CLINICAL UTILITY GENE CARD UPDATE

Clinical utility gene card for: Hypophosphatasia – update 2013

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Hypophosphatasia (HP), HPP, rathbun disease and phosphoethanolaminuria.

1.2 OMIM# of the disease

146300, 241500 and 241510

1.3 Name of the analysed genes or DNA/chromosome segments

Alkaline phosphatase (AP) liver type (ALPL), 1p36.1-p34.

Used other names: TNAP and tissue nonspecific AP.

1.4 OMIM# of the gene(s)

171760.

1.5 Mutational spectrum

Over 250 different disease-causing mutations have been reported in the ALPL gene mutations.

Database http://www.sesep.uvsq.fr/03_hypo_mutations.php. The distribution is as follows: 75.5% missense mutations; 10.5% small deletions; 6% splicing mutations; 4% nonsense mutations; 2% small insertions; and 1% or less: complex insertion/deletions, large deletions and mutations in the regulatory sequence. The large proportion of missense mutations with various effects on the enzymatic activity of AP, based upon *in vitro* studies, has been correlated with the high clinical variability.¹ A number of missense mutations exhibit a dominant-negative effect^{2–5} explaining dominant inheritance of mild forms of the disease.^{6–8}

1.6 Analytical methods

The main strategy for mutation screening consists in sequencing of genomic exonic DNA, including flanking intronic sequences. This allows the detection of approximately 95% of mutations in patients with HP. The analysis may be completed by screening for

large deletions by quantitative multiplex PCR of short fragments,⁹ but this does not significantly increase the detection rate because large deletions seem rare in the ALPL gene. For prenatal diagnosis, a set of linked microsatellites sequences strongly linked to the ALPL gene may be used for indirect diagnosis and/or excluding maternal cell contamination.

1.7 Analytical validation

The existence of mutations is confirmed by testing the parental DNA or, when the parental DNA is not available, by sequencing a second and independent PCR product. Newly discovered missense mutations may be tested *in vitro* by site-directed mutagenesis for enzymatic activity, protein stability, cell localisation and so on, clarifying their disease-causing role and estimating their degree of severity.¹

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)

According to a report from 1957 in Toronto, Canada,¹⁰ the incidence of severe cases of HP (perinatal and infantile forms) is 1 in 100 000. On the basis of molecular diagnosis in France and Europe, the incidence of severe forms has been estimated at 1/300 000, a lower value that may reflect a founder effect previously observed in the region of Toronto.¹¹ Study of the prevalence of mild forms (prenatal benign, childhood, adult and odontoHP) has not been reported yet, but it is expected higher because of low selective pressure and because heterozygotes for some mutations may express the disease.

1.9 If applicable, prevalence in the ethnic group of investigated person

Greenberg *et al.*¹² suggested that the disease prevalence in Canadian Mennonites could be up to 1 in 2500. HP seems very rare in populations of black ancestry.¹³

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1.10 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	☒	☐
B. Predictive Testing	☒	☐
C. Risk assessment in relatives	☒	☐
D. Prenatal	☒	☐

Comment:

Not applicable.

2. TEST CHARACTERISTICS

Genotype or disease		A: True positives	C: False negative
		B: False positives	D: True negative
		Present	Absent
Test			
Positive	A	B	Sensitivity: $A/(A + C)$ Specificity: $D/(D + B)$
Negative	C	D	Positive predictive value: $A/(A + B)$ Negative predictive value: $D/(C + D)$

2.1 Analytical sensitivity

(proportion of positive tests if the genotype is present)

Nearly 95%.

2.2 Analytical specificity

(proportion of negative tests if the genotype is not present)

Nearly 100%.

2.3 Clinical sensitivity

(proportion of positive tests if the disease is present)

The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases, a general statement should be given, even if a quantification can only be made case by case.

Nearly 95%.

2.4 Clinical specificity

(proportion of negative tests if the disease is not present)

The clinical specificity can be dependent on variable factors such as age or family history. In such cases, a general statement should be given, even if a quantification can only be made case by case.

Nearly 100%.

2.5 Positive clinical predictive value

(life-time risk to develop the disease if the test is positive)

100% in recessive inheritance.

