European Journal of Human Genetics (2011) 19; doi:10.1038/ejhg.2011.14

www.nature.com/ejhg

CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Gitelman syndrome

Nine VAM Knoers*,[1], Olivier Devuyst[2] and Erik-Jan Kamsteeg[3]

European Journal of Human Genetics (2011) **19,** doi:10.1038/ejhg.2011.14; published online 23 February 2011

1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)
Gitelman syndrome, Gitelman's syndrome, familial hypokalemia-hypomagnesemia.

1.2 OMIM# of the disease
263800.

1.3 Name of the analysed genes or DNA/chromosome segments
SLC12A3, *CLCNKB*.

1.4 OMIM# of the gene(s)
600968, 602023.

1.5 Mutational spectrum
There are more than 140 different mutations in *SLC12A3*.[1,2,4,8,9,11,14–16] These mutations include missense-, nonsense-, frame-shift-, and splice-site mutations. In addition, deletions of (part) the gene have been identified.

Only a few mutations in *CLCNKB* have been identified; patients with *CLCNKB* mutations have a highly variable phenotype, ranging from an antenatal onset of Bartter syndrome on one side of the spectrum, to a phenotype closely resembling Gitelman syndrome at the other side. Therefore, there is an indication to screen the *CLCNKB* gene in patients with the Gitelman phenotype who do not have mutations in the *SLC12A3* gene.

1.6 Analytical methods
Direct automated sequencing for mutations.

MLPA for deletions.

1.7 Analytical validation
Internal validation through analysis of known mutations in anonymized samples.

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)
1 in 40 000.

1.9 If applicable, prevalence in the ethnic group of investigated person
Not applicable.

1.10 Diagnostic setting

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

Comment: a prenatal test is technically feasible, but as yet has never been asked for because of the good prognosis in the majority of patients.

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)
For both genes nearly 100% for the coding regions and splice sites.

2.2 Analytical specificity (proportion of negative tests if the genotype is not present)
100% for both genes.

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.

80% for *SLC12A3*, but in 30% only one mutant *SLC12A3* allele is detected.

[1]Department of Medical Genetics, University Medical Centre Utrecht, Utrecht, The Netherlands; [2]Division of Nephrology, Université catholique de Louvain Medical School, Brussels, Belgium; [3]Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
*Correspondence: Professor N Knoers, Department of Medical Genetics, University Medical Centre Utrecht, P.O. Box 85090, 3508 AB Utrecht, The Netherlands.
Tel: +31 88 7553837; Fax: +31 88 7555301; E-mail: v.v.a.knoers@umcutrecht.nl

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%, but the symptoms may be very mild and the disease may only be detected during biological check-up, including measurement of serum Mg^{2+} and urinary Ca^{2+}.

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:
If both *SLC12A3* and *CLCNKB* are excluded in this non-affected person the negative predictive value is >90%.

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 made other than through a genetic test?

No	☐ (Continue with 3.1.4)	
Yes	☒	
	Clinically[3]	☒
	Imaging	☐
	Endoscopy	☐
	Biochemistry	☒
	Electrophysiology	☐
	Other (please describe):	☒ Blunted response to hydrochlorothiazide diuretics

3.1.2 Describe the burden of alternative diagnostic methods to the patient?
The tests are primarily blood and urine tests. So, the only burden is the drawing of a blood sample, which is also necessary for the genetic test.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
Genetic testing is at the moment more expensive than biochemistry, but this may change in future.

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

No.	☒	
Yes.	☐	
	Therapy (please describe)	*See management (review in [5,6,10,12,13])*
	Prognosis (please describe)	*(review in [5,6,10,12,13])*

(Continued)

	The long-term prognosis of Gitelman syndrome appears to be excellent, with the restriction that the molecular counterpart of the disease has only been identified in 1996 and that long-term clinical studies are lacking. The potential severity of Gitelman syndrome has been emphasized, with a significant reduction of the quality of life and fatigue able to hamper some patients in their daily activities. Manifestations such as early onset (before age 6 years), growth retardation, invalidating chondrocalcinosis, tetany, rhabdomyolysis, seizures and ventricular arrythmia have been described in a limited number of cases.[7] Progression to renal insufficiency is extremely rare in GS. As yet, only one patient who developed chronic renal insufficiency and subsequent progression to end-stage renal disease has been reported.
Management (please describe)	*Most asymptomatic patients with GS remain untreated and are monitored ambulatory (generally by nephrologists) with low frequency (1–2 times per year). At each visit complaints related to hypokalemia (fatigue, muscle weakness, constipation, cardiac arrhythmias) and hypomagnesemia (tetany, cramps, paraesthesias, joint and muscle pain) as well as serum levels of K^+, bicarbonate and Mg^{2+} should be evaluated. In view of the assumption that chondrocalcinosis is due to magnesium deficiency (magnesium is a co-factor of various pyrophospatases, including alkaline phosphatase), there is a clear argument for lifelong supplementation of magnesium. Magnesium is also important for the normalization of K^+ stores. Normalization of serum magnesium is difficult to achieve as high doses of magnesium cause diarrhea. The bio-availability of magnesium preparations is different. Magnesium-oxide and magnesium-sulfate have a significantly lower bio-availability compared with magnesium-chloride, magnesium-lactate and magnesium-aspartate. We recommend the administration of magnesium-chloride orally to compensate for renal Mg^{2+} and Cl^- losses. Initial daily dose is 3 mmol mg/m^2 per 24 h or 4–5 mg/kg per 24 h. This dose should be divided in 3–4 administrations to avoid diarrhea and has to be adjusted according to serum magnesium levels. The dose usually has to be increased during periods of undercurrent infections especially those accompanied by vomiting and diarrhea. In case of acute tetany, 20% $MgCl_2$ should be administered intravenously (0.1 mmol mg/kg per dose) and can be repeated every 6 h. Complaints related to chondrocalcinosis (mainly pseudogout attacks) are caused by the deposition of calcium pyrophosphate dehydrate crystals in synovium and the synovial fluid and can be reduced by Mg^{2+} supplementation. The symptoms can be controlled by NSAID and joint surgery is generally not required. If symptomatic hypokalemia is not corrected by $MgCl_2$ administration, it can be treated by drugs that antagonize the activity of aldosterone or block the sodium channel ENaC in the collecting duct. We prefer the combination of amiloride (5–10 mg/1.73 m^2 per day) with KCl (1–3 mmol/kg per day divided in 3–4 doses).[13] Amiloride should be started with caution to avoid hypotension. Growth and puberty delay in some patients with severe GS can be corrected by adequate Mg and K supplementation and a growth-promoting effect of indomethacin was also reported in GS patients. Cardiac work-up is recommended to screen for risk factors of cardiac arrhythmias. All patients with GS are encouraged to maintain high-sodium and high potassium diet. Patients with Gitelman syndrome often show a preference for salty aliments, as a compensatory mechanism for the renal salt-wasting.[10]*

