Diagnosis and Management in Rubinstein-Taybi Syndrome: First International Consensus Statement

Didier Lacombe, Agnes Bloch-Zupan, Cecilie Bredrup, Edward B. Cooper, Sofia Douzgou, Sixto Garcia Minaur, Hulya Kayserili, Lidia Larizza, Vanesa López-González, Leonie A. Menke, Donatella Milani, Francesco Saettini, Cathy A. Stevens, Lloyd Tooke, Jill A Van der Zee, Maria M. Van Genderen, Julien Van Gils, Jane Waite, Jean-Louis Adrien, Oliver Bartsch, Pierre Bitoun, Antonia H.M. Bouts, Anna M. Cueto-González, Elena Dominguez-Garrido, Floor Duijkers, Patricia Fergelot, Elizabeth Halstead, Sylvia A. Huisman, Camilla Meossi, Jo Mullins, Sarah M. Nikkel, Chris Oliver, Elisabetta Prada, Alessandra Rei, Ilka Riddle, Cristina Rodriguez-Fonseca, Rebecca Rodriguez Pena, Janet Russell, Alicia Saba, Fernando Santos-Simarro, Brittany N. Simpson, David F Smith, Markus F. Stevens, Katalin Szakszon, Emmanuelle Taupiac, Nadia Totaro, Irene Valenzuela Palafoll, Daniëlle C.M. Van Der Kaay, Michiel P. Van Wijk, Klea Vyshka, Susan Wiley, and Raoul C. Hennekam

Supplementary Materials

METHODS

The RTS consensus group comprised of 52 participants from 41 institutions in 11 countries. The group consisted of clinicians, scientists and 6 patient group representatives. The clinicians practiced in North America and Europe. A modified Delphi consensus process was adopted. Discussions took place via video conference calls, e-mail communications and file exchanges. All known support groups were contacted by email to identify key issues that should be addressed during the consensus process. Subsequently, issues to be addressed were determined by the consensus group in a video conference call. A plenary face-to-face two-day meeting of 27 participants (including 4 patient group representatives) was held in September 2022 in Bergen, Norway. Consensus recommendations were voted on by 46 participants (See Text Box S1). This consensus statement summarises the outcome of the discussions, and details the consensus on clinical and molecular aspects, care and management.

Text Box 1: Details of Consensus Voting Process

Each recommendation was voted for (patient group representatives did not vote) and was scored as:

A Evidence or general agreement indicate full agreement with the recommendation:	+++	≥70% of votes
B Evidence or general agreement favour the recommendation	++	50-69% of votes
C Evidence or general agreement are weak for the recommendation	+	26-49% of votes
D Insufficient evidence or general agreement for the recommendation	-	<26% of votes

Voting was performed digitally by .. co-authors of the guidelines. For all recommendations ..%

was in full agreement with the recommendations

Testing Clinical Diagnostic Criteria

After having defined the clinical diagnostic criteria we evaluated whether the set of diagnostic features reliably allowed recognition of a group of 100 individuals with molecularly confirmed RTS that were not part of the group of patients on which the criteria were build (Table S1). All individuals scored 5 or higher, indicating none would have been missed as having RTS based on clinical criteria (complete sensitivity) (Table S2). Only a single patient scored in the group Possibly RTS, all others scored in the group Likely RTS (n= 42) or Definitively RTS (n=52).

Subsequently, we evaluated whether 45 individuals with a specific group of pathological *CREBBP* or *EP300* variants, who have been considered to have a separate entity (Menke-Hennekam syndrome [MIM #618332 / #618333]) would be correctly distinguished from RTS (Table S2). Results showed that none scored as definitive or likely RTS, 9 as possibly RTS, and 36 as unlikely RTS, so the patients were correctly scored indeed.

