p.Leu 237 Pro	L237P	-	severe	1	41
p.Pro 248 Asn	P248Q	< 1	mild to severe	2	38
p.Ile 255 Thr	I255T	1.6	moderate	1	unpublished

All patients described in table 2 are homoallelic * in frame deletion of aminoacids 188-221

features include various degrees of hemolytic anemia from well tolerated to severe transfusion dependent forms. The high rate of red blood cells destruction is responsible for the splenomegaly. The accumulation of porphyrins in red blood cells mainly in reticulocytes can be detected by flow cytometry since these porphyrin-accumulating cells are red fluorescent. Diffuse tissue accumulation of porphyrins is responsible for tooth discoloration and dentine disorders; ocular involvement including chronic ulcerative keratitis and scleromalacia; as well as osteodystrophia combining osteolysis of light exposed extremities and osteoporosis (2, 10, 11).

Phenotypic heterogeneity is a common finding in CEP, the interdependence between disease severity and porphyrin excess has been pointed out (16). Adult late onset forms exhibit a mild phenotype often restricted to skin photosensitivity (5, 40) and associated with myelodysplasia (22, 43) or thrombocytopenia (24). On the opposite side of the clinical spectrum, extremely severe forms, starting during pregnancy, are dominated by severe hemolytic anemia responsible for hydrops foetalis and death in utero (8, 17, 26). The earliest diagnosis is advisable since special care should be taken in affected newborns to avoid phototherapy for the treatment of neonatal jaundice.

Phenotypic variability has been reported in the same family among patients harbouring the same gene defect (missense p.Ser47Pro) at the homozygous state (18). In this large Palestinian family, the severity of cutaneous lesions varied greatly among first degree relatives, with no evidence for hematological disease. Most affected siblings had severe mutilating lesions, while the younger sister, who experienced a better photoprotection, showed mainly hypertrichosis and mild deformities of the hands. Surprisingly, another sibling had no skin lesion and limited porphyrinuria, albeit homozygous for the same molecular defect.

Phenotypic variability in unrelated patients harbouring the same molecular defect has been studied in detail (38). Again, a large scale of disease severity was observed relative to cutaneous involvement, ranging from severe mutilating lesions to mild features, considering a relatively frequent mutant (p.Pro248Asn) in Spanish patients.

GENOTYPE/PHENOTYPE CORRELATION

Comprehensive phenotypic studies are necessary to evaluate phenotype/genotype correlations. Clinical profiles can be classified, as proposed by RJ Desnick (10), in three classes: 1- severe, birth onset forms responsible for fetal ascites, transfusion dependency, and mutilating skin lesions; 2- moderate forms including latent chronic hemolysis, and limited cutaneous involvement; 3- mild and late-onset forms mainly restricted to cutaneous symptoms or associated with late-onset thrombocytopenia (24).

Such phenotypic analyses require a detailed scoring evaluation including symptoms at diagnosis, clinical presentation, clinical course, photoprotective practices, and treatment.

On the other side, genotyping analyses rely on mutation analysis at the gene level. The deleterious effect of a given mutation can be assessed by different methods, according to the molecular defect: missense mutants are ideally characterised by procaryotic expression (10, 14, 32); splicing defects are demonstrated by RT-PCR analysis (32); promoter mutations are analysed in reporter gene systems (33); the use of *in silico* predictions can be also helpful. However, it is important to be conscious of the limits of each technique. Actually, *in vitro* systems cannot rule out post-translational modifications or integrated gene regulations. Fortunately, few coding SNPs have been identified on human UROS gene in the HapMap database and variant alleles have low frequencies (0.005 to 0.01) in population studies available from the NCBI-linked databases. Two non-synonymous coding SNPs have been described: *rs17153561* (c.371 A>G / p.Lys124Arg) and *rs17173752* (c.512 T>G / p.Val171Gly) in exons 6 and 8, respectively. Concerning the enzyme defect, some explanations rely on structure-function analyses of single mutants (23). The interaction between UROS monomers was excluded by early studies (39). The complexity of ligand binding at the catalytic site has been elegantly analysed by NMR technology (7).

The task of drawing correlations between genotype and phenotype is not straightforward in CEP. A main drawback is the rarity of the disease; about 200 cases have been reported in the world. The molecular lesions are mostly heterogeneous (figure 2 and table I). Although a common missense mutation is present in about 30 % alleles, few mutants are recurrent, most are private, occurring in less than two families. Moreover, the natural history of the disease has evolved thanks to the availability of a curative

