

Chapter 2

Molecular Genetics of Hypophosphatasia and Phenotype-Genotype Correlations

Etienne Mornet

Abstract Hypophosphatasia (HPP) is due to deficient activity of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNAP). This enzyme cleaves extracellular substrates inorganic pyrophosphates (PPi), pyridoxal-5'-phosphate (PLP), phosphoethanolamine (PEA) and nucleotides, and probably other substrates not yet identified. During the last 15 years the role of TNAP in mineralization, and to a less degree in brain, has been investigated, providing hypotheses and explanations for both bone and neuronal HPP phenotypes. *ALPL*, the gene encoding TNAP, is subject to many mutations, mostly missense mutations. A few number of mutations are recurrently found and may be quite frequent in particular populations. This reflects founder effects. The great variety of mutations results in a great number of compound heterozygous genotypes and in highly variable clinical expressivity. A good correlation was observed between the severity of the disease and in vitro enzymatic activity of the mutant protein measured after site-directed mutagenesis. Many missense mutations found in severe hypophosphatasia produced a mutant protein that failed to reach the cell membrane, was accumulated in the cis-Golgi and was subsequently degraded in the proteasome. Missense mutations located in the catalytic site or in the homodimer interface were often shown by site-directed mutagenesis to have a dominant negative effect. Currently molecular diagnosis of HPP is based on the sequencing of the coding sequence of *ALPL* that allows detection of approximately 95 % of mutations in severe cases. In addition, other genes, especially genes encoding proteins involved in the regulation of extracellular PPi concentration, could modify the phenotype (modifier genes).

Keywords Hypophosphatasia • Genotype-phenotype correlation • Mutation • Tissue-nonspecific alkaline hypophosphatasia

E. Mornet (✉)

Unité de Génétique Constitutionnelle, Centre Hospitalier de Versailles, Le Chesnay, France
e-mail: emornet@ch-versailles.fr

2.1 Introduction

For geneticists dealing with genotype-phenotype correlation, Hypophosphatasia (HPP) is a challenging model of inherited disorder because it cumulates various deviations from Mendelian transmission : variable expressivity, even in patients sharing the same genotype, dominant or recessive inheritance of moderate forms, incomplete penetrance of dominant forms, and parental bias of transmission in the so-called prenatal benign form of HPP. The study of the *ALPL* mutations by various experimental approaches including site-directed mutagenesis, 3D modeling and immunofluorescence have been very informative to progress in understanding the particular genetic aspects of HPP.

2.2 The Tissue-Nonspecific Alkaline Phosphatase (TNAP)

2.2.1 Alkaline Phosphatases

Alkaline phosphatases (E.C.3.1.3.1) (APs) form a large family of enzymes common to all organisms. The core fold and the active-site architecture of the enzyme have been shown to be similar in bacteria, archea and eukaryotes (Wende et al. 2010). APs catalyze the hydrolysis of phosphomonoesters with release of inorganic phosphate (Schwartz and Lipmann 1961). The catalytic activity of APs depends on a multimeric configuration of identical monomers. Each identical subunit possesses one active site and contains two Zn^{2+} and one Mg^{2+} ions that stabilize the tertiary structure (Kim and Wyckoff 1991). APs are believed to be homodimeric in serum and in membranes, but the tissue-nonspecific isoform could exist as homodimeric and/or homotetrameric structure in membranes (Hawrylak and Stinson 1987).

In humans, three out of four AP isozymes are tissue-specific : one is placental (PLAP), the second appears in germ cells (GCAP), and the third in the intestine (IAP). They are 90–98 % homologous, and their genes are tandemly arranged on chromosome 2q37.1, likely arising from relatively recent ancestral duplications. The fourth, TNAP, is 50 % identical to the other three, suggesting that it arised from a more ancient duplication. It is ubiquitous but strongly expressed in liver, bone and kidney (Stigbrand 1984; Millan 1992), in cerebral cortex (Fonta et al. 2004) and in developing spinal cord (Narisawa et al. 1994). Its gene is located on chromosome 1p34–36 (Greenberg et al. 1990).