Furthermore, we investigated the specificity by evaluating the clinical diagnostic scores in three entities that may resemble RTS and are not uncommon, i.e. Floating-Harbor syndrome (FHS; MIM #136140) (n=45), Wiedemann-Steiner syndrome (WDSTS; MIM #605130)(n=46), and Cornelia de Lange syndrome (CDLS; MIM #122470)(n=100) (Table S2). Results showed that none of the individuals with FHS and CDLS fulfilled the criteria for a definitive diagnosis of RTS, but one of the WDSTS patients had such a score. In addition one of the WDSTS patients had a score within the Likely RTS group but was found by the present authors to have a classical RTS facial Gestalt. Further studies to explain this unusual phenotype are planned. Furthermore, 8 of the 46 WDSTS individuals, and 1 of the 100 CDLS individuals fulfilled the criteria for Likely RTS, indicating that specificity was very high, but not complete.

Table S1. Comparison of the clinical diagnostic criteria in individuals with molecularly confirmed Rubinstein-Taybi syndrome (RTS) to (molecularly confirmed) Floating-Harbor syndrome (FHS), Cornelia de Lange syndrome (CdLS), Wiedemann-Steiner syndrome (WDSTS), and Menke-Hennekam syndrome (MKHKS)[a]

	RTS[1]		**FHS** [5-10]	**CdLS** [2-4]	**WDSTS** [11-12]	**MKHKS** [13-14]
	CREBBP	***EP300***	***SRCAP***	***NIPBL, SMC1A, RAD21***	***KMT2A***	***CREBBP, EP300***
	(n=308)	*(n=52)*	*(n=64)*	*(n=100)*	*(n=104)*	*(n=24)*
Cardinal features						
Angulated thumbs	49	2	0	0	0	0
Broad thumbs	96	69	22[e]	0	22	0
Broad halluces	95	81	22[e]	0	22	13
Highly arched eyebrows	85	65	0[e]	78	20[e]	9
Downslanted palpebral fissures	79	56	0[e]	1	50	13
Convex nasal ridge	81	44	15[e]	0	5[e]	9
Columella below alae nasi	88	92	95[e]	1	15[e]	9
Highly arched palate	77	67	0[e]	25	30[e]	38
Grimacing smile	47	94	0[e]	0	5[5]	0
Microcephaly	54	87	22	77	35[d]	45[e]
Postnatal growth retardation	75	66	83	36	58[d]	42
Delayed development / ID[b]	99	94	81	99	97	90
Suggestive features						
Maternal pre-eclampsia	3	23	0	0	0	0
Hypertrichosis	76	51	0	52	75	18
Keloids[c]	23	10	0	0	0	0
Other features						
Prenatal growth retardation	25	42	27	42	25[d]	17
Obesity	29	39	5	12	0	29
Long eyelashes	89	90	90[e]	90	70	25
Epicanthal folds	44	15	5[5]	6	?	27
Micrognathia	61	42	?	56	5[5]	58
Low-set ears	44	27	0	56	?	50
Cardiovascular anomalies	35	26	4	30	28	17
Urinary tract anomalies	28	24	13	48	29	21
Scoliosis	18	25	?	7	21	25
Epilepsy	25	10	11	24	20	21
Autism/Autism spectrum disorders	49	25	?	53	21	65

[a] All molecularly confirmed patients; values in percentages (not in all patients information on all features were available); [b] ID = intellectual disability (of any degree); [c] On trunk and upper arms; [d] Below 5th centile; [e] Estimate based on published pictures and unpublished personal observations; [f] Highest frequency on individual body site

Table S2. Comparison of clinical diagnostic features in individuals with molecularly confirmed Rubinstein-Taybi syndrome (RTS) compared to (molecularly confirmed) Cornelia de Lange syndrome (CdLS), Floating-Harbor syndrome (FHS), Wiedemann-Steiner syndrome (WDSTS), and Menke-Hennekam syndrome (MKHKS).