Table 3. Predicted and observed severity of compound mutants

1st mutant allele		2nd mutant allele				
Description	Activity in E coli (%)	Description	Activity in E coli (%)	Affected families	Resulting phenotype	References
c.01-86 C>A	43	c.398insG		1	mild	32
p.Leu 04 Phe	1.8	p.Cys 73 Arg	< 1 - 2	1	moderate to severe	10, 42
		p.Val 82 Phe	36	1	mild	10, 42
		c.63+1 G>A		1	moderate	10, 42
p.Cys 73 Arg	< 1 - 2	c.01-86 C>A	43*	1	mild	10, 33
		c.01-76 G>A	54*	1	mild	10, 33
		c.01-70 T>C	< 3*	1	severe	10, 33
		p.Pro 53 Leu	1.2	1	severe	12
		p.Ala 66 Val	14.5	1	mild	10, 40
		p.Ala 69 Thr	< 1 - 2	1	moderate to severe	32
		p.Ala 104 Val	7.7	1	moderate	10, 42
		p.Asn 187 Pro	< 1	1	severe	14
		c.562-23 A>G		2	moderate	14, 20
		p.Thr 228 Met	< 1 - 3	4	moderate to severe	10, 14, 38
		p.Gly 236 Val		1	severe	41
		p.Pro 248 Asn	< 1	4	moderate	14, 38
		c.672 ins 28		1	severe	32
p.Val 99Ala	5.6 - 7	c.633 ins A		1	moderate	4, 10, 42
p.Gly 188 Trp	1.7	p.Glu 81 Asp	30	1	mild	32
p.Gly 225 Ser	1.2	c.01-90 C>A	8.3*	1	severe	10, 33
		c.01-76 G>A	54*	1	mild	5
		p.Tyr 19 Cys	1.1	1	severe	10, 42
		p.Thr 228 Met	< 1 - 3	1	mild	42
p.Thr 228 Met	< 1 - 3	c.21 del G		1	severe	32
		c.01-70 T>A		1	moderate	unpublished
p.Asn 249 X		p.Thr 62 Ala	< 1	1	mild	42
		p.Ser 212 Pro	< 1	1	severe	36
		p.Leu 237 Pro		1	severe	21

* in promoter mutants the residual activity is measured by luciferase assay

treatment. Indeed, bone marrow transplantation is proposed as early as possible in childhood, to increase its efficiency, and prevent the development of severe untreatable forms (11, 34). Finally, the availability of prenatal diagnosis in affected families has also reduced the actual prevalence of newly diagnosed patients.

As registered in Table II, a significant proportion of mutants (14/43) have been observed at the homoallelic state, due to high consanguinity levels in the corresponding families. Two mutants, p.Cys73Arg and p.Pro248Asn, are homoallelic in more than one family and less associated with consanguinity. The prevalent mutant, p.Cys73Arg, is evenly responsible for a severe phenotype: hydrops fetalis and death in utero are frequently observed; severe hemolysis and mutilations are responsible for reduced life expectancy in homozygous patients (10, 12, 14, 38, 40, 42). However, as already mentioned, phenotypic variability has been elegantly described in two homozygous patients with the p.Pro248Asn mutant (38). Surprisingly, *in vitro* measurements of UROS residual activity using expression studies in *E coli* and luciferase assay (promoter mutants) predicted very low residual activities in most mutants, although all types of clinical severity were observed at the homozygous state.

Most non consanguineous patients have compound heterozygosity (table III). *In vitro* predictions of UROS protein (*E coli* expression) or promoter (luciferase assay) residual activity are well suited to the evaluation of clinical outcome and severity of the disease. As a general rule, when the residual activity of the first mutant allele is below 1-2 %, the residual activity of the second mutant allele is below 1-2 % in severe forms, and above 5-10 % in moderate or mild forms. This statement is verified in heteroallelic patients harbouring the common severe mutant p.Cys73Arg or the missense mutant p.Leu04Phe. The association of p.Leu04Phe mutant with potentially severe mutations p.Cys73Arg, or splicing defects (c.63+1 G>A / exon 2 deletion, or p.Val82Phe / exon 4 deletion) is described as either a mild, moderate or severe phenotype, depending on the severity of the second mutant. The rule is less obvious in some families who experienced moderate to severe forms linked to the same genotype (see p.Cys73Arg / p.Thr228Met, and p.Gly225Ser / p.Thr228Met, in Table III).

The potential role of sequence variations involving modifier genes is an attractive hypothesis to explain the modulation of CEP phenotypic expression. The molecular basis of phenotypic variability in CEP has not been explored thoroughly, given the small number of affected individuals. Candidate modifier genes are numerous, among enzymes involved in porphyrin metabolism and transport or in photoprotection. The recent demonstration of an authentic CEP disease due to a molecular defect in a transacting gene involved in the regulation of the heme biosynthetic pathway (the erythroid specific transcription factor GATA-1) is a compelling observation in the field (27).

Progress towards a better understanding of the molecular basis of phenotype/genotype correlations is directly linked to the development of a comprehensive registry of the disease and will benefit immediately to patient management, concerning conventional treatments as well as gene-based therapies.

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