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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: 15q13.3 microdeletion syndrome

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

15q13.3 microdeletion syndrome/Del(15)(q13.3)/15q13.3 monosomy syndrome.

1.2 OMIM# of the disease

612001.

1.3 Name of the analysed genes or DNA/chromosome segments

15q13.2q13.3, RefSeq NC_000015.9 (hg19 human reference sequence, February 2009, build 37).

1.4 OMIM# of the gene(s)

Putative candidate genes: *CHRNA7*, 118511; *KLF13*, 605328; *TRPM1*, 603576; *FAN1*, 613534.

Other genes in the critical deleted region (BP4-BP5): *MTMR10*, not applicable; *MIR211*, 613753; *OTUD7A*, 612024.

1.5 Mutational spectrum

The syndrome is caused by microdeletions in the 15q13.2q13.3 region. The proximal portion of chromosome 15q is an highly unstable genomic region very rich in segmentally duplicated sequences that give rise to several genomic rearrangements, whose breakpoints (BPs) cluster within the duplicated sequences.[1] Typical 15q13.3 heterozygous microdeletions are approximately 1.5–2 Mb in size (*chr15.hg19:g.(?_31,073,600)_(32,445,407_?)del*) and are mediated by non-allelic homologous recombination (NAHR) between segmental duplication BPs BP4 and BP5, telomeric to the Prader–Willi/Angelman syndrome critical region (15q11q13).[2–14] The 15q13.3 BP4-BP5 locus is a site of inversion polymorphisms, and the 15q13.3 microdeletions seem to arise preferentially from chromosomes carrying an inversion in the BP4-BP5 region, which, by placing the duplicons in direct orientation, creates a configuration predisposing to NAHR.[2,15] A small number of atypical larger 15q13.3 microdeletions (∼3.4–3.8 Mb in size), mediated by NAHR between segmental duplication BPs BP3 and BP5, have also been reported in the literature; clinical features in these carrier subjects, however, are generally similar and not more severe than those observed in individuals harbouring typical BP4-BP5 microdeletions.[2,7–9]

The ∼1.5 Mb of unique sequence between the two segmental duplication blocks at BP4 and BP5 represents the critical region of the 15q13.3 genomic variations, being contained in all the microdeletions identified so far.[2–14] It encompasses a core set of seven genes (six protein-coding genes and one miRNA gene), including *FAN1*, a newly identified candidate gene for the neuropsychiatric phenotypes associated with the 15q13.3 microdeletions. *FAN1*, *Fanconi-associated nuclease 1,* encodes a DNA repair nuclease operating within the Fanconi anaemia pathway, specifically involved in the repair of highly cytotoxic DNA interstrand cross-links, which prevent strand separation and blocks replication during mitosis.[16] A cluster of rare nonsynonymous single-nucleotide variants located within a 20-kb window that spans several key functional domains of *FAN1* have recently been associated with schizophrenia (SCZ) and autism (ASD) in two independent data sets, suggesting a possible implication of abnormalities in DNA repair in the neurodevelopmental phenotypes associated with the 15q13.3 microdeletions.[17]

The *KLF13* gene, also contained in the ∼1.5 Mb BP4-BP5 critical region, represents the most important candidate for the cardiac abnormalities observed in some 15q13.3 microdeletion carriers.[9,11] It encodes the Kruppel-Like transcription Factor 13, a member of the Kruppel-like family of zinc-finger proteins, and is highly expressed in the early forming heart. The klf13 protein is part of an early regulatory network critical for cardiac gene transcription and heart development, and knockdown of klf13 levels in Xenopus embryos has been associated with a severe cardiac phenotype, including lack of ventricular trabeculation, atrial septal defects, delayed atrioventricular cushion formation and maturation of valves.[18]

Finally, *CHRNA7* represents the strongest candidate gene for the neurodevelopmental phenotypes associated with the 15q13.3 microdeletions. It is located in the 15q13.3 critical region, and encodes the α7 subunit of the neuronal nicotinic acetylcholine receptor, a synaptic ion channel protein mediating neuronal signal transmission, widely expressed in the brain; both human and mouse model studies have provided evidences for association of the *CHRNA7* gene with epilepsy and abnormal EEG, as well as with SCZ and its endophenotypes, and bipolar disorder.[19–25] A number of patients harbouring smaller microdeletions of an approximately 400–700 kb in size, which usually only include the *CHRNA7* gene, have recently been reported in the literature; these

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atypical smaller rearrangements map to the distal region of the larger ~1.5 Mb microdeletion and are mediated by NAHR between the *CHRNA7*-LCR and BP5.[4,11,26–28] The range of clinical symptoms in the probands harbouring these smaller microdeletions is usually very similar to that observed in the subjects with the classical ~1.5 Mb rearrangements, which suggests that the *CHRNA7* gene may be responsible for the majority of the abnormal phenotypes associated with the 15q13.3 microdeletion syndrome. Sequencing of the coding regions of the *CHRNA7* gene on the intact chromosome, in eight patients carrying a heterozygous ~1.5 Mb microdeletion and in one patient harbouring a heterozygous ~500 kb microdeletion of only *CHRNA7*, did not unmask any relevant recessive-acting mutation, which suggests that haploinsufficiency of the gene may represent the principal mechanism underlying pathogenicity.[11]

