CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Lesch–Nyhan syndrome

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Hypoxanthine guanine phosphoribosyltransferase (HPRT)-1 deficiency
HPRT1 deficiency
HPRT deficiency
HPRT deficiency, complete
HPRT deficiency, grade IV

1.2 OMIM# of the disease

300322.

1.3 Name of the analyzed genes or DNA/chromosome segments

HPRT1.

1.4 OMIM# of the gene(s)

308000.

1.5 Mutational spectrum

Human HPRT is encoded by a single structural gene spanning approximately 45 kb on the long arm of the X chromosome at Xq26, and consists of nine exons with a coding sequence of 654 bp. Documented mutations in HPRT deficiency show a high degree of heterogeneity in type and location within the *HPRT1* gene: deletions, insertions, duplications, and point mutations have been described as the cause of HPRT deficiency. To date, more than 300 disease-associated mutations have been found.^{1–4}

1.6 Analytical methods

HPRT1 gene is a housekeeping gene and it is expressed in peripheral blood. Most HPRT-deficient patients, biochemically diagnosed by a null HPRT activity in erythrocytes, present HPRT mRNA expression, and molecular diagnosis can be accomplished by RNA extraction, reverse transcription-PCR, and HPRT complementary DNA (including 3' and 5' regions) sequencing. In other cases, genomic DNA sequencing of the nine HPRT1 exons, with its intronic flanking sequences, may be necessary. In some cases, the HPRT coding region is normal and the patients present a decrease HPRT mRNA expression of unknown origin. In these patients quantification of HPRT mRNA by real-time PCR may be used for molecular diagnosis.^{5–9}

Inheritance of HPRT deficiency is X-linked recessive. Thus, males are generally affected and heterozygous females are carriers.

However, at least five females with Lesch–Nyhan syndrome have been described, with different molecular alterations accounting for their HPRT deficiency.^{10–16} Carrier diagnosis is an important issue for most HPRT-deficient families. Female carriers cannot be detected without the help of a laboratory, as they are usually asymptomatic. Carrier status cannot be accurately assessed by biochemical and enzymatic methods. HPRT activity is most often normal in hemolysate of the peripheral blood of female carriers due to selection against HPRT-deficient erythrocyte precursors. Enzymatic diagnosis of the carrier state can be performed by the identification of HPRT-deficient hair follicles or cultured fibroblasts because of their mosaicism in terms of HPRT activity, although such diagnosis is not infallible. HPRT-deficient cells from carrier females can be selected based on their 6-thioguanine resistances. Proliferation assay of peripheral blood T lymphocytes in the presence of 6-thioguanine is diagnostic in most cases. However, faster and more accurate carrier diagnosis can be performed by molecular methods. Carrier diagnosis can be accomplished by genomic DNA sequencing of the *HPRT1* gene fragment where the mutation was found in the family propositus. When propositus mutation is not available, amplification of the nine HPRT1 exons, with its intronic flanking sequences, may be necessary. If a deletion has been found in the propositus, gene dosage may be accomplished by quantitative PCR or multiplex ligation-dependent probe amplification.^{17–18}

Prenatal diagnosis for Lesch–Nyhan syndrome can be performed with amniotic cells obtained by amniocentesis at about 15–18 week's gestation, or chorionic villus cells obtained at about 10–12 week's gestation. Both HPRT enzymatic assay and molecular analysis for the known disease-causing mutation can be performed.

1.7 Analytical validation

Mutation found in HPRT complementary DNA must be confirmed at genomic level.

1.8 Estimated frequency of the disease

(Incidence at birth ('birth prevalence') or population prevalence):

The prevalence of the disease is estimated to be 1/380 000 live births in Canada, and 1/235 000 live births in Spain.¹⁹

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

There is no difference in prevalence for a specific ethnic group.

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1.10 Diagnostic setting

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

Comment: When enzymatic diagnosis is not available clinical and molecular diagnosis must be performed.

2. TEST CHARACTERISTICS

Genotype or disease		A: True positives	C: False negative
		B: False positives	D: True negative
Test	Present	Absent	
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)

About 95% (In a 5% of patients the molecular defect causing HPRT deficiency is not found. These patients present decreased HPRT1 expression of unknown cause.)