2.2.2 Structure of the TNAP According to Modelling from PLAP

For many years the only source of structural information on APs was the crystallographic coordinates of the *E. coli* AP (Kim and Wyckoff 1991). Building a

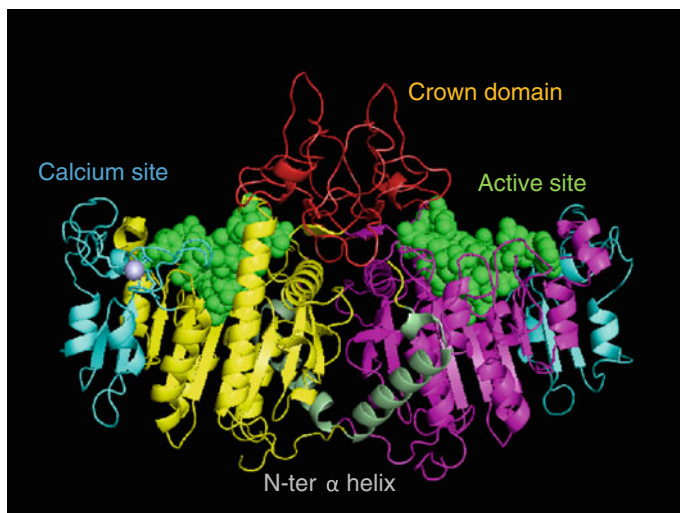


Fig. 2.1 Three-dimensional model of TNAP based on the crystal structure of the placental isoform (Le Du et al. 2001). The two identical monomers forming the homodimer are displayed in yellow and magenta. The functional domains are identified by distinct colours. The active site is represented in green spacefill, the crown domain in red, the calcium binding site in blue (calcium atom is shown in blue spacefill), and the N-ter α helix in green ribbon. The homodimer interface also includes residues from the crown domain and the N-ter alpha helix

three-dimensional model of human TNAP using alignment to the structure of *E. coli* AP as a template evidenced a number of regions that could not be modelled (Zurutuza et al. 1999), suggesting that human APs have functions that do not exist in *E. coli* AP. When the three-dimensional structure of the first mammalian AP, i.e. PLAP, was elucidated (Le Du et al. 2001), these regions were modelled and evidence was provided for their conservation in mammals (Le Du and Millan 2002) and for their functional role (Le Du et al. 2001; Mornet et al. 2001). Now, the accumulation of molecular and structural data suggests that APs progressively acquired specialization and new functions during evolution.

Five functional domains have been identified in TNAP (Fig. 2.1). The active site is the centre of the catalytic activity. It is conserved in all species including *E. coli*. The crown domain is a key factor of uncompetitive inhibition (Kozlenkov et al. 2004), heat-stability (Bossi et al. 1993) and allosteric behaviour (Hoylaerts et al. 1997). Together with the N-terminal arm, the crown domain contributes to stabilize the dimeric structure. It may be also involved in the binding of TNAP to collagen (Hoylaerts and Millan 1991; Bossi et al. 1993), corroborating previous studies suggesting this property of TNAP (Vittur et al. 1984; Wu et al. 1991). The crown domain is highly conserved in mammals. The homodimer interface is crucial because dimerization is indispensable for allostery and because APs are active only in dimeric form (Bossi et al. 1993). Monomer-monomer interactions are made of noncovalent hydrogen bonds and of van der Waals and hydrophobic contacts, and

involve about 90 residues and 25 % of the overall surface of the protein (Millan 2006). Interestingly, whereas the distribution of hydrophobic/hydrophilic amino acids significantly differ from an isoform to another one, it has been suggested that TNAP monomer could dimerize with the intestinal isoform (IAP) monomer (Vergnes et al. 2000). The exact role of the calcium site remains to be elucidated. However this site is conserved among vertebrates, suggesting a possible vertebrate-specific function (Brun-Heath et al. 2005). The N-terminal α helix is essential for stability and allosteric properties of the enzyme (Hoylaerts et al. 2006).