Up to 30–40% in mild forms with dominant inheritance, depending on the mutation.

2.6 Negative clinical predictive value

(probability not to developing the disease if the test is negative)

Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested: 100%.

Index case in that family had not been tested: 95%.

3. CLINICAL UTILITY

3.1 (Differential) diagnostics: The tested person is clinically affected
(To be answered if in 1.10 'A' was marked)

(1) Diagnosis: based on clinical courses and severity, HP has been divided into six major subtypes with different prognoses. The perinatal form is the most severe one. It results in stillbirth or death a few days after birth due to hypoplastic lungs, difficulty to treat seizures, extensive hypomineralisation, deformities of bone and disturbances of the Ca/P metabolism. In the prenatal benign form, despite prenatal findings on fetal ultrasound, there is a spontaneous improvement of skeletal defects. The patients manifest limb shortening and bowing and often dimples overlaying the long bones anomalies, and ultrasounds reveal progressive improvement of the skeletal anomalies and mineralisation during the third trimester of the pregnancy and after birth.^{14–16} Clinical signs of the infantile form appear during the first 6 months of life including rickets, premature craniosynostosis, irritability, seizures and nephrocalcinosis due to hypercalciuria. Later, premature loss of deciduous teeth is common. Death within the first year of life is common, but the precise risk is not understood. The childhood form in most cases presents after the first 6 months of life and is characterised by rickets causing a short stature, delayed walking and a waddling gait due to bone deformities and pain of the lower extremities. Later, premature loss of teeth often leads to diagnosis. It occurs before 5 years of age, and teeth are generally lost with intact root. Adult HP presents with osteomalacia, chondrocalcinosis, osteoarthropathy and stress fractures during middle age in patients who often had a history of mild rickets in childhood. Many patients present loss of permanent teeth. Odontohypophosphatasia is characterised by premature exfoliation of primary and/or permanent teeth and/or severe dental caries, not associated with abnormalities of the skeletal system. However, it should be noticed that the disease spectrum is a continuum, and that these six clinical subtypes can overlap significantly; for example, patients with adult HP often had musculoskeletal symptoms already in childhood. The infantile and the childhood form might be difficult to distinguish, because early symptoms might be present in the first months of life in both subtypes. In addition, dental abnormalities are frequent in other forms of HP. According to the severity of the disorder, some dental defects were infrequent, whereas other are always present.¹⁷ They consist of abnormal tooth shape (small bulbous crown, cervical constrictions and enlarged pulp spaces), abnormal tooth structure (enamel, dentin and cementum formation), tooth colour, dental anomalies of tooth eruption/exfoliation with premature loss of predominantly the primary and also the permanent dentition. Delayed eruption of teeth and primary teeth impaction (ankylosis) are also recorded.

(2) Differential diagnosis: The differential diagnosis of HP depends on the age at which the diagnosis is considered.

In utero: osteogenesis imperfecta (OI) type II, campomelic dysplasia and chondrodysplasias with bone mineralisation defect

At birth: outwardly difficult to distinguish, radiographs readily distinguish OI (type II) campomelic dysplasia and chondrodysplasias with bone mineralisation defect, from HP.

Infancy and childhood: inborn errors of energy metabolism, organic acidemia, primary and secondary rickets, neglect and non-accidental trauma.

- Nutritional and/or vitamin D deficiency, vitamin D resistance or renal osteodystrophy
- OI (typically type III in infancy or type IV later on)
- Cleidocranial dysostosis (OMIM 119600)

- Cole–Carpenter syndrome (OMIM 112240)
- Hadju–Cheney syndrome (OMIM 102500)
- Chronic recurrent multifocal osteomyelitis (OMIM 259680)¹⁸
- Idiopathic juvenile osteoporosis (OMIM 259750)
- Renal osteodystrophy
- Adult and ontoHP
- Osteoarthritis and pseudogout
- Osteopenia/osteoporosis
- Diseases with paraspinal ligament ossification (Forestier disease, arthropathy with calcium deposition)
- Premature exfoliation of teeth can occur in a context of periodontal disease, as part of a connective tissue disorder such as Ehlers–Danlos syndrome (130050 type IV; 130080 type VIII), or associated with neutropenia, such as ELA2-related neutropenia (OMIM 202700), Papillon–Lefevre syndrome (OMIM 245000) and Haim–Munk syndrome (HMS OMIM 245010), Chediak–Higashi syndrome (OMIM 214500) or as Aggressive periodontitis (OMIM 170650). However, in HP, premature loss of primary and eventually then permanent teeth occurs without root resorption (fully rooted teeth) and without inflammation of the gingivae and periodontium and shows on radiograph alveolar bone loss.
- Dentin dysplasia type I (OMIM 125400)