Recently, eight severely affected patients harbouring a homozygous BP4-BP5 microdeletion ($n=5$) or a homozygous ~500 kb microdeletion of *CHRNA7* ($n=3$) have also been described.[29–32] Interestingly, although the clinical phenotypes observed in the homozygous carriers are more severe but overall consistent with those of the patients harbouring the heterozygous microdeletions, all the five patients with homozygous BP4-BP5 microdeletions identified so far also present with a severe visual impairment phenotype, characterized by optic nerve atrophy or retinal dystrophy, never observed in individuals with 15q13.3 heterozygous microdeletions.[11,29–31] The *TRPM1* gene represents the most interesting candidate at 15q13.3 for the severe visual abnormalities observed in the homozygous BP4-BP5 microdeletion carriers. It encodes the transient receptor potential cation channel M1, a calcium permeable cation channel that mediates synaptic transmission from photoreceptors to ON bipolar cells, promoting a change in the membrane potential that results in the light-evoked response of the ON bipolar cells.[33] Mutations in the *TRPM1* gene have been identified as an important cause of autosomal-recessive complete congenital stationary night blindness in humans.[34]

Importantly, Fejgin *et al* have recently generated the first mouse model of the human 15q13.3 microdeletion syndrome (*Df[h15q13]*/+) by hemizigous deletion of the orthologous genomic region on mouse chromosome 7. *Df(h15q13)*/+ mice show similarities to several alterations related to the 15q13.3 microdeletion syndrome, including increased aggression and body weight, and a complex but pronounced seizure phenotype, with both sensitization (preictal events, absence-like seizures) and protection (clonic, tonic seizures) components. Notably, although several psychiatric phenotypes are difficult to evaluate in animal models, *Df(h15q13)*/+ mice also display a number of features relevant to SCZ, such as SCZ-related auditory processing deficits and impaired long-term spatial reference memory, which underscores the important translational potential of this novel tool for the understanding of the human phenotypes associated with the 15q13.3 microdeletion syndrome.[35]

The 15q13.3 microdeletions published in the literature and those submitted without publication are available in a number of resources, including the DECIPHER, BBGRE and ISCA databases,[36–38] each holding genomic and associated phenotypic data from ~26 000, ~5000 and ~32 000 phenotypically abnormal individuals, or the CHOP CNV and DGV databases,[39,40] 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

The increased use of array-CGH and SNP-arrays for genetic diagnosis has led to the identification of new microdeletion/microduplication syndromes and enabled genotype–phenotype correlations to be made. 15q13.3 microdeletions are mainly detected by whole-genome array-CGH and SNP-arrays. Real-time quantitative PCR (RT-qPCR), FISH, MLPA are generally used for validation or family studies. Conventional cytogenetics is normal except for rare cases of mosaicism (estimated 1%), which are difficult to detect by qPCR studies or array-CGH, but can be identified by SNP-arrays or FISH studies.

1.7 Analytical validation

FISH, RT-qPCR, array-CGH, MLPA are performed, depending on the analytical method used in the genetic laboratory.

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

Prevalence at birth is approximately 3:10 000 individuals in the general population.[41]

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: Prenatal diagnosis is technically possible for affected families with parents carrying the pathogenic variation, however, given the variable expressivity and incomplete penetrance of the microdeletion, phenotypic outcomes cannot be reliably predicted. Preimplantation genetic diagnosis may also be an option for these families, in accordance with the regulation and facilities in each specific country.

2. TEST CHARACTERISTICS

	Genotype or disease		A: True positives	C: False negative
			B: False positives	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 15q13.3 microdeletions are associated with considerable intra- and inter-familial phenotypic variability and a straightforward clinically recognizable phenotype has not yet been identified for these patients, consequently, genetic testing is necessary to make a reliable diagnosis of this syndrome. The variable phenotypic expressivity may be in part dependent on a number of additional factors, including differences in genetic background, epigenetic phenomena or environmental factors, which hamper clinical diagnosis in that the majority of them are still unknown and therefore cannot be tested, or because their effects cannot be reliable predicted. The most common clinical features observed among 15q13.3 microdeletion carriers include: developmental delay, impaired language skills, mild to moderate intellectual disability, seizures and/or abnormal EEG results, SCZ, ASD and other neurobehavioural problems, such as poor attention span, hyperactivity and impulsive/aggressive behaviour, non-CNS phenotypes, such as mild facial/digital dysmorphisms, short stature and hypotonia.

