deutsche gesellschaft für humangenetik e.v.

Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

Indication criteria for disease:
Type I (classic) Lissencephaly

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2. Disease characteristics

2.1 Name of the Disease (Synonyms):
Type I Lissencephaly (classic lissencephaly)
Miller-Dieker syndrome (MDS)
Lissencephaly, X-linked (XLIS)
Double cortex syndrome (subcortical laminar heterotopia, SCLH, or subcortical band heterotypia, SBH)

2.2 OMIM# of the Disease:
607432 (Lissencephaly, Type I)
247200 (Miller-Dieker syndrome)
300067 (Lissencephaly, X-linked, SCLH)

2.3 Name of the Analysed Genes or DNA/Chromosome Segments:
PAFAH1B1 (Platelet-activating factor acetylhydrolase isoform 1B, alpha subunit) or LIS1, chromosome 17p13.3
DCX (Doublecortin), chromosome Xq22.3-q23
TUBA1A (alpha-1A-Tubulin / TUBA3), chromosome 12q12-q14

2.4 OMIM# of the Gene(s):
601545 PAFAH1B1 (LIS1)
300121 DCX
602529 TUBA1A

2.5 Mutational Spectrum:
Large deletions which include the PAFAH1B1 (LIS1) gene and neighbouring genes in region 17p13, in particular the 3' from LIS1 located 14-3-3-epsilon / YWHAE gene, lead to Miller-Dieker syndrome.
Smaller intragenic deletions, duplications as well as missense and nonsense mutations within the PAFAH1B1 (LIS1) gene cause type I lissencephaly in males and females.
Heterozygous missense mutations within the TUBA1A gene also cause type I lissencephaly in males and females.
Intragenic deletions, duplications, missense and nonsense mutations within the X-chromosomal DCX gene cause subcortical band heterotopia in heterozygous females and severe type I lissencephaly in hemizygous males.

2.6 Analytical Methods:
Large deletions which include the PAFAH1B1 (LIS1) gene and neighbouring genes of the 17p13 region can be detected with the following methods:
- Fluorescence in situ hybridisation (FISH) with a commercially available PAFAH1B1 (LIS1) specific probe or
- Multiplex ligation probe assay (MLPA) with Salsa P061 Lissencephaly test kit of MRC Holland. It contains: the amplicons of the YWHAE and HIC1 genes in the region 5' to LIS1; exons 1 and 5 to 11 of the LIS1 gene; and amplicons of the KIAA0664, GARNL4, and TRPV1 genes in the region 3' to LIS1.
In case of Miller-Dieker syndrome, beside FISH also karyotyping of the patient (in particular for diagnosis of a ring chromosome) is indicated. For the diagnosis of a possible unbalanced translocation, the parents are karyotyped, inclusive FISH with a PAFAH1B1 (LIS1) probe.
Intragenic deletions and duplications within the LIS1 and DCX genes can be detected with the MLPA kit mentioned above. It also contains exons 3 to 9 of DCX.
Smaller intragenic deletions, duplications and base pair substitutions are detected by sequencing the complete coding regions and the exon-intron junctions of the LIS1 (exons 2 to 11), DCX (exons 4 to 9), and TUBA1A (exons 1 to 4) genes.

2.7 Analytical Validation
- *Participation in FISH/deletion proficiency tests (e.g. BvDH)*
- *Parallel analysis of positive and negative control probes during molecular-genetic deletion screening*
- *yearly EQMN proficiency test for DNA sequencing*

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
There are no empirical prevalence data for lissencephaly in the German population. A prevalence of ca. 1:85.000 was determined by de Rijk-van Andel et al (1991) in the Netherlands.

2.9 If applicable, prevalence in the ethnic group of investigated person:
The lissencephaly appears to be equally prevalent in all populations worldwide.

