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ORIGINAL PAPER

Genetics of Hypophosphatasia

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Abstract Hypophosphatasia (HPP) results from mutations in the ALPL gene, mostly missense mutations. The gene is subject to a very high allelic heterogeneity, and some of these mutations have a dominant negative effect, two features that explain the most part of the clinical heterogeneity. Severe forms of the disease (perinatal and infantile) are inherited as an autosomal recessive trait. In the milder forms, autosomal recessive and autosomal dominant inheritance coexist. Experimental data show that there is a good correlation between the severity of the disease and in vitro alkaline phosphatase activity of the mutant protein. As a consequence of the existence of dominant mutations, moderate forms may be recessively or dominantly inherited and are expected more frequent than severe forms. The incidence of severe forms, inherited as a recessive trait, has been estimated at 1/300,000 in Europe. Genetic counseling is difficult in families where the mode of inheritance is unclear, or in prenatal context because of the prenatal benign form that may mimic severe perinatal HPP. During the ten last years, the mechanism of mineralization has been greatly deciphered, pointing out others gene that could modulate the HPP phenotype and explain particular cases where the phenotype does not correlate with the phenotype.

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Introduction

HPP is due to mutations in the *ALPL* gene (MIM 171760) encoding tissue nonspecific alkaline phosphatase (TNSALP). TNSALP is a membrane phosphomonoesterase active in a dimeric and/or multimeric form that dephosphorylates various substrates, especially inorganic pyrophosphate, a central actor of bone mineralization, and pyridoxal phosphate, involved in the production of the neurotransmitter GABA.

As previously detailed (other manuscripts in the same issue), HPP is clinically very heterogeneous, with a continuum of severity ranging from a perinatal form detectable in utero and often lethal, to a dental form characterized by the absence of bone symptom. Severe forms (perinatal and infantile) are inherited as an autosomal recessive trait. In the milder forms, autosomal recessive and autosomal dominant inheritance coexist. Often, however, there are clinical signs in the heterozygote while these signs are not found in the parents, which may reflect incomplete penetrance [13, 28] or improvement of the condition from childhood to adulthood. In addition, the dominant forms of HPP could be more frequent than recessive forms but not exhaustively identified, given the mild clinical signs. In our experience, nearly half of cases of moderate forms of HPP are expressed at the heterozygous state [5], and more the clinical form is moderate more the inheritance is dominant. In some cases, there is intrafamilial phenotypic heterogeneity, for instance coexistence of childhood and infantile forms within the same family, making difficult genetic counseling. However, the

coexistence of radically different clinical forms (for example perinatal and adult) has never been observed in patients with the same genotype. These observations, however, suggest the role of other genes (modifier genes), and perhaps environmental and epigenetic factors.

The Liver/Bone/Kidney Alkaline Phosphatase (*ALPL*) Gene and the Mutations Responsible for Hypophosphatasia

The *ALPL* Gene

ALPL consists of 12 exons distributed over 50 kb [50]. Two transcripts have notably been identified, driven by two alternative exons 1 in the 5′-untranslated region [50] and responsible for differential transcription and subsequent cotranslational and post-translational modifications [22, 41, 44]. The transcription of the upstream exon 1A is preferentially driven in osteoblasts, whereas transcription is preferentially initiated with exon 1B in liver and kidney [22, 41, 45]. More recently, it was shown that AP activity detected in the parenchyma and in endothelial cells of brain from human and other species results from the expression of the ALPL gene driven by the bone promoter [1]. However, a remarkable species specificity was highlighted by the finding of an additional transcript starting with exon 1B in mouse neurons. The mechanism of tissue-specific regulation of TNAP is not yet elucidated.

The Hypophosphatasia Mutations

Since the first mutation was identified in the *ALPL* gene [49], more than 260 distinct mutations have been described. A constantly updated list of mutations is available online (http://www.sesep.uvsq.fr/database_hypo/Mutation.html). Most of them (75 %) are missense mutations. The remaining reported mutations are deletions (10.6 %), splicing mutations (6 %), nonsense mutations (4 %), small insertions (2.2 %), a complex deletion + insertion, and a nucleotide substitution affecting the major transcription initiation site. Two gross deletions [40], 2 de novo mutations [42, 58] and a homozygous mutation, resulting from paternal isodisomy of chromosome 1 (Watanabe et al. [46] were also reported.

