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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: 16p13.11 microdeletion syndrome

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

16p13.11 microdeletion syndrome/Del(16)(p13.11)/16p13.11 monosomy syndrome.

1.2 OMIM# of the disease

Not applicable.

1.3 Name of the analysed genes or DNA/chromosome segments

16p13.11-p12.3: chr16:14.66–18.70 Mb, RefSeq NC_000016.9 (hg19 human reference sequence, February 2009, build 37).

1.4 OMIM# of the gene(s)

Putative candidate genes: *NDE1*, 609449; *NTAN1*, not applicable.

Other genes in the critical deleted region (chr16: 15.48–16.32 Mb, GRCh37/hg19): *MPV17L*, not applicable; *C16orf45*, not applicable; *KIAA0430*, 614593; *MYH11*, 160745; *FOPNL*, not applicable; *ABCC1*, 158343; *ABCC6*, 603234.

Review of the analytical and clinical validity as well as of the clinical utility of DNA-based testing for microdeletions at the 16p13.11 locus in diagnostic and prenatal settings and for risk assessment in relatives.

1.5 Mutational spectrum

The syndrome is caused by microdeletions in the 16p13.11-p12.3 genomic region. The 16p13.11 locus is a genomic hotspot particularly rich in low-copy repeats (LCRs), highly homologous DNA sequences that increase the likelihood of copy number mutations through non-allelic homologous recombination.[1] The 16p13.11 region can be subdivided into three single-copy sequence intervals called interval I, II and III, each flanked by LCRs.[2] Typical 16p13.11 microdeletions have very variable size (from 0.8 to 3.3 Mb), and encompass one or more of the three intervals.[2–12]

Interval II (chr16:15.48–16.32 Mb, GRCh37/hg19) represents the critical region of the genomic variation, being contained in the great majority of the 16p13.11 microdeletions identified so far.[2–12] It encompasses a core set of eight protein-coding genes, including *NDE1*, the strongest candidate gene for the neurodevelopmental phenotypes associated with the 16p13.11 microdeletions. *NDE1* encodes the nuclear distribution protein nudE homolog 1, a centrosomal protein that has a crucial role in the process of mammalian encephalisation and human cerebral cortex growth.[13] Loss of *NDE1* in mice causes profound defects in cerebral corticogenesis and neuronal proliferation and migration, and mutations in *NDE1* have been associated with extreme microlissencephaly in humans.[14,15] *NTAN1* represents another important candidate gene at the 16p13.11 locus, although not included in the critical deleted region. It is located in interval I and encodes the asparagine-specific N-terminal amidase, an enzyme involved in the regulation of the *in vivo* half life of proteins. Inactivation of the *NTAN1* gene in mice has been associated with abnormal neurological features such as altered social behaviour and impaired spatial and non-spatial learning and memory.[16,17] Sequencing of the *NDE1* gene and of the entire 16p13.11 homologous region of the intact chromosome in mentally retarded and epileptic patients carrying the heterozygous microdeletion, did not unmask any relevant recessive-acting mutation, which suggests that haploinsufficiency of one or more dosage-balanced genes included in the region represents one of the principal mechanisms responsible for the pathogenicity of the microdeletion.[4,8]

Mutations published in the literature and mutations submitted without publication are available in a number of resources, including the BBGRE, DECIPHER and ISCA databases,[12,18,19] each holding genomic and associated phenotypic data from ~5000, ~26 000 and ~32 000 phenotypically abnormal individuals, or the CHOP CNV and DGV databases,[20,21] holding CNV data derived from ~2000 and ~12 000 healthy individuals, respectively. By facilitating interactions between researchers, these international resources provide important tools for genetic research and medical care, aiding the understanding of genotype/phenotype correlations and the identification of the disease-causing genes, with consequent improvements in diagnosis, management and therapy for affected individuals.

1.6 Analytical methods

FISH, MLPA, array CGH, real-time quantitative PCR (RT-qPCR), SNP-arrays, sequencing. Conventional cytogenetics is usually normal except for rare cases of mosaicism, which are difficult to detect by qPCR studies, but can be identified by array CGH, SNP-arrays or FISH studies.

1.7 Analytical validation

MLPA, array CGH, FISH and/or RT-qPCR, depending on the analytical method used.

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

Prevalence at birth is about 1:14 000 if we only consider carriers affected with a disease, but it is much higher if we consider all the mutation carriers, approximately 1:2300 individuals in the general population.[2,4,6,12]

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:
Given the highly variable phenotypic manifestations, genetic testing is necessary to make a reliable diagnosis. Analysis of the inheritance pattern of the variations within families is essential to determine the potential need for genetic testing in other relatives, and for assessing the possibility of prenatal diagnosis.