2.2.3 TNAP Substrates and Functions

TNAP cleaves extracellular substrates such as inorganic pyrophosphates (PPi), pyridoxal-5'-phosphate (PLP), phosphoethanolamine (PEA) and nucleotides. However, the demonstration that PEA is also a natural substrate of TNAP in vivo remains to be confirmed (Millan 2006), and it remains possible that all substrates of TNAP are not yet identified. The exact function of TNAP in bone and dental mineralization has now been greatly deciphered and involves hydrolysis of PPi, and perhaps mammalian-specific activities such as collagen (Hoylaerts et al. 1997) and calcium (Mornet et al. 2001) binding.

2.2.3.1 Inorganic Pyrophosphate (PPi)

TNAP is present in matrix vesicles and activity of TNAP is required to generate the inorganic phosphate (Pi) needed for hydroxyapatite crystallization (Fallon et al. 1980). Because PPi suppresses the formation and growth of hydroxyapatite crystals (Meyer 1984), the ability of TNAP to hydrolyze PPi promotes osteoblastic mineralization (Rezende et al. 1994), resulting in antagonistic roles of the plasma cell membrane glycoprotein-1 (PC1) that products PPi from dNTPs, and TNAP that hydrolyzes PPi to generate Pi (Hessle et al. 2002) (Fig. 2.2). Finally five proteins have been identified as central regulators of extracellular PPi and Pi levels: TNAP, which hydrolyzes PPi, PC-1 which generates PPi, the multiple-pass transmembrane protein ANKH, which mediates intracellular to extracellular channeling of PPi (Ho et al. 2000; Harmey et al. 2004), osteopontin (OPN), another mineralization inhibitor, and PHOSPHO1, a phosphatase involved in the first step of mineralization in matrix vesicles (Yadav et al. 2011) (Fig. 2.2).

2.2.3.2 Pyridoxal 5'-Phosphate (PLP)

It is known that pyridoxine-responsive seizures are an indicator of hypophosphatasia severity and lethal prognosis (Litmanovitz et al. 2002; Nunes et al. 2002; Baumgartner-Sigl et al. 2007). PLP is the phosphorylated version of pyridoxine

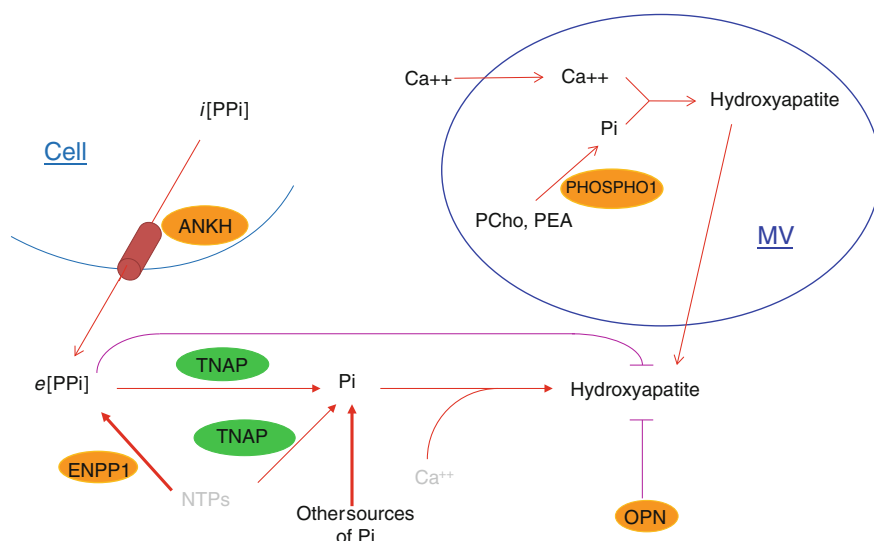


Fig. 2.2 Schematic representation of the key players in bone mineralization and its regulation [adapted from (Hessle et al. 2002; Harney et al. 2004; Orimo 2010; Yadav et al. 2011)]. MV = matrix vesicle; PEA = Phosphoethanolamine, PPi = inorganic pyrophosphate (i = intracellular, e = extracellular), Pi = inorganic phosphate; NTPs = nucleotide triphosphates. ENPP1 = ectonucleotide pyrophosphatase/phosphodiesterase 1; OPN = osteopontin; TNAP = tissue-nonspecific alkaline phosphatase; ANKH = progressive ankylosis protein homolog; PEA = phosphoethanolamine; PCho = phosphocholine; PHOSPHO1 = phosphatase orphan 1