2.2 Analytical specificity

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

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 performed case by case.

About 95% (In a 5% of patients the molecular defect causing HPRT deficiency is not found. These patients present decreased HPRT1 expression of unknown cause.)

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 performed case by case.

100%.

2.5 Positive clinical predictive value

(lifetime risk to develop the disease if the test is positive)

100%.

2.6 Negative clinical predictive value

(probability not to develop 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:

In some rare cases (5%) standard genetic tests are not informative for diagnosis in spite of the HPRT enzymatic activity is null or decreased. In these cases diagnosis has to be made by enzymatic methods.

3. CLINICAL UTILITY

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

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

No ☐ (Continue with 3.1.4)

Yes ☒

Clinically

☒

Imaging

☐

Endoscopy

☐

Biochemistry

☒

Electrophysiology

☐

Other (please describe)

☒

Hypoxanthine guanine phosphoribosyl-transferase enzymatic activity

3.1.2 Describe the burden of alternative diagnostic methods to the patient

Enzymatic test for HPRT activity in hemolysate or intact cells are of diagnostic and pronostic value.

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

Enzymatic test are laborious and they are not available in many laboratories (see <http://www.lesch-nyhan.org> and <http://www.orpha.net> for the list).

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

No

Yes ☒

Therapy

No

(please describe)

Prognosis

Yes, Partial hypoxanthine guanine phosphoribosyl-transferase-deficient patients and attenuated variants of Lesch-Nyhan disease presented a better prognosis. Single point mutations are the main cause of partial deficiency of the enzyme, whereas Lesch-Nyhan syndrome with severe phenotype is caused mainly by mutations that modify the size of the predicted protein.²⁰⁻²⁵

Management

No

(please describe)

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)

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

If the test result is positive (please describe)

If the test result is negative (please describe)

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

3.3 Genetic risk assessment in family members of a diseased person

(To be answered, if in 1.10 'C' was marked)

Molecular testing of potential heterozygous carrier in a family.

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

Yes.

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

No.

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

Yes.

3.4 Prenatal diagnosis

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

Prenatal diagnosis possible when the causal mutation identified in the index case and diagnosis of the carrier performed.

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).