A few number of mutations are recurrently found and may be quite frequent in particular populations. For instance, the mutations c.1559delT and p.F327L represent 40.9 and 13.6 % of HPP chromosomes, respectively, in the Japanese population [23], the mutation c.571G>A (p.E191K) is found in half of patients from European ancestry affected with moderate HPP [12], and the mutation c.1001G>A (p.G334D) represents most of HPP chromosomes in the Canadian Mennonite community [9]. In USA, the missense mutation c.1133A>T (p.D378V) probably originating from northwest Europe represents 14 % of HPP chromosomes and is a common cause of the dominant prenatal benign HPP [30]. This reflects founder effects, that is, ancient ancestral mutations that occurred on single chromosomes and spread throughout populations of small sizes in limited area. Except one case [56], HPP was never reported in populations from black African ancestry.

Genotype–Phenotype Correlations

For geneticists dealing with genotype–phenotype correlations, HPP is a very interesting disease because of its extremely large clinical spectrum and because the disease may be dominantly or recessively inherited. The great variety of mutations results in a great number of compound heterozygous genotypes and in highly variable clinical expressivity. This makes difficult to assess to a mutation a degree of severity. However, attempts to assess the relative importance of missense mutations and the genotype–phenotype relationship were performed for a number of mutations by using site-directed mutagenesis. These experiments allowed to study alkaline phosphatase activity, cell localization, and degradation of mutant proteins.

A good correlation was observed between the severity of the disease and in vitro enzymatic activity of the mutant protein [59]. Patients with moderate HPP carry at least one mutation that, when tested, exhibits significant residual enzymatic activity, while patients with severe HPP carry mutations that, when tested, mostly do not produce enzymatic activity. Results of in vitro assays of mutations are listed in the Tissue Nonspecific Alkaline Phosphatase Gene Mutations Database (http://www.sesep.uvsq.fr/03_hypo_mutations.php). Moreover, as the level of serum alkaline phosphatase correlates with the severity [53], the expected mean AP activity of genotypes with missense mutations tested by site-directed mutagenesis also correlates with the observed phenotype, suggesting that in vitro assessment of mutations is relevant to evaluate the severity of a mutation.

By using immunofluorescence and biochemical treatments such as cell-surface biotinylation, digestion with phosphatidylinositol-specific phospholipase C, various mutations were characterized for their cell localization and their ability to undergo post-translational processes or to be degraded [2, 7, 8, 16–19, 31, 32, 38, 39, 47]. These studies showed that most of the missense mutations found in severe HPP produced a mutant protein that failed to reach the cell membrane was accumulated in the cis-Golgi and was subsequently degraded in the proteasome. By contrast, the missense mutations responsible for moderate HPP were found to be at least in part correctly localized to the cell membrane.

In addition, the severe missense mutations were shown to mostly affect residues localized in crucial domains of the protein while mutations found in mild forms affected residues more randomly dispatched [26, 27, 59].

These complementary approaches converge to improve our understanding of genotype–phenotype relationships and provide a classification of mutations according to their effect.

The Dominant Effect of TNAP Mutations

Dominant transmission of HPP has been suggested on the basis of pedigree and laboratory data [3, 4, 25, 54, 55]. Molecular diagnosis, now routinely performed, confirms that dominant inheritance is common in moderate forms of HPP and that milder is the disease more the inheritance is autosomal dominant (Table 1) [5]. Today, at least 22 missense mutations were shown to have a dominant negative effect by site-directed mutagenesis (Table 2). However, while the penetrance of the disease in recessive HPP is considered as complete, in dominant forms the penetrance may vary from a mutation to another one, and even with the same mutation from a patient to another one. The dominant negative effect was often demonstrated by using site-directed mutagenesis. Immunofluorescence studies with fusions GFP-TNAP or CFP-TNAP proteins showed that the mutant protein may sequestrate the heterodimer in the cytoplasm, explaining the dominant negative effect [21]. AP activity assays showed that the mutant protein inhibited the normal monomer in the heterodimer made of mutant and normal proteins, resulting in decreased levels of alkaline phosphatase activity. Instead of the 50 % expected in heterozygotes, alkaline phosphatase activities were found to range from 20 to 40 % of wild type [20]. The most strongest in vitro inhibition was found with mutation p.D378V, a mutation found in patients with the perinatal benign form of HPP. Interestingly, parents of these patients express only very mild symptoms (mostly premature loss of teeth) or even may be completely unaffected [25, 29, 35]. This is also the case of families with mild HPP due to other dominant missense mutations. So, dominance is sometimes difficult to demonstrate by using familial analysis. This may be attributable both to the progressive improvement of affected patients from infancy to adulthood and to epigenetic factors involved in the variable expression of the disease. It is possible that in particular stages of development, alkaline phosphatase requirements are beyond the capacity of the heterozygous cell, resulting in HPP symptoms. Then, AP requirements may be less important and filled by the heterozygous cell, which may explain the improvement in adult patients. It is also possible that the maternal alkaline phosphatase plays a role via fetal–maternal exchanges, as suggested by the prenatal benign form that seems to be observed only when the mutation is inherited from the mother [25, 35, 51, 52].