2.10 Diagnostic Setting:

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

Comment: *A predictive diagnosis of type I lissencephaly is possible in female relatives of male patients with X-linked type I lissencephaly and of female patients with double cortex syndrome. Initially symptom-free females with a heterozygous DCX gene mutation have an increased risk to manifest an epilepsy as adults.*

3. Test characteristics

		genotype or disease	
		present	absent
test	pos.	A	B
	neg.	C	D

A: true positives C: false negatives
B: false positives D: true negatives

sensitivity:	A/(A+C)
specificity:	D/(D+B)
pos. predict. value:	A/(A+B)
neg. predict. value:	D/(C+D)

3.1 **Analytical Sensitivity**
(proportion of positive tests if the genotype is present)
For the diagnosis of a submicroscopic deletion 17p13.3 by FISH with a commercial PAFAH1B1 (LIS1) probe: 99% (as declared by Vysis).
For the diagnosis of intragenic LIS1 or DCX deletions by MLPA: not yet validated.
For the diagnosis of intragenic LIS1, DCX, or TUBA1A mutations by sequencing the complete coding region: almost 100%.

3.2 **Analytical Specificity**
(proportion of negative tests if the genotype is not present)
Almost 100% if rare and still undescribed polymorphisms are excluded by analysis of the parents and of controls.

3.3 **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.
The clinical diagnosis of type I lissencephaly can be made by cranial MRT. If a definite agyria-pachygyria spectrum (with appropriate anterior-posterior or posterior-anterior gradients of severity) and, in addition, either seizure susceptibility (abnormal EEG) or overt epilepsy is present, the clinical sensitivity is approx. 40-70%.

3.4 **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.
almost 100%.

3.5 **Positive clinical predictive value**
(life time risk to develop the disease if the test is positive).
For type I lissencephaly with LIS1 or TUBA1A gene mutations and for male patients with a DCX gene mutation: almost 100%.
For females with heterozygous DCX gene mutation: depending on X inactivation, approx. 80% are assumed.

3.6 **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:
almost 100%

Index case in that family had not been tested:
almost 100%

4. Clinical Utility

4.1 (Differential)diagnosis: The tested person ist clinically affected
(To be answered if in 2.10 "A" was marked)

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

No. ☐ (continue with 4.1.4)
Yes, ☒
clinically. ☐
imaging. ☒
endoscopy. ☐
biochemistry. ☐
electrophysiology. ☐
other (please describe)

4.1.2 Describe the burden of alternative diagnostic methods to the patient
A cranial MRT is essential for diagnosing a type I lissencephaly. In infants and small children this procedure must be performed in general anaesthesia.

4.1.3 How ist the cost effectiveness of alternative diagnostic methods to be judged?

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

No. ☐

Yes. ☒

Therapy (please describe)	*Prophylactic use of anticonvulsive drugs, physiotherapy.*
Prognosis (please describe)	*Life expectancy is reduced in children with type I lissencephaly.*
Management (please describe)	*The result of genetic diagnosis leads the way to optimized individual supportive measures.*

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

(To be answered if in 2.10 "B" was marked)

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

If the test result is positive (please describe)
Yes. Females with a DCX gene mutation have an increased risk of epilepsy.

If the test result is negative (please describe)
No.

4.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been done (please describe)?
No specific options, prevention not possible.

4.3 Genetic risk assessment in family members of a diseased person

(To be answered if in 2.10 "C" was marked)

4.3.1 Does the result of a genetic test resolve the genetic situation in that family?
Yes.

4.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes.

4.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
A DCX mutation in a boy with type I lissencephaly enables a predictive diagnosis of a double cortex syndrome / band heterotopia in his female relatives, particularly in his mother and sister(s).

4.4 Prenatal diagnosis

(To be answered if in 2.10 "D" was marked)

4.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnostic?
Yes.

5. 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)
A definite genetic diagnosis gives the disease and its cause a name. Identification of a genetic cause eliminates other causes (exogenous poisons, "incorrect conduct") from consideration which may be relieving.
Mutations for non-sexlinked lissencephalies are, as a rule, dominant de novo mutations. This explains the in most cases small recurrence risk.
If a Miller-Dieker syndrome is due to a familial translocation, the carriers with an increased risk for a child with MDS can be identified and a prenatal diagnosis can be offered to them.