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CLINICAL UTILITY GENE CARD UPDATE

Clinical utility gene card for: Lesch–Nyhan syndrome - update 2013

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Hypoxanthine guanine phosphoribosyltransferase 1 deficiency
HGPRT deficiency
HPRT deficiency
HPRT deficiency, complete
Lesch–Nyhan disease
Lesch–Nyhan syndrome

1.2 OMIM# of the disease

300322.

1.3 Name of the analysed 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 ~45 Kb on the long arm of the X chromosome at Xq26, and consists of nine exons with a coding sequence of 654 bp.[1] 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.[2–4]

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 polymerase chain reaction (RT-PCR), and HPRT cDNA (including 3′ and 5′ regions) sequencing.[5–6] In other cases, *HPRT* gene mutations leading to the absence of HPRT mRNA (no transcription and/or mRNA instability), genomic DNA sequencing of the nine *HPRT1* exons, with its intronic flanquing sequences, may be necessary.[7] In some cases, the HPRT coding region is normal and the patients presents a decrease HPRT mRNA expression of unknown origin. In these patients quantification of HPRT mRNA by RT-PCR may be employed for molecular diagnosis.[8–9] In a few cases, large deletion of regions of the *HPRT* gene, including the promoter, must be investigated by array comparative genomic hybridation (arrays CGH or aCGH) methodology.

Inheritance of HPRT deficiency is X-linked recessive.[10–11] Thus males are generally affected and heterozygous female are carriers. However, at least five females with Lesch–Nyhan syndrome have been described, with different molecular alterations accounting for their HPRT deficiency.[12–16] 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 in most of the cases. HPRT activity is most often normal in haemolysate 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.[17] HPRT-deficient cells from carrier females can be selected based on their six-thioguanine resistances. Proliferation assay of peripheral blood T-lymphocytes in the presence of six-thioguanine is diagnostic in most cases.[18] 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 flankuing sequences, may be necessary. If a deletion has been found in the propositus, gene dosage may be accomplished by qPCR or MLPA. In those cases in which the patients HPRT coding region is normally associated with a decrease HPRT mRNA expression of unknown origin,[8–9,19] quantification of HPRT mRNA by real time PCR may be employed for carrier diagnosis.

Prenatal diagnosis for Lesch–Nyhan syndrome can be performed with amniotic cells obtained by amniocentesis at about 15–18 weeks' gestation, or chorionic villus cells obtained at about 10–12 weeks' gestation. Both HPRT enzymatic assay and molecular analysis for the known disease-causing mutation can be performed. Quantification of HPRT mRNA by real time PCR may be employed for prenatal

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diagnosis when a decrease HPRT mRNA expression is suspected as the cause of HPRT deficiency.[20]

1.7 Analytical validation
Mutation found in HPRT cDNA 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.[21]

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

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 B: False positives	C: False negative 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)
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)[8–9,19]

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 made 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 made case by case.

100%.

2.5 Positive clinical predictive value
(life time 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:
100%.

3. CLINICAL UTILITY

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

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)	☒ HPRT enzymatic activity

3.1.2 Describe the burden of alternative diagnostic methods to the patient
Enzymatic test for HPRT activity in haemolysate 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 www.lesch-nyhan.org and orpha.net for the list).

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

No	☐	
Yes	☒	
	Therapy (please describe)	No
	Prognosis (please describe)	Yes, partial HPRT-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.[21–28]
	Management (please describe)	No

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 done (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 done

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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