3.1.1 Can a diagnosis be made other than through a genetic test?

No	☐ (continue with 3.1.4)
Yes	☒
	Clinically ☒
	Imaging ☒
	Endoscopy ☐
	Biochemistry ☒
	Electrophysiology ☒
	Other (please describe)

3.1.2 Describe the burden of alternative diagnostic methods to the patient

Diagnosis of HP often can cause considerable problems. On one hand, it is a rare disease with a variety of differential diagnoses. On the other hand, different HP subtypes present a partly comparable spectrum of symptoms. Conventional alternative diagnosis is based on laboratory assays and radiographic imaging and may be confirmed by genetic testing. Total serum AP activity is below the age-related normal range. AP activity depends on age, sex and on laboratory procedures. However, a reduced AP activity is only a helpful diagnostic indicator but it is not HP specific. Other conditions may also show reduced levels of AP including early pregnancy, hypothyroidism, anaemia, coeliac disease or zinc deficiency. In general, residual serum AP activity has directly been linked to disease severity. Patients with perinatal forms often have a total serum AP <20% of the normal range, whereas a milder form (infantile or childhood form) has to be considered, if AP values are clearly below the lower limit. Patients with ontoHP and some with a mild end of the childhood HP spectrum have values slightly below the lower limit. Patients with singular heterozygous mutations or autosomal-dominant inheritance often exhibit a considerable residual AP activity. Separation of an autosomal dominant with a compound heterozygous disease state on the basis of the biochemical AP activity, however, is usually impossible.

Reduced enzyme activity results in accumulation of its substrates including pyridoxal-5'-phosphate, inorganic pyrophosphate and phosphoethanolamine, which can be detected in serum and urine. Often serum calcium and phosphate are normal or slightly increased. Urinary calcium excretion might be above the normal range. Careful surveillance including ophthalmological and neurological examination is recommended in young patients with newly diagnosed craniosynostosis, perhaps complimented by an invasive epidural monitoring of intracranial pressure.

Sequencing of the *ALPL* gene is essential to confirm the diagnosis of HP when biochemical and clinical data are not clear enough or in the prenatal assessment of severe HP in couples with a previously affected child or pregnancy. Genetic consultation is recommended before genetic testing is done.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?

Biochemical testing does not exclude genetic testing and *vice versa*. Both diagnostic procedures add to the clinical picture and to aspects of severity and complications in the follow-up. Biochemical testing is inexpensive and may be measured in any routine laboratory. However, in order to avoid diagnosis pitfalls, appropriate collection tubes (serum separator tubes) and correct reference range matched for sex and age must be used.

3.1.4 Will disease management be influenced by the result of a genetic test?

No	☐
Yes	☒
Therapy	Treatment with bisphosphonates has been reported disappointing ¹⁹ and even detrimental, ²⁰ whereas teriparatide (the recombinant human parathyroid hormone PTH 1–34) was successfully used to improve and resolve metatarsal stress fractures in adult HP, however, depending on the number of mutations and on the nature of the mutation. ^{21–24} Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to provide clinical improvement with reduced pain, increased muscle strength and a normalised walking distance ^{25,26} (see also management section).
(please describe)	Enzyme replacement therapy (ERT) has been investigated and successively tested in mice. ²⁷ Clinical trials in infants and young children with severe HP showed very encouraging results, ²⁸ and ERT could be available soon for HP patients. Genetic testing can confirm the clinical/biochemical diagnosis but should not delay starting treatment in severe forms.
Prognosis	Other therapeutic approaches are in development, including a gene therapy vector that shows promising results in a mouse model of hypophosphatasia. ²⁹
(please describe)	The prognosis depends on clinical course and severity. The most severe types of HP, that is, perinatal and infantile forms, are often diagnosed on clinical and radiological criteria, and genetic testing confirms the diagnosis and is helpful for genetic counselling. However, childhood and adult forms, as well as ontoHP, are more difficult to diagnose on clinical, radiological and biochemical criteria, and clinicians having uncertainties may request genetic testing to argue for the diagnosis. The perinatal form is almost always lethal within days or weeks. However, in the rare prenatal benign form, there is a progressive

