European Journal of Human Genetics (2010) 19; doi:10.1038/ejhg.2010.124

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CLINICAL UTILITY GENE CARD

Rubinstein–Taybi syndrome (CREBBP, EP300)

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European Journal of Human Genetics (2010) **19,** doi:10.1038/ejhg.2010.124; published online 28 July 2010

1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)
Rubinstein–Taybi syndrome (RSTS, Broad thumb–hallux syndrome).[1]

1.2 OMIM# of the disease
180849.

1.3 Name of the analyzed genes or DNA/chromosome segments
CREBBP, EP300 (E1A binding protein p300).

1.4 OMIM# of the genes
600140 (CREBBP), 602700 (EP300).

1.5 Mutational spectrum
Mainly frameshift, nonsense, splice site and missense mutations. Less frequently large deletions (one or more exons) and rarely balanced inversions and translocations. Mutations are heterozygous, and mosaic mutations have been described. At present, more than 100 pathogenic mutations are known for the two genes together, but mutations in EP300 are much less common (only 11 so far).[2–9] Mutations may remove the 5′ or the 3′end of CREBBP and adjacent genomic segments, which causes the 16p13.3 contiguous gene deletion syndrome.[10–12]

For both genes a mutation database is available that also includes unpublished mutations:

CREBBP: http://chromium.liacs.nl/LOVD2/home.php?select_db=CREBBP

EP300: http://chromium.liacs.nl/LOVD2/home.php?select_db=EP300

1.6 Analytical methods
Genomic sequencing of the coding regions, MLPA and quantitative multiplex fluorescent-PCR for all coding exons for the detection of large deletions and duplications. Microarray-based chromosome analysis or fluorescence *in situ* hybridization for the sizing of large deletions removing the first or last coding exon.[11,12] Conventional cytogenetics is usually normal except for rare cases resulting from balanced translocations.

1.7 Analytical validation
Direct sequencing of both DNA strands; verification of sequence and MLPA results on a second DNA extraction or second PCR or hybridization (MLPA).

1.8 Estimated frequency of the disease
Birth prevalence is 1:100 000–1:125 000.[13]

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	☒	☐

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	Pos. predict. value:	A/(A+B)
			Neg. predict. value:	D/(C+D)

2.1 Analytical sensitivity
(proportion of negative tests if the genotype is not present)
Nearly 100%, if the entire coding regions are sequenced and MLPA for all coding exons is performed. Mosaic mutations can be difficult to detect. Balanced translocations can only be detected by karyotyping.

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

2.3 Clinical sensitivity
(proportion of positive tests if the disease is present)
The clinical sensitivity is ~30–70%, depending on variable factors, such as clinical characteristics and age at diagnosis.

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2.4 Clinical specificity
(proportion of negative tests if the disease is not present)
Depends on the quality of clinical assessment due to variable expression of the disease. As most apparently healthy carriers show at least minimal manifestations of the disease on careful examination, the clinical specificity is nearly 100%. In familial cases, mosaicism can be found in 'healthy' truly asymptomatic persons.

2.5 Positive clinical predictive value
(life-time risk to develop the disease if the test is positive)
100% penetrance with variable clinical expression.

2.6 Negative clinical predictive value
(probability not to develop the disease if the test is negative)
Index case in case that family had been tested:
Practically 100%.
Index case in case that family had not been tested:
Not relevant, RSTS is a congenital disorder. In addition, almost all patients occur from *de novo* mutations, therefore, the recurrence risk is low (<1%).[13]

3. CLINICAL UTILITY

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

No	☐
Yes	☒
Clinically	☒
Imaging	☐
Endoscopy	☐
Biochemistry	☐
Electrophysiology	☐
Other (please describe)	☐

3.1.2 Describe the burden of alternative diagnostic methods to the patient
The burden of clinical assessment is usually low. However, a clinical diagnosis cannot be made in all cases, but only in typical cases, and can be difficult at a very young age. The burden for the family of uncertainty about the diagnosis for a prolonged period of time is high.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
In patients with the typical phenotype the cost effectiveness is high, but it decreases significantly with increasing uncertainty of the diagnosis. An early genetically proven diagnosis may avoid later alternative and expensive diagnostics and/or management strategies. Lack of a molecularly confirmed diagnosis also means that parents do not have the option for prenatal studies in future pregnancies.

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

No	☐
Yes	☒

Therapy: Depends on clinical manifestations: tube feeding, speech therapy, cardiac surgery, correction of glaucoma, orthopedic surgery for thumbs, hips and spine and antibiotic prophylaxis for airway infections.
Prognosis: Good for life expectancy, moderate for developmental abilities. A small subset of patients may have life-threatening malformations, which may be more frequent in those with the chromosome 16p13.3 contiguous gene deletion syndrome.[11]
Management: Highly dependent on age and phenotype: screening for cardiac and renal defects, immunologic check-up, prevention of infections,detection of diminished vision and hearing loss. Cancer surveillance. Management of behavioral problems. Social support through patient organizations.

3.2.1 Will the result of a genetic test influence lifestyle and prevention?
If the test result is positive
Not applicable.
If the test result is negative
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.

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?
Yes, if the parents are tested too.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes, if the parents are also negative no further testing in clinically unaffected relatives is needed.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Only minimally affected relatives can be diagnosed by the test and may then profit from preventive measures (see 3.1.4). Furthermore prenatal diagnosis is possible for further pregnancies.

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?

Parents can be given accurate information about the cause of the disorder and recurrence risk.

Support for family by support organization.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

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).

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