(vitamin B6) (see Chap. 11). TNAP hydrolyzes PLP, and the unphosphorylated vitamin PL crosses the blood-brain barrier, to be re-generated as PLP into the cell (Whyte 2001) where it plays a crucial role as co-enzyme for the glutamic acid decarboxylase, an enzyme responsible for gamma-aminobutyric acid synthesis (Baxter 2003). Consequently, in patients with hypophosphatasia, inability to cleave PLP may result in a central nervous system-localized vitamin B6 deficiency and seizures (Waymire et al. 1995) (see also Chap. 14). Interestingly, in patients affected with Mabry's Disease, a particular form of hyperphosphatasia characterized by neurologic defects and seizures, pyridoxine responsiveness of the electroencephalographic abnormalities suggests that TNAP could be also involved in the intraneuronal balance between PL and PLP (Thompson et al. 2006). Mabry's disease has been shown in at least a part of cases, to be due to mutations in PIG (Phosphatidylinositol Glycan anchor biosynthesis) genes resulting in absence of membrane anchoring and secretion of TNAP (Krawitz et al. 2010; Horn et al. 2011; Krawitz et al. 2012; Murakami et al. 2012; Thompson et al. 2012; Krawitz et al. 2013) (see also Chap. 16).

Studies of alkaline phosphatase activity in primates brain supports the important role of this enzyme in neurotransmission (Fonta et al. 2004; Fonta et al. 2005), and the bone isoform of TNAP has been shown to be the only AP expressed in human

brain (Brun-Heath et al. 2011). In addition, kinetic characterization of TNAP mutations evidenced that some mutations were efficient in hydrolyzing PPi but inefficient in hydrolyzing PLP (Di Mauro et al. 2002), which could explain why some patients manifest more severe seizures than others.

2.2.3.3 Nucleotides

In rat, TNAP is able to hydrolyze ATP, ADP and AMP (Say et al. 1991) (see Chap. 4). In mouse TNAP has been recently highlighted as one of the three phosphatases (along with prostatic acid phosphatase [PAP] and ecto-5'-nucleotidase [NT5E]) generating adenosine from AMP in dorsal root ganglia (DRG) neurons (Street et al. 2013). Adenosine shows antinociceptive properties and, as other nucleosides, plays a key role in pain signaling and sensory biology, suggesting that mutations in *ALPL* could result in a lower concentration of adenosine in DRG neurons. This could explain bone, joint, and muscle pain suffered by a proportion of HPP patients (see Chap. 13).

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

2.3.1 The *ALPL* Gene

ALPL consists of 12 exons distributed over 65 kb. Two transcripts have notably been identified, driven by two alternative exons 1 in the 5'-untranslated region (UTR) (Weiss et al. 1988b) and responsible for differential transcription and subsequent co-translational and post-translational modifications (Matsuura et al. 1990; Terao et al. 1990; Studer et al. 1991). The transcription of the upstream exon 1A is preferentially driven in osteoblasts, whereas transcription is preferentially initiated with exon 1B in liver and kidney (Toh et al. 1989; Matsuura et al. 1990; Studer et al. 1991). 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 (Brun-Heath et al. 2011). 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. In addition three transcript variants of the bone *ALPL* are thus far identified (<http://www.ncbi.nlm.nih.gov/gene/249>), the longest variant NM_00478.4 harboring the 12 exons, and two shorter variants lacking a portion of the 5' coding region, NM_001177520.1. and NM_001127501.2. The latter was also reported in a patient with adult HPP (Mentrup et al. 2011).