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)
Nearly 100% using analytical methods described above.

2.2 Analytical specificity
(Proportion of negative tests if the genotype is not present)
Nearly 100% using analytical methods described above.

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.

Variable. The 16p13.11 microdeletions are pleiotropic genomic variants with broad phenotypic manifestations, including neurodevelopmental phenotypes such as autism, mental retardation, epilepsy and learning difficulties and non-CNS phenotypes such as physical dysmorphisms and congenital anomalies.[2–12] This variable phenotypic expressivity represents a challenge for clinical diagnosis because similar clinical features have been associated with a number of other genomic variations (eg, del1q21.1 or del15q11.2), and a characteristic common phenotype for the 16p13.11 microdeletion carriers has not yet been identified. Furthermore, clinical diagnosis can also be hampered by the presence of 'second-hits', additional pathogenic variations in other genomic regions that act in concert with the 16p13.11 microdeletions, and are able to exacerbate or mask some of their phenotypic symptoms. Given these clinical diagnostic limitations, at present, genetic testing is necessary in order to make a secure diagnosis of this syndrome.

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.

Variable. The microdeletion generally shows incomplete penetrance, with some of the carriers being completely unaffected, also within high-risk families.[4,6,7,12]

2.5 Positive clinical predictive value
(Lifetime risk to develop the disease if the test is positive)
Variable, because of incomplete penetrance of the genomic variation, but higher in males.[12]

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:
Practically 100%.

Index case in that family had not been tested:
Nearly 100%. Because of the increased risk based on family history, it is advisable to test also an individual not showing clinical symptoms, however, given the incomplete penetrance of the microdeletion, also a carrier subject within an high-risk family can be completely unaffected.

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)	

3.1.2 Describe the burden of alternative diagnostic methods to the patient
Not applicable.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
Not applicable.

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

No ☐

Yes ☒

Therapy (please describe)	Depends on clinical manifestations and symptoms severity, most commonly: psychotherapy and medications for the treatment of autistic traits, psychotic symptoms, anxiety, obsessive compulsive disorder and other behavioural problems such as aggression and self-mutilation; medications for the treatment of seizures; speech therapy and special educational programmes for children with speech and language delay and learning difficulties; nasogastric tube for feeding difficulties; physical therapy and special equipment for motor delay; surgery to correct heart defects, cleft lip/palate and other congenital anomalies; additional clinical features, such as cataracts, gastro-oesophageal reflux or hearing loss are treatable with standard methods.
Prognosis (please describe)	Moderate. Therapies are generally helpful and improve quality of life of affected individuals, although patients with seizures resistant to medications have been reported in the literature.[4,8]
Management (please describe)	A positive genetic test orients towards targeted screening and intervention, and provides awareness about potential challenges in treatment. Targeted screening includes: brain imaging studies for the detection of anomalies in brain structure; screening for physical dismorphisms and congenital anomalies (eg, cleft lip/palate, heart and kidney defects, genital defects); detection of behavioural problems, speech delay and learning difficulties; screening for hypotonia, feeding difficulties and delayed motor skills; detection of hearing loss and eye problems. Family support through patient organisations is generally available.

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)?
No special options; prevention is not possible.

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?
Yes. Genetic tests allow the establishment of whether a microdeletion occurred *de novo* or has been inherited from a parent, and therefore suggest if genetic testing is needed also for other family members. However, in rare cases of parental mosaicism, it may be more difficult to detect carrier status in a parent.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes. If the microdeletion has not been inherited from a parent and there is no evidence of parental mosaicism, there is no obligation for other family members to undergo genetic testing, and parents are aware that the likelihood of having another child with the same syndrome is almost certainly not higher than that observed in the general population.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Yes. If the microdeletion is detected in a parent of the index patient, prenatal diagnosis is possible for future pregnancies.

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 diagnosis?
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).

A characteristic common phenotype for the 16p13.11 microdeletion carriers has not yet been identified, consequently, genetic testing is necessary to make a reliable diagnosis of this syndrome. A positive genetic test provides specific information about the possible clinical manifestations and orients clinicians towards targeted screening and intervention. Analysis of the inheritance pattern of the genomic variation has direct consequences for the genetic counselling of relatives and provides indications about the clinical utility of prenatal testing. Although there is no specific cure for this syndrome, detailed analysis of the genomic variations detected by genetic testing may help to identify the specific disease-causing genes in the pathogenic region and to clarify the yet poorly understood disease pathophysiology, thus providing critical means for the design of new treatments.

CONFLICT OF INTEREST

David A Collier is a full-time employee of Eli Lilly & Co. Ltd and a Visiting Professor at King's College London. Maria Tropeano and Joris Andrieux declare no conflict of interest.

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