Clinical Diagnostic criteria for RTS	RTS	CdLS			FHS	WDSTS	MKHKS
	(n=100)	*(n=100)*			*(n=45)*	*(n=46)*	*(n=45)*
	CREBBP/ EP300[1]	*NIPBL*	*RAD21*	*SMC1A*	*SRCAP*	*KMT2A*	*CREBBP/EP300*
Cardinal features							
Cardinal score positive	97/100	1/60	1/25	1/15	10/45	16/46	5/45
Skeletal features score positive	98/100	0/60	0/25	0/15	10/45	10/46	2/45
3 or more facial signs	89/100	1/60	0/25	0/15	0/45	7/46	2/45
Growth features score positive	75/100	58/60	17/25	14/15	38/45	28/46	27/45
Abn development scores positive	99/100	60/60	24/25	14/15	45/45	45/46	43/45
Suggestive features							
Suggestive score positive	45/100	49/60	6/25	8/15	0/45	17/46	4/45
Total score							
Definitive RTS	55/100	0/60	0/25	0/15	0/45	1/46	0/45
Likely RTS	38/100	1/60	0/25	0/15	0/45	8/46	0/45
Possible RTS	7/100	35/60	4/25	7/15	10/45	19/46	9/45
Unlikely RTS	0/100	24/60	21/25	8/15	35/45	18/46	36/45

[1] 81 patients with CREBBP variant or microdeletion involving CREBBP, 19 with an EP300 variant

Table S3. Overview of the main eye characteristics in individuals with RTS as available in literature.

Eye finding	Frequency	Age of onset	Age at which screening is indicated	References
Anatomical				
Lacrimal duct obstruction	++	C	Infancy	17,18, 21-23
Microphthalmia	o	C		
Corneal opacities, keratoglobus/conus	o*	any age		
Congenital glaucoma	+	C	neonatal	19-22
Iris malformations	o	C		
Cataract	+*	congenital, juvenile	neonatal; during follow up visits	18-21
Microphakia	o	C		
Coloboma	+	C		17, 18, 20, 21
Macular anomalies, pigment changes, foveal hypoplasia	+++	C (foveal hypoplasia)	childhood	21
Peripheral retinal avascularity	o	C		
Optic nerve atrophy	o	mostly congenital		
Functional				
Visual impairment	+	any age	childhood	21
Refractive error requiring glasses	+++*	any age	< 3 yr	16, 19-21
Strabismus	++	any age	< 3 yr	15-22
Nystagmus	o	congenital		
Photophobia	++++	any age		21
ptosis	o			
Abnormal electroretinogram	+++			21

++++, ≥75%; +++, 50–75%;++, 25–50%; +, 5–25%; o, reported only in case reports or small case series. C= congenital, *increasing with age

Menses Survey

Methods

A survey using social media was set out between July 20 and October 19, 2022, by the support groups from France, Italy, Netherlands and Spain, asking participants data on age, diagnostic confirmation (clinically, cytogenetically, molecularly, and subdivision into *CREBBP* and *EP300* variants), age of menarche, metrorrhagia, hypermenorrhagia, painful menses, nature and results of any treatment, and any other issues related to menses. Specifically also those without any problem related to menses were invited to react. Numbers were too small to make a distinction between the country of origin of respondents.

Results

Family members of 76 females responded. Age varied between 11.0yr and 62yr (mean 20.9yr; median 20.1yr). The diagnosis was based on clinical characteristics in 26/76 females, cytogenetic studies in 1/76, and molecular results in 49/76 (27 *CREBBP* variants, 6 *EP300* variants, and 16 a molecular variant but uncertain in which gene).

Menses had not started yet in 9 females (ages 11-17 yr) or never started in a 62yr-old female as hysterectomy was performed before menses started (was not uncommon practice in ~1960).

Menarche occurred between 9.6yr and 17yr (mean 14.1yr; median 14.2yr). None of the participants were definitively postmenopausal, although in one 43-year-old female menses had markedly decreased in frequency and blood loss from the age of 41 years.

At the time of the survey 21 females used hormonal contraceptives (oral pill in 15, injection pill in 6); reasons for the contraceptives were hypermenorrhagias, metrorrhagias, very painful periods, marked behavioural problems during periods, inability to deal with periods independently, or a combination of these. Invariably the contraceptives were successful in decreasing the menses problems.

In the ones without hormonal contraceptives (n=45) there were 19 with metrorrhagias (42%), 10 hypermenorrhagias (22%), and 9 with markedly painful periods (20%).