2.3.2 The Hypophosphatasia Mutations

Since the first mutation was identified in the *ALPL* gene (Weiss et al. 1988a), around 300 distinct mutations have been reported. A constantly updated list of mutations is available online (http://www.sesep.uvsq.fr/database_hypo/Mutation.html). Most of them (74 %) are missense mutations. The remaining reported mutations are deletions (11 %), splicing mutations (6 %), nonsense mutations (4 %), small insertions (2 %), a complex deletion + insertion and a nucleotide substitution affecting the major transcription initiation site. Two gross deletions (Spentchian et al. 2006), 2 de novo mutations (Taillandier et al. 2005; Zhang et al. 2012) and a homozygous mutation resulting from paternal isodisomy of chromosome 1 (Watanabe et al. 2012) were also reported.

A small number of mutations are recurrently found and may be quite frequent in particular populations. This reflects founder effects, i.e. ancient ancestral mutations that occurred on single chromosomes and spread throughout populations of small sizes in limited area. For instance, the mutations c.1559delT and p.F327L represent 40.9 and 13.6 % of HPP chromosomes, respectively, in the Japanese population (Michigami et al. 2005) (see also Chap. 14), the mutation c.571G > A (p.E191 K) is found in half of patients from European ancestry affected with moderate HPP (Herasse et al. 2002), and the mutation c.1001G > A (p.G334D) represents most of HPP chromosomes in the Canadian Mennonite community (Greenberg et al. 1993). In USA, the missense mutation c.1133A > T (p.D378 V), probably originating from North-West Europe where it is rare represents 14 % of HPP chromosomes and is a common cause of dominant prenatal benign HPP (Mumm et al. 2007).

Except one case (Whyte et al. 2006), HPP was never reported in populations from black African ancestry.

2.3.3 Genotype-Phenotype Correlations

The great variety of *ALPL* 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 correlation was observed between the severity of the disease and in vitro enzymatic activity of the mutant protein (Zurutuza et al. 1999). Patients with recessive 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 product enzymatic activity. The results of in vitro assays of over 80 mutations are listed in the Tissue Nonspecific Alkaline

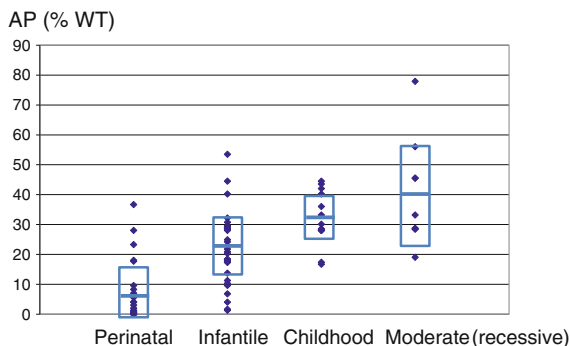


Fig. 2.3 Expected mean AP calculated from the 2 mutations composing the genotype ($n = 81$). Expected mean alkaline phosphatase relative level calculated from in vitro assays of the two missense mutations composing a genotype. Eighty-one distinct unrelated genotypes were tested. Heretozygous patients, i.e. with dominant HPP, are not shown since the model assumes that the mean activity reflects absence of dominant negative effect

Phosphatase Gene Mutations Database (http://www.sesep.uvsq.fr/03_hypo_mutations.php). Moreover, similarly to the level of serum alkaline phosphatase that correlates with the severity (Whyte 1994), the expected mean AP activity of recessive 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 (Fig. 2.3).

By using GFP fusion proteins or 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 (Cai et al. 1998; Fukushi et al. 1998; Shibata et al. 1998; Fukushi-Irie et al. 2000; Ito et al. 2002; Ishida et al. 2003; Komaru et al. 2005; Watanabe et al. 2005; Nasu et al. 2006; Brun-Heath et al. 2007; Numa et al. 2008; Ishida et al. 2011; Mentrup et al. 2011; Satou et al. 2012). These studies showed that most of the missense mutations found in severe HPP product a mutant protein that fails to reach the cell membrane, is accumulated in the cis-Golgi and is 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.

Analysis of the 3D model of TNAP showed that severe missense mutations mostly affect residues localized in crucial domains of the protein while mutations found in mild forms affect residues more randomly dispatched (Zurutuza et al. 1999; Mornet et al. 2001; Mornet 2008).