Molecular diagnosis in the proband allows a more accurate and faster carrier and prenatal diagnosis in relatives.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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- 4 Official website of the Lesch-Nyhan disease International Study Group <http://www.lesch-nyhan.org>.
- 5 Wilson JM, Stout JT, Palella TD, Davidson BL, Kelley WN, Caskey CT: A molecular survey of hypoxanthine-guanine phosphoribosyltransferase deficiency in man. *J Clin Invest* 1986; **77**: 188–195.
- 6 Davidson BL, Tarle SA, Palella TD, Kelley WN: Molecular basis of hypoxanthine-guanine phosphoribosyltransferase deficiency in ten subjects determined by direct sequencing of amplified transcripts. *J Clin Invest* 1989; **84**: 342–346.
- 7 Gibbs RA, Nguyen PN, Edwards A, Civitello AB, Caskey CT: Multiplex DNA deletion detection and exon sequencing of the hypoxanthine phosphoribosyltransferase gene in Lesch-Nyhan families. *Genomics* 1990; **7**: 235–244.
- 8 Dawson PA, Gordon RB, Keough DT, Emmerson BT: Normal HPRT coding region in a male with gout due to HPRT deficiency. *Molec Genet Metab* 2005; **85**: 78–80.
- 9 García MG, Torres RJ, Prior C, Puig JG: Normal HPRT coding region in complete and partial HPRT deficiency. *Mol Genet Metab* 2008; **94**: 167–172.
- 10 Lesch M, Nyhan WL: A familial disorder of uric acid metabolism and central nervous system function. *Am J Med* 1964; **36**: 561–570.
- 11 Seegmiller JE, Rosenbloom FM, Kelley WN: Enzyme defect associated with a sex-linked human neurological disorder and excessive purine synthesis. *Science* 1967; **155**: 1682–1684.
- 12 Ogasawara N, Stout JT, Goto H *et al*: Molecular Analysis of a female Lesch-Nyhan patients. *J Clin Invest* 1989; **84**: 1024–1027.
- 13 Rinat C, Zoref-Shani E, Ben-Neriah Z. *et al*: Molecular, biochemical, and genetic characterization of a female patient with Lesch-Nyhan disease. *Mol Genet Metab* 2006; **87**: 249–252.
- 14 De Gregorio L, Jinnah HA, Harris JC *et al*: Lesch-Nyhan disease in a female with a clinically normal monozygotic twin. *Mol Genet Metab* 2005; **85**: 70–77.
- 15 De Gregorio L, Nyhan WL, Serafin E, Chamoles NA: An unexpected affected female patient in a classical Lesch-Nyhan family. *Mol Genet Metab* 2000; **69**: 263–268.
- 16 Aral B, de Saint Basile G, Al-Garawi S, Kamoun P, Ceballos-Picot I: Novel nonsense mutation in the hypoxanthine guanine phosphoribosyltransferase gene and nonrandom X-inactivation causing Lesch-Nyhan syndrome in a female patient. *Hum Mutat* 1996; **7**: 52–58.
- 17 Page T, Bakay B, Nissinen E, Nyhan WL: Hypoxanthine-guanine phosphoribosyltransferase variants: correlation of clinical phenotype with enzyme activity. *J Inher Metab Dis* 1981; **4**: 203–206.
- 18 O'Neill JP: Mutation carrier testing in Lesch-Nyhan syndrome families: HPRT mutant frequency and mutation analysis with peripheral blood T lymphocytes. *Genet Test* 2004; **8**: 51–64.
- 19 Torres RJ, Puig JG: Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency: Lesch-Nyhan syndrome. *Orphanet J Rare Dis* 2007; **2**: 48.
- 20 Kelley WN, Rosenbloom FM, Henderson JF, Seegmiller JE: A specific enzyme defect in gout associated with overproduction of uric acid. *Proc Natl Acad Sci USA* 1967; **57**: 1735–1739.
- 21 Puig JG, Torres RJ, Mateos F *et al*: The spectrum of hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency. Clinical experience based on the spectrum of hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency. Clinical experience based on 22 patients from 18 Spanish families. *Medicine (Balt)* 2001; **80**: 102–112.
- 22 Dussol B, Ceballos-Picot I, Aral B *et al*: Kelley-Seegmiller syndrome due to a new variant of the hypoxanthine-guanine phosphoribosyltransferase (I136T) encoding gene (HPRT Marseille). *J Inher Metab Dis* 2004; **27**: 543–545.
- 23 Ea HK, Bardin T, Jinnah HA *et al*: Severe gouty arthritis and mild neurologic symptoms due to F199C, a newly identified variant of the hypoxanthine guanine phosphoribosyltransferase. *Arthritis Rheum* 2009; **60**: 2201–2204.
- 24 Jinnah HA, Visser JE, Harris JC, *et al*: Lesch-Nyhan Disease International Study Group: Delineation of the motor disorder of Lesch-Nyhan disease. *Brain* 2006; **129**: 1201–1217.
- 25 Jinnah HA, Ceballos-Picot I, Torres RJ, *et al*: Lesch-Nyhan Disease International Study Group: Attenuated variants of Lesch-Nyhan disease. *Brain* 2010; **133**: 671–689.

- 1 Edwards A, Voss H, Rice P *et al*: Automated DNA sequencing of the human HPRT locus. *Genomics* 1990; **6**: 593–608.
- 2 Jinnah HA, De Gregorio L, Harris JC, Nyhan WL, O'Neill JP: The spectrum of inherited mutations causing HPRT deficiency: 75 new cases and a review of 196 previously reported cases. *Mutat Res* 2000; **463**: 309–326.
- 3 Torres RJ, Mateos FA, Molano J *et al*: Molecular basis of hypoxanthine-guanine phosphoribosyltransferase deficiency in thirteen Spanish families. *Hum Mutat* 2000; **15**: 383.