Other characteristics that have been mentioned were headaches (n=4), polycystic ovaries (n=3), and a malformed uterus (n=1).

Table S4. Summary of background to recommendations (see main text) on behaviour for children and adults with RTS.

Characteristic	*Strength of evidence for recommendation*	*Recommendation*
Challenging behaviour	No RTS specific studies; strong evidence for intellectual disability in general	Provide signposting to high-quality accessible psychoeducational materials regarding how challenging behaviours develop (e.g. https://www.challengingbehaviour.org.uk/)
	No RTS specific studies; strong evidence for intellectual disability in general	Behavioural intervention based on a functional assessment
	No RTS specific studies; good evidence for intellectual disability in general	Health assessment if pain is suspected as contributing to behaviour
	Tentative evidence that set-shifting difficulties may be associated with adherence to routines;	Provide signposting to high-quality accessible psychoeducational materials regarding how challenging behaviours develop (e.g. https://www.challengingbehaviour.org.uk/)
Emotions	No RTS specific studies; adequate evidence for intellectual disability in general	Psychological Intervention: (Consider behavioural approaches for anxiety. Adapted CBT may be appropriate for some individuals with mild intellectual disabilities.)
Repetitive behaviour	No RTS specific studies; adequate evidence for intellectual disability in general	Consider utilising behavioural interventions for adherence to routines (e.g. visual schedules, flexible scheduling; providing a cue prior to a change). Consider assessment of executive function to supplement clinical formulation if challenging behaviour is related to change or adherence to routines
	No RTS specific studies; adequate evidence for intellectual disability in general	Parent education: e.g. inform parents about potential mechanisms underpinning repetitive questioning and cross sectional evidence of potential reductions in questions with age/ability.
Autism spectrum disorder	Emerging evidence that symbolic play, language, and imitation development is similar in those with RTS and severe ID to those with autism	Some families may wish to be signposted to early behavioural and developmental support strategies for children with autism. Also see repetitive behaviour recommendations
Social cognitive abilities	No RTS specific studies; adequate evidence in intellectual disability in general	Individuals may be responsive to interventions designed for people with intellectual disability that are designed to protect them from abuse.[23-25] Generalisation and maintainance of these skills needs to be considered and reviewed.
Self-regulation, impulsivity, activity		Provide family with information on inhibitory control and working memory and how these abilities may be supported/developed.
Treshold for pain	No RTS specific studies; adequate evidence in intellectual disability in general	Engage family to build a description of child's individual 'pain signature' and share with all professionals working with individual.

References

1. Fergelot, P. et al. Phenotype and genotype in 52 patients with Rubinstein–Taybi syndrome caused by EP300 mutations. *Am. J. Med. Genet. A* **170,** 3069-3082 (2016).

2. Huisman, S. et al. Phenotypes and genotypes in individuals with SMC1A variants. *Am. J. Med. Genet. A* **173**, 2108-2125 (2017).

3. Kline, A.D. et al. Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. *Nat. Rev. Genet.* **19**, 649-666 (2018).

4. Krab, L.C. et al. Delineation of phenotypes and genotypes related to cohesin structural protein RAD21. *Hum. Genet.* **139**, 575-592 (2020).

5. Budisteanu, M. et al. Floating-Harbor syndrome: presentation of the first Romanian patient with a SRCAP mutation and review of the literature. *Balkan J. Med. Genet*. **21**, 83-86 (2018).

6. Hood, R.L. et al. Mutations in SRCAP, encoding SNF2-related CREBBP activator protein, cause Floating-Harbor syndrome. *Am. J. Hum. Genet.* **90**, 308-313 (2012).

7. Le Goff, C. et al. Not all Floating-Harbor syndrome cases are due to mutations in exon 34 of SRCAP. *Hum. Mutat.* **34**, 88-92 (2013).

8. Nikkel, S.M. et al. The phenotype of Floating-Harbor syndrome : clinical characterization of 52 individuals with mutations in exon 34 of SRCAP. *Orphanet J. Med. Genet.* **8**, 63 (2013).