Table 1 Inheritance of HPP according to the clinical form of patients

Clinical form	Dominant HPP	Recessive HPP	Total
Odonto.	36 (75 %)	12 (25 %)	48
Adult	20 (61 %)	13 (39 %)	33
Prenatal benign	4 (57 %)	3 (43 %)	7
Childhood	12 (33 %)	24 (66 %)	36
Infantile	2 (3 %)	75 (97 %)	77
Perinatal	7 (6 %)[a]	103 (94 %)	110
Total	81	230	311

The numbers correspond to the HPP patients tested in Versailles between 1997 and 2011. Patients with one heterozygous mutation were classified with dominant HPP after exhaustive sequencing of the *ALPL* coding sequence, including exon–intron borders and untranslated sequences of exons 1 and 2. Depending on the mutation found, a large deletion was also searched by qPCR or QMPSF

[a] Perinatal HPP cases with only one detected heterozygous mutation may correspond to dominant prenatal benign HPP (fetuses for which the pregnancy was terminated on the basis of clinical signs detected by ultrasound) or to recessive perinatal HPP for which the second mutation was not detected (intronic mutation, mutation in the regulatory sequence)

Incidence of HPP

The overall incidence of HPP is unknown. However, as a consequence of the existence of two modes of inheritance, it is expected that the incidence of severe forms strongly differ from moderate forms. The incidence of severe forms was estimated at 1/100,000 in Canada [6] and more recently 1/300,000 in Europe [28]. The higher frequency observed in Fraser's study may be due to the founder effect observed in the Canadian Mennonite population [9] in the Toronto's area where was performed this study. In Japan, the prevalence of severe HPP may be estimated at 1/150,000 on the basis of the prevalence of the frequent mutation c.1559delT and its relative proportion in HPP chromosomes [23, 34, 48].[1]

The incidence of milder forms remains difficult to estimate because of incomplete penetrance and possible dominant inheritance. However, it is likely that these milder forms are more common than severe forms [28].

[1] Prevalence of severe HPP in Japan:
c.1559delT represents 40.9 % of severe allele [23]
Frequency of homozygotes for c.1559delT = 1/900,000 [48]
→ allele frequency of c.1559delT = 1/950
$q = 1/950 \times 1/0.409 = 0.00257 = 1/389 \rightarrow q^2 = 1/150{,}000$

Table 2 The mutations found in patients carrying only one heterozygous mutation

Mutation	Residual activity (%WT)	Dominant negative effect (%WT)	Mutation	Residual activity (%WT)	Dominant negative effect (%WT)
p.G456W	0.8	14.5	p.R71H	1.0	30.5
p.G420A	4.2	19.7	p.E429K	1.3	31.0
p.D378V	1.2	19.9	p.G339R	1.1	33.0
p.L414M	0.4	23.5	p.R71C	2.5	35.0
p.P108L	1.9	24.0	p.S445P	2.1	35.1
p.G63V	0.8	26.0	p.R164W	0.6	36.7
p.N417S	3.0	26.5	p.N478I	1.5	38.2
p.E452K	1.4	27.5	p.G334R	5.0	39.0
p.T100M	1.3	28.2	p.E476A	0.4	39.3
p.R391H	0	29.1	p.G334D	1.7	40.0
p.V382I	0[a]	30[a]	p.A116T	0.6	40.0

The dominant negative effect by inhibition of the mutated monomer onto the wild-type (WT) monomer was measured by cotransfecting WT and mutant cDNAs in COS cells and assaying the AP activity. Absence of dominant negative effect by inhibition is expected to produce 50 % of WT activity

[a] As reported by [43]

Genetic Counseling

Genetic counseling of HPP is complicated by the inheritance that may be autosomal dominant or autosomal recessive and by the existence of the uncommon prenatal benign form. The risk of recurrence of severe forms is 25 %. In moderate forms, it may be 25 % (recessive transmission), 50 % (dominant transmission), or still different (less than 50 %) due to the variable expressivity of dominant forms [13, 20]. The mutations detected in dominant forms and responsible for moderate HPP are also found in severe recessive HPP, associated with other mutations [11, 13, 15, 20]; Mumm et al. [30]. Testing patient's relatives is useful since heterozygotes may express a mild form of the disease. In regard to the frequency of the disease (1/300,000 in Europe), testing spouses of carriers is not relevant unless there is a history of consanguinity.