improvement of skeletal defects during the third trimester of the pregnancy, and patients finally are affected with mild HP^{14,15} or with more severe, non-lethal, however, clinical forms of HP.¹⁶ Approximately one-half of the patients with the infantile form die from respiratory complications. Longevity studies were not reported in the infantile and childhood forms. Patients affected with adult or odontoHP are believed to have a normal lifespan.

Management (please describe) Currently, there is no available curative treatment of HP. Therefore, symptomatic treatment in order to improve the clinical features, especially with regard to pain, seizures and other metabolic phenomena (eg, nephrocalcinosis), is of major interest.

Seizures observed in a number of patients with perinatal and infantile HP are pyridoxine responsive and may be therefore treated by using vitamin B6. However, patients may become refractory to this, and in some cases vitamin B6 is not able to control seizures.^{30–32}

NSAIDs: the presence of hyperprostaglandinism in childhood HP has been described.^{26,33,34} In trials not placebo-controlled, an anti-inflammatory treatment using NSAIDs resulted in a significant improvement of physical activity, a reduction in pain-related complaints and normalisation of prostaglandin (PG) levels.²⁶ After drug withdrawal, the positive effect persisted for another 3–6 weeks. NSAID treatment was safe and should be considered in patients with significant complaints about pain.

Diet and vitaminotherapy: treatment with zinc and magnesium, the catalytic ions of the enzyme and pyridoxal 5'-phosphate were reported to have no significant long-term benefit for HP patients.^{10,35} Dietary phosphate restriction is recommended for patients with high serum levels of phosphate. Indeed, patients are often hyperphosphatemic and show nephrocalcinosis.

Furthermore, Pi competitively inhibits TNAP activity and gene expression, which might lower AP activity secondary to the genetic defect.³⁶ Especially, for children with persistent growth retardation, an adequate nutrition with the support of a professional dietician is of major importance.³⁷

Supplementation with vitamin D can be recommended according to the guidelines for healthy children. Further, additional vitamin D therapy, as it is used in vitamin D-deficient rickets, should be avoided. An additional supplementation of calcium may result in hypercalcemia and formation of kidney stones.

Physiotherapy: physical exercises like cycling and swimming, as well as physiotherapy, seem to be useful tools for muscle building in order to stabilise the skeleton.

Whether a physical workout leads to appositional growth of bone in HP has not been evaluated so far. The maintenance of physical function is of major importance. Especially, in severe forms of disease, trauma to the skeleton must be avoided because resulting fractures take a long time to heal and might be difficult to treat. Surgical as well as conservative therapeutic approaches should be discussed with a HP-experienced clinical centre.

Neurosurgery: premature fusion of cranial sutures may result in secondary ectopia of the cerebellar tonsils (Chiari I malformation) or formation of hydrosyringomyelia.

Neurosurgical interventions are necessary in patients with neurological complications secondary to craniosynostosis, like permanent headache, paralysis or numbness of extremities, as well as papilledema due to elevated

intracranial pressure.³⁸ With regard to the progressive nature of craniosynostosis, careful surveillance including ophthalmic reassessment, neurological examination and radiographic imaging is recommended throughout childhood until adolescence, and, in presence of Chiari I malformation or hydrosyringomyelia, probably throughout lifetime.

-The dentist, especially the paediatric dentist, has a crucial role in the early detection of the milder forms of HP (childhood, adult and odontoHP), as she/he is, most likely, the first health professional to meet the patient and to propose diagnosis hypotheses regarding to the premature loss of primary and, eventually, permanent teeth.