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):
Not applicable.
If the test result is negative (please describe):
Not applicable.

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)?
Not applicable.

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

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?
Not applicable.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Not applicable.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Not applicable.

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

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnostic?
Not applicable. See also comment at 1.10.

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)

Yes, for the confirmation of the diagnosis and for genetic counselling.

ACKNOWLEDGEMENTS

OD and NK were supported by EUNEFRON, an FP7 project of the European Community (GA# 201590). This work was supported by EuroGentest, an EU-FP6 supported NoE, contract number 512148 (EuroGentest Unit 3: 'Clinical genetics, community genetics and public health', Workpackage 3.2).

1 Simon DB, Nelson-Williams C, Bia MJ *et al*: Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. *Nat Genet* 1996; **12**: 24–30.
2 Lemmink HH, Knoers NV, Károlyi L *et al*: Novel mutations in the thiazide-sensitive NaCl cotransporter gene in patients with Gitelman syndrome with predominant localization to the C-terminal domain. *Kidney Int* 1998; **54**: 720–730.
3 Ring T, Knoers N, Oh MS, Halperin ML: Reevaluation of the criteria for the clinical diagnosis of Gitelman syndrome. *Pediatr Nephrol* 2002; **17**: 612–616.
4 Reissinger A, Ludwig M, Utsch B *et al*: Novel NCCT gene mutations as a cause of Gitelman's syndrome and a systematic review of mutant and polymorphic NCCT alleles. *Kidney Blood Press Res* 2002; **25**: 354–362.
5 Knoers NVAM, Starremans PGJF, Monnens LAH: Hypokalaemic tubular disorders; in Daviesion AM, Cameron JS, Grunfeld J-P, Ponticelli C. Ritz E, Winearls CG, van Ypersele C (eds): *Oxford Textbook of Clinical Nephrology.* 3rd edn. Oxford: Oxford University Press, 2005, pp 955–1004.
6 Knoers NV: Gitelman syndrome. *Adv Chronic Kidney Dis* 2006; **13**: 148–154.
7 Riveira-Munoz E, Chang Q, Bindels RJ, Devuyst O: Gitelman syndrome: towards genotype-phenotype correlations? *Pediatr Nephrol* 2007; **22**: 326–332.
8 Bouwer ST, Coto E, Santos F, Angelicheva D, Chandler D, Kalaydjieva L: The Gitelman syndrome mutation, IVS9+1G>T, is common across Europe. *Kidney Int* 2007; **72**: 898.
9 Riveira-Munoz E, Chang Q, Godefroid N *et al*: Transcriptional and functional analyses of SLC12A3 mutations: New clues for the pathogenesis of Gitelman's syndrome. *J Am Soc Nephrol* 2007; **18**: 1271–1283.
10 Devuyst O: Salt wasting and blood pressure. *Nat Genet* 2008; **40**: 495–496.
11 Shao L, Liu L, Miao Z *et al*: A novel SLC12A3 splicing mutation skipping of two exons and preliminary screening for alternative splice variants in human kidney. *Am J Nephrol* 2008; **28**: 900–907.
12 Devuyst O, Konrad M, Jeunemaitre X: Tubular disorders of electrolyte regulation; in Avner ED, Harmon WE, Niaudet P, Yoshikawa N (eds): *Pediatric Nephrology.* 6th edn. New York: Springer, 2009, pp 929–978.
13 Knoers NV: Inherited forms of renal hypomagnesemia: an update. *Pediatr Nephrol* 2009; **24**: 697–705.
14 Nozu K, Iijima K, Nozu Y *et al*: A deep intronic mutation in the SLC12A3 gene leads to Gitelman syndrome. *Pediatr Res* 2009; **66**: 590–593.
15 Qin L, Shao L, Ren H *et al*: Identification of five novel variants in the thiazide-sensitive NaCl co-transporter gene in Chinese patients with Gitelman syndrome. *Nephrology (Carlton)* 2009; **14**: 52–58.
16 Hsu YJ, Yang SS, Chu NF, Sytwu HK, Cheng CJ, Lin SH: Heterozygous mutations of the sodium chloride cotransporter in Chinese children: prevalence and association with blood pressure. *Nephrol Dial Transplant* 2009; **24**: 1170–1175.