9. Rots, D. et al. Truncating SRCAP variants outside the Floating-Harbor syndrome locus cause a distinct neurodevelopmental disorder with a specific DNA methylation signature. *Am. J. Hum. Genet.* **108**, 1053-1068 (2021).

10. Seifert, W. et al. Expanding spectrum of exon 33 and 34 mutations in SRCAP and follow-up in patients with Floating-Harbor syndrome. *BMC Med. Genet.* **15**, 127 (2014).

11. Di Fede, E. et al. Expanding the phenotype associated to KMT2A variants: overlapping clinical signs between Wiedemann-Steiner and Rubinstein-Taybi syndromes. *Eur. J. Hum. Genet.* **29**, 88-98 (2021).

12. Sheppard, S.E. et al. Expanding the genotype and phenotypic spectrum in a diverse cohort of 104 individuals with Wiedemann-Steiner syndrome. *Am. J. Med. Genet. A* **185**, 1649-1665 (2021).

13. Menke, L.A. et al. CREBBP mutations in individuals without Rubinstein-Taybi syndrome phenotype. *Am. J. Med. Genet. A* **170**, 2681-2693 (2016).

14. Menke, L.A. et al. Further delineation of an entity caused by CREBBP and EP300 mutations but not resembling Rubinstein-Taybi syndrome. *Am. J. Med. Genet. A* **176,** 862-876 (2018).

15. Choi, N. et al. Genetic and clinical heterogeneity in Korean patients with Rubinstein-Taybi syndrome. *Mol. Genet. Genom. Med.* **9**, e1791 (2021).

16. Cohen, J.L. et al. EP300-related Rubinstein-Taybi syndrome: Highlighted rare phenotypic findings and a genotype-phenotype meta-analysis of 74 patients. *Am. J. Med. Genet. A* **182**, 2926-2938 (2020).

17. Enomoto, Y. et al. Divergent variant patterns among 19 patients with Rubinstein-Taybi syndrome uncovered by comprehensive genetic analysis including whole genome sequencing. *Clin. Genet.* **101**, 335-345 (2022).

18. Spena, S. et al. Insights into genotype-phenotype correlations from CREBBP point mutation screening in a cohort of 46 Rubinstein-Taybi syndrome patients. *Clin. Genet.* **88**, 431-40 (2015).

19. Stevens, C.A., Pouncey, J. & Knowles, D. Adults with Rubinstein-Taybi syndrome. *Am. J.Med. Genet. A* **155**, 1680–1684 (2011).

20. Tekendo-Ngongang, C. et al. Rubinstein–Taybi syndrome in diverse populations. *Am. J. Med. Genet. A* **182**, 2939–2950 (2020).

21. Van Genderen , M.M., Kinds, G.F., Riemslag, F.C.C. & Hennekam, R.C.M.*. Ocular features in Rubinstein-Taybi syndrome: Investigation of 24 patients and review of the literature. *Br. J. Ophthalmol.* **84**(, 1177–1184 (2000). *23/24 patients described in Van Genderen *et al* were subsequently molecularly confirmed as having RTS (personal communication RC Hennekam)

22. Yu S., et al. Clinical exome sequencing identifies novel CREBBP variants in 18 Chinese Rubinstein–Taybi Syndrome kids with high frequency of polydactyly. *Mol. Genet. Genom. Med.* **7**, 1–15 (2019).

23.Bruder, C., Kroese, B. & Bland S. The efficacy of interventions designed to prevent and protect people with intellectual disabilities from sexual abuse: A review of the literature. *J. Adult. Protect*. **7**, 4-18 (2005).

24. Fisher, M. H., Burke, M. M., & Griffin, M. M. Teaching young adults with disabilities to respond appropriately to lures from strangers. *J. Appl. Behav. Anal.* **46**, 528-533 (2013).

25. Fisher, M. H. Evaluation of a stranger safety training programme for adults with Williams syndrome. *J. Intellect. Disabil. Res.* **58**, 903-914 (2014).