In prenatal context, it may be difficult to distinguish prenatal benign HPP and perinatal severe HPP. In fact, prenatal benign HPP was previously described with mild outcome [25, 35], but several years of experience suggest that it may result in variable outcome, ranging from mild HPP to infantile non-lethal HPP [52]. Combined with clinical examination, the identification of the mutations and the prediction of their degree of severity could be very useful to distinguish severe and benign prenatal HPP. However, testing new mutations by in vitro functional tests remains time-consuming and existing in silico predictive tools still show relatively low predictive powers.

Is HPP an Oligogenic Disease?

In a few proportion of patients, estimated to 5 %, no mutation in the ALPL gene was found, which may suggest intronic mutations or mutations in the regulatory sequence, but also possible mutations in other genes. In addition, there is evidence of patients with the same genotype but significant different phenotypes although these differences mostly correspond to adjacent classes of severity (childhood and infantile for instance) [36, 52, 56]. This may be due to environmental or epigenetic factors but also to modifiers genes. Since the mechanism of mineralization

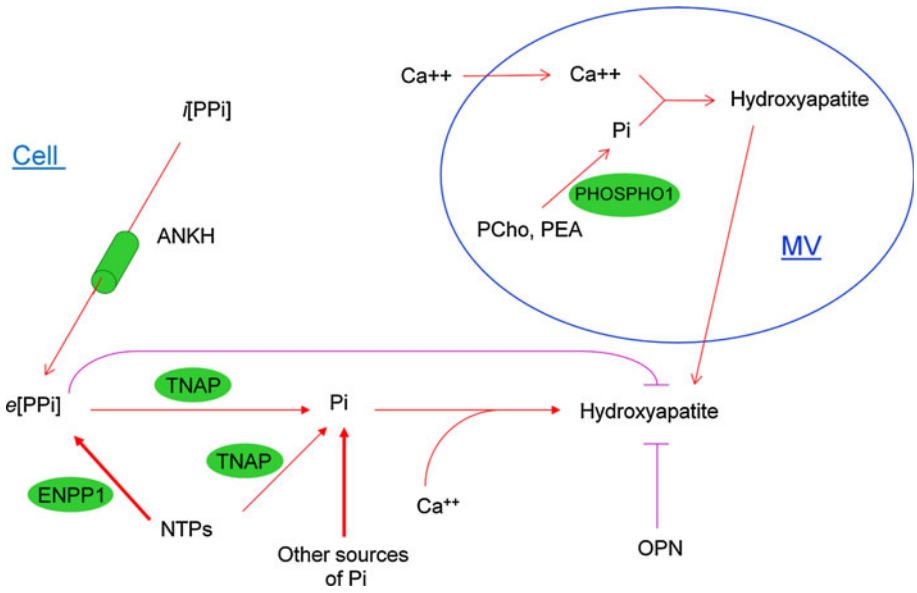

Fig. 1 Schematic representation of the key players in bone mineralization and its regulation [adapted from [10, 14, 33, 57]]. *MV* matrix vesicle, *PEA* phosphoethanolamine, *PPi* inorganic pyrophosphate, *Pi* inorganic phosphate, *NTPs* nucleotide triphosphates

has been greatly deciphered [24, 57], a series of genes involved in Pi and PPi metabolism have been suggested as possible modifiers of the HPP phenotype (Fig. 1), especially the genes encoding ENPP1, an antagonist to TNSALP that produces PPi [14, 37], ANK, a transmembrane protein exporting intracellular PPi [10], OPN, an inhibitor of mineralization that binds hydroxyapatite [10] an PHOSPHO1 a phosphatase involved in the initiation of mineralization [57]. Although there is no yet direct proof of implication of these genes in the modulation of the HPP phenotype, exhaustive sequencing of these genes by using NGS should efficiently answer the question.

Disclosures

Conflict of interest Author Etienne Mornet declares that he has no conflict of interest.

Animal/Human Studies This article does not contain any studies with human or animal subjects performed by the author.

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