As previously indicated neurologic symptoms of HPP (seizures) are observed in the most severe forms of the disease and are assumed to be related to the deficiency of TNAP to dephosphorylate PLP at the surface of neuronal cells (see Chap. 14). Most of the patients presenting with seizures have no detectable serum ALP activity, suggesting that neuronal forms of HPP result from absence of TNAP and that dephosphorylation of PLP may be fulfilled by only very residual ALP activity.

Alternatively, the ability of mutant TNAP to metabolize substrates may differ from one substrate to another, depending on the mutation, as previously shown *in vitro* for PLP and PPi (Di Mauro et al. 2002). Consequently neuronal phenotype of HPP could depend on the substrat-specificity allowed by the mutation together with its too low ALP activity. Interestingly missense mutations observed in patients with seizures seem to be located in particular regions of the TNAP protein, especially the active site and the calcium site (our unpublished data).

2.3.4 The Dominant Effect of TNAP Mutations

Dominant transmission of HPP has been suggested on the basis of pedigree and laboratory data (Whyte et al. 1979; Whyte et al. 1982; Eastman and Bixler 1983; Eberic et al. 1984; Moore et al. 1999; Hu et al. 2000). 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 (Fauvert et al. 2009). Thus far, at least 22 missense mutations were shown to have a dominant negative effect by site-directed mutagenesis (Table 2.1). Corroborating the idea that the dominant negative effect is due to negative interactions between wild-type and mutant monomers, most of the mutations with a dominant negative effect affect residues located in the active site and the homodimer interface, especially the crown domain which constitute the top of the

Table 2.1 The mutations with a dominant negative effect

Mutation	Residual activity (%WT)	Dominant negative effect (%WT)	Mutation	Residual activity (%WT)	Dominant negative effect (%WT)
p.G456 W	0.8	14.5	p.R71H	1.0	30.5
p.G420A	4.2	19.7	p.E429 K	1.3	31.0
p.D378 V	1.2	19.9	p.G339R	1.1	33.0
p.L414 M	0.4	23.5	p.R71C	2.5	35.0
p.P108L	1.9	24.0	p.S445P	2.1	35.1
p.G63 V	0.8	26.0	p.R184 W	0.6	36.7
p.N417S	3.0	26.5	p.N478I	1.5	38.2
p.E452 K	1.4	27.5	p.G334R	5.0	39.0
p.T100 M	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 inhibition of the activity of the mutated monomer onto the wild type (WT) monomer was measured by co-transfecting 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

^aAs reported by Takinami et al. 2004 (Takinami et al. 2004)

homodimer interface (Fauvert et al. 2009). However, it has been also suggested that dominant negative effects could arise from negative interactions between monomers, homodimers, or multimers, forming aggregates (Lia-Baldini et al. 2008; Sultana et al. 2013).

While the penetrance of the disease (the proportion of affected persons among the persons carrying the affected genotype) in recessive HPP is assumed 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. Thus, dominance is sometimes difficult to demonstrate by using familial analysis. 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 sequester the heterodimer in the cytoplasm, explaining the dominant negative effect (Lia-Baldini et al. 2008). 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 (Lia-Baldini et al. 2001). The most strong in vitro inhibition was found with mutation p.D378 V, 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 (Moore et al. 1999; Pauli et al. 1999; Muller et al. 2000). This is also the case of families with mild HPP due to other dominant missense mutations. This may be attributable both to the progressive improvement of affected patients from infancy to adulthood and to genetic or 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 dominant prenatal benign form that is mostly observed when the mutation is inherited from the mother (Moore et al. 1999; Pauli et al. 1999; Wenkert et al. 2011).

2.3.5 Prevalence 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 (Fraser 1957) and more recently 1/300 000 in Europe (Mornet et al. 2011). The higher frequency observed in Fraser's study may be due to the founder effect observed in the Canadian Menonite population (Greenberg et al. 1993) in the Toronto's area where this study was performed.

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 since heterozygotes may be affected (Mornet et al. 2011).