Regular orodental monitoring by a HP-experienced dentist or orthodontist seems to be very important. The emphasis is placed on oral hygiene, appropriate use of fluoride and preventive treatment. Early loss of both primary and/or permanent teeth may be very distressful and may impair maxillary or mandibular development and therefore could be managed through prosthetic appliances.

Prosthetic replacement is helpful for general and linguistic development, as well as social integration of patients in preschool or school or after through adulthood. Possible loosening of remaining teeth should be noted in planning removable dentures. Removable dentures could be considered from 3 years of age.

The successful use of dental implants in adult HP patients has been described in the literature and might be considered as a possible treatment option by the multidisciplinary team of health professionals managing the patient.³⁹

3.2 Predictive setting: The tested person is clinically unaffected but carries an increased risk based on family history

(To be answered if in 1.10 'B' was marked)

The age of onset is variable depending on the severity of the disease (for review, see Whyte⁴⁰), and the penetrance is not complete, especially in pedigrees where patients are affected with mild forms of HP. Thus, it makes sense to perform genetic testing in relatives of patients. This is interesting for genetic counselling and may help to prevent/delay the onset of clinical symptoms. However, because of the clinical variability and reduced penetrance of some mutations, the predictive power may considerably vary between mutations. The test needs complete information of the tested person about what to expect from the test, and it must be noticed that it may be proposed to relatives of probands only when the familial mutations have been previously characterised.

3.2.1 Will the result of a genetic test influence lifestyle and prevention?

If the test result is positive (please describe)

In case of positive test, medical management for prevention of clinical symptoms is required, as described above.

If the test result is negative (please describe)

In case of negative result, the patient has to be reassured and considered as normal with regard to HP.

3.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been done (please describe)?

In general, a person at-risk or with a high probability of being affected by the disease should follow the same recommendations for diagnosis

and management of potential symptoms and complications, and should be referred to genetic counselling. In general, the clinical suspicion of the disease being present in addition to biochemical testing/confirmation makes the overall diagnosis quite likely.

3.3 Genetic risk assessment in family members of a diseased person (To be answered if in 1.10 'C' was marked)

Severe forms of the disease (perinatal and infantile) are transmitted as an autosomal-recessive trait, whereas both autosomal-recessive and autosomal-dominant transmission have been shown in clinically milder forms. Therefore, the risk of recurrence of severe forms is 25%. In moderate forms, it may be 25% (recessive transmission), 50% (dominant transmission) or still different (<50%) due to incomplete penetrance in dominant forms. The mutations detected in dominant forms and responsible for moderate HP are also found in severe recessive HP, associated with other mutations. Thus, siblings of probands with severe HP may develop moderate symptoms, with eventually early loss of teeth but limited if not absent skeletal disease.

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?

A negative test may resolve the genetic situation as the disease is very rare, and the tested person/couple have (almost) no risk for having affected children.

A positive test may lead to propose to test the partner, although the couple remain at low risk for severe HP.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?

In a family with phenotypically comparable affected siblings, a genetic test might not be essential in the yet untested healthy individual.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?

If a mutation of the index case has been shown to exhibit a dominant-negative effect, a relative carrying this mutation has a risk for developing mild HP (depending on the mutation). However, in this constellation there is still a significant variability in the expectable clinical features.

3.4 Prenatal diagnosis

(To be answered if in 1.10 'D' was marked)

For both modes of inheritance, prenatal diagnosis for pregnancies at increased risk is possible if disease-causing mutation(s) of an affected family member is (are) known.

In the prenatal benign form of HP, despite prenatal signs, there may be a spontaneous improvement of skeletal defects. Ultrasounds reveal progressive improvement of the skeletal deformities and mineralisation during the third trimester of the pregnancy.^{14–16,41} The distinction between severe and benign prenatal forms may be difficult and need to combine mutation characterisation and careful ultrasound examination.⁴²

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnostic?

Yes.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe).

Genetic testing always has to be founded on genetic counselling. Genetic results with no particular immediate consequence, like in mild autosomal-dominant forms of the disease, still do have significant impact on the long-term decisions in life like partnership, parenthood and long-term surveillance of future medical symptoms. Thus, a test result can be quite useful in the long run, but it also can have stressful implications, especially for the development of a child, and therefore needs to give a complete explanation for parents and psychological support.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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