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 15q13.3 microdeletions are characterized by incomplete penetrance, with some of the carriers being apparently healthy, also within high-risk pedigrees.[6–11,29,31]

2.5 Positive clinical predictive value
(**life-time risk to develop the disease if the test is positive**).
The life-time risk of developing a pathological phenotype is highly variable because of incomplete penetrance of the genomic variation, although clinical symptoms have been more commonly observed in males than in females.[6,8,11] In order to provide an estimation of the disease risk associated with the 15q13.3 microdeletions, we calculated the overall penetrance of the genomic variation for the neurodevelopmental phenotypes most commonly observed among carriers, including developmental delay (DD), ASD, epilepsy and SCZ. Penetrance calculations provided a total median penetrance value of 44%, with ∼95% credible intervals of 29–63%, which suggests that 15q13.3 microdeletion carriers have an overall risk of developing a neurodevelopmental disorder of ∼44%. Estimation of penetrance was performed with the Bayesian method described by Vassos *et al*[42] using a median CNV frequency of 0.31% for cases affected with DD, ASD, epilepsy and SCZ,[3,4,7,9,10,12–14] and a CNV frequency of 0.014% for controls.[3,4,7,10,14] Life-time morbid risk for the four disorders was approximated at 3.7%, and calculated as follows:

$$P(D) = P(DD) + (P(ASD) - P(ASD/DD)) + (P(Epil) - P(Epil/DD) - P(Epil/ASD)) + (P(SCZ) - P(SCZ/DD) - P(SCZ/ASD) - P(SCZ/Epil))$$

assuming population frequencies of 2% for DD,[43] 1% for ASD,[44,45] 0.85% for epilepsy (http://www.parliament.uk/briefing-papers/sn05691.pdf),[46] and 0.72% for SCZ,[42,47] and correcting for co-morbidity rates of 10% for ASD/DD,[48] 22% for epilepsy/DD,[48] 8% for epilepsy/ASD,[49] 4.4% for SCZ/DD,[50,51] 2.4% for SCZ/ASD[52] and 2.4% for SCZ/epilepsy.[53]

Importantly, Kirov *et al* recently reported an overall penetrance estimation of 40% (95% CI = 21–72%) for 15q13.3 microdeletions in SCZ and early-onset developmental disorders, which is very close to our estimate of 44% (95% CI = 29–63%) for neurodevelopmental disorders, although the authors did not specifically include the epilepsy phenotype in their calculations, and accounted instead for various congenital malformations.[41]

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)	Differs according to clinical manifestations and symptoms severity, most commonly: learning support, special educational programmes and speech therapy for patients affected by learning disability and speech–language delay; psychotherapy and medications for the treatment of schizophrenia, autism spectrum disorder, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, anxiety and other behavioural problems, such

	as aggressive behaviour and rage, impulsive behaviour and self-injurious behaviour; medications for the treatment of seizures; physiotherapy and exercises for delay in mobility/hypotonia; nasogastric tube for feeding difficulties; surgical procedures to correct cardiac defects, genital abnormalities and other congenital anomalies; additional medical issues, such as hearing loss, strabismus, foot problems or dental problems should be addressed by standard methods.
Prognosis (please describe)	Moderate. Early intervention programmes generally improve outcomes, especially for patients affected by intellectual disability, speech and language delay, behavioural problems and delay in mobility/hypotonia. Some cases of seizures resistant to treatment have been reported in the literature.[2,11,29–31]
Management (please describe)	Molecular confirmation of the syndrome orients clinicians towards targeted screening and intervention, and provides awareness about potential challenges in treatment. Targeted screening includes: Neuropsychological assessment to identify developmental and learning disabilities, and/or behavioural problems; brain imaging studies for the detection of abnormalities in brain structure; EEG for suspected epilepsy; general clinical examination to identify delay in mobility/hypotonia, feeding difficulties, physical dysmorphisms, hearing, vision and/or dental problems; cardiac ultrasound to screen for congenital heart defects. Social support through patient organizations 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. Establishing whether the microdeletion occurred *de novo* or secondarily to a chromosomal rearrangement in one of the parents suggests if genetic testing is needed also for other family members. The possibility of parental mosaicism should also be considered when evaluating carrier status in the parents.

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

Yes. If the microdeletion is not inherited and there is no evidence of parental mosaicism, there is no obligation for other family members to undergo genetic testing, and risk to siblings is almost certainly not higher than that of 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. Prenatal diagnosis is technically possible when the microdeletion is detected in a parent of the index patient, although, given the incomplete penetrance and highly variable expressivity, it is not possible to reliably predict the phenotypic outcome.

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 straightforward clinically recognizable phenotype has not yet been identified for the 15q13.3 microdeletion carriers, consequently, genetic testing is necessary to make a reliable diagnosis of this syndrome. Although there is no specific cure, a molecular confirmation of the syndrome is likely to lead to a better prognosis, in that it provides specific information about the possible clinical manifestations and orients clinicians towards targeted screening and intervention. A positive genetic test may save the patient from undergoing additional diagnostic procedures and alleviates psychological stress due to uncertain diagnosis. Finally, analysis of the inheritance pattern of the genomic variation within families enables accurate genetic counselling of relatives and allows carrier parents of the index case to make informed reproductive decisions.

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. The remaining authors declare no conflict of interest.

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