2.4 Molecular Diagnosis and Genetic Counselling

In addition to clinical and radiographic examinations (see Chap. 1), hypophosphatasia diagnosis is based on laboratory assays, and from 1990s, molecular biology.

2.4.1 Laboratory Assays

Total serum alkaline phosphatase activity is markedly reduced in HPP. So, the diagnosis can be suggested in patients where serum AP activity is clearly and consistently subnormal. In general, the more severe the disease, the lower the serum AP activity level (Whyte 1994). However, AP activity is only a helpful diagnostic indicator because other conditions may also show this finding: early pregnancy, drugs administration, hypothyroidism, anemia etc. It must be also noticed that serum AP dramatically varies with age and sex, so that patients and controls must be matched for these two parameters. Serum PLP and urinary PEA may be also used for diagnosis of HPP, however PEA is not pathognomonic since it is observed in a variety of other conditions, including several metabolic bone diseases, and some hypophosphatasia patients may have normal PEA excretion. PLP may be a sensitive marker for HPP (Whyte 1994) and there is a correlation between the severity of the disease and the level of serum PLP.

Heterozygous carriers for severe forms are usually clinically normal but often show modestly reduced serum AP activity and increased urinary PEA (Rasmussen 1968).

2.4.2 Molecular Biology

Screening for mutations in the *ALPL* gene is essential to confirm the hypophosphatasia diagnosis and to offer molecular prenatal diagnosis to families affected with severe forms of the disease. Mutation screening is usually performed by sequencing the *ALPL* coding sequence in genomic DNA. The exons are small and few in number, making the analysis relatively easy. But some mutations remain undetectable because they lie in intronic or regulatory sequences. In our experience, by using sequencing, approximately 95 % of mutations are detected in severe

(perinatal and infantile) hypophosphatasia, while patients with mild forms often carry only one detected mutated allele. This may be due to failure to detect the second allelic mutation or to expression of the disease at the heterozygous state.

Prenatal assessment of severe hypophosphatasia by mutation analysis of chorionic villus DNA is now well documented (Henthorn and Whyte 1995; Orimo et al. 1996; Mornet et al. 1999; Watanabe et al. 2007). It seems that mutation analysis is more reliable than alkaline phosphatase assay of chorionic villus at least for heterozygote detection where low AP values may be misinterpreted (Mornet et al. 1999).

Genetic counselling 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 (Lia-Baldini et al. 2001; Herasse et al. 2003). The mutations detected in dominant forms and responsible for moderate HPP are also found in severe recessive HPP, associated to other mutations (Henthorn et al. 1992; Hu et al. 2000; Lia-Baldini et al. 2001; Herasse et al. 2003; Mumm et al. 2007; Fauvert et al. 2009). 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 (Moore et al. 1999; Pauli et al. 1999), but several years of experience suggest that it may result in variable outcome, ranging from mild HPP to infantile non lethal HPP (Wenkert et al. 2011). 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 remain time-consuming and existing in silico predictive tools still show relatively low predictive powers.

2.5 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) (Whyte et al. 2006; Petkovic Ramadza et al. 2009; Wenkert et al. 2011). This may be due to environmental or epigenetic factors but also to modifiers genes. Since the mechanism of mineralization has been greatly deciphered (Millan 2006; Yadav et al. 2011), a series of genes involved in Pi and PPi metabolism has been suggested as possible modifiers of the HPP phenotype (Fig. 2.2), especially the

genes encoding ENPP1 (Ectonucleotide pyrophosphatase/phosphodiesterase), an antagonist to TNAP that produces PPi (Hessle et al. 2002; Rodrigues et al. 2011), ANK (ankylosis protein), a transmembrane protein exporting intracellular PPi (Harmey et al. 2004), OPN, an inhibitor of mineralization that binds hydroxyapatite (Harmey et al. 2004) and PHOSPHO1 a phosphatase involved in the initiation of mineralization (Yadav et al. 2011). Although there is no yet direct proof of implication of these genes in the modulation of the HPP phenotype, exhaustive sequencing of these genes should efficiently answer the question.

Conflict of Interest The author states the absence of conflict of interest.

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