Recommendations

R1

The clinical diagnosis of RTS is based on a combination of signs and symptoms (Table 1) which allows the clinical diagnosis to be definitive, likely, possible or unlikely. A definitive diagnosis is reached irrespective of the presence of a causative variant in a gene known to cause RTS; a likely or possible diagnosis needs further confirmation by molecular testing before the definitive diagnosis can be made.

Strength of recommendation: ***A+++***

R2

When evaluating physical characteristics of RTS, familial resemblances should be taken into account.

Strength of recommendation: ***A+++***

R3

A set of criteria based on physical, cognitive and behavioural characteristics, to indicate the severity of RTS, should be developed in collaboration with families of individuals with RTS.

Strength of recommendation: ***A++***

R4

Molecular confirmation of the diagnosis RTS is recommended as it can be obtained in 75-80% of individuals in whom clinically the diagnosis is expected.

Strength of recommendation: ***A+++***

R5

Families of individuals with RTS should be made aware that the type and site of variants in *CREBBP* and *EP300* do not correlate with a specific phenotype with respect to external morphology, malformations, cognition or behavior.

Strength of recommendation: ***A+++***

R6

Families of individuals with RTS should be informed that the empirical recurrence risk after the birth of a child with RTS is estimated as 0.5-1%. The recurrence risk for an individual with RTS is 50%.

Strength of recommendation: ***A+++***

R7

Families should be informed that reliable prenatal diagnostic studies of RTS are possible if in an earlier affected child a causal variant of *CREBBP* or *EP300* has been identified.

Strength of recommendation: ***A+++***

R8

In half of the newborns with RTS breastfeeding proves possible, and breastfeeding should be carefully assessed and assisted by a breastfeeding consultant.

Strength of recommendation: ***A++/B+***

R9

The use of growth charts specific for individuals with RTS facilitates adequate monitoring of growth in every infant and child with RTS.

Strength of recommendation: ***A+++***

R10

Every newborn suspected or proven to have RTS should be assessed within days for congenital anomalies of the eyes, heart and kidneys.

Strength of recommendation: ***A+++***

R11

Every newborn with RTS who demonstrates symptoms such as muscle weakness, jitteriness, or seizures should be screened for hypoglycemia.

Strength of recommendation: ***A+++***

R12

In every child with RTS in whom growth differs markedly from the expected growth pattern, evaluation for the presence of growth hormone deficiency is indicated. If present, treatment is as in the general population.

Strength of recommendation: ***A+++***

R13

Sexual education appropriate to the level of emotional and cognitive functioning should be offered to every adolescent and adult with RTS, and contraception options should be discussed.

Strength of recommendation: ***A+++***

R14

Feeding problems are common in infants with RTS and should be managed according to standard treatment. Involvement of dieticians is often helpful.

Strength of recommendation: ***A+++***

R15

Gastro-oesophageal reflux disease is common in children and adults with RTS and needs nutritional and medical treatment. If persisting despite adequate treatment, assessment by a gastroenterologist may be warranted.

Strength of recommendation: ***A+++***

R16

Chronic constipation is very common in children and adults with RTS and should be treated preferably with diet and osmotic laxatives.

Strength of recommendation: ***A+++***

R17

Cardiovascular evaluation including cardiac sonography should be performed in individuals with RTS at the time of diagnosis.

Strength of recommendation: ***A+++***

R18

Surveillance for hypertension in adults with RTS should be performed as in the general population.

Strength of recommendation: ***A+++***

R19

If unexplained recurrent lower respiratory tract infections occur in an individual with RTS, further studies directed to micro-aspirations and gastro-oesophageal reflux are indicated.

Strength of recommendation: ***A+++***

R20

Every individual with RTS should have an ophthalmological examination at diagnosis because of the high frequency of congenital ocular anomalies, some of which need immediate treatment.

Strength of recommendation: ***A+++***

R21

Regular ocular examinations of individuals with RTS are necessary at all ages as refractive errors, cataract, and retinal pigmentary changes may become apparent at any age.
Strength of recommendation: ***A+++***

R22

Gradual introduction of glasses in situations in which an individual with RTS benefits most of them, improves the chance of acceptance.
Strength of recommendation: ***A++***

R23

Regular evaluation of hearing should be performed in all individuals with RTS.
Strength of recommendation: ***A+++***

R24

Obstructive sleep apnea in children and adults with RTS may cause major health problems and needs careful evaluation for causal factors and treatment.
Strength of recommendation: ***A+++***

R25

Assessment of sleep in individuals with RTS using a questionnaire validated for individuals with intellectual disability can be instrumental in offering optimal care.
Strength of recommendation: ***A++/B+***

R26

Health care professionals arranging anesthesia should be aware of the potentially problematic anesthesia in children and adults with RTS with particular attention to airway management and implications for postoperative care.
Strength of recommendation: ***A+++***

R27

Due to increased risk with anesthesia, efforts should be made to combine non-emergent procedures into a single anesthetic event to mitigate potential perioperative morbidity.
Strength of recommendation: ***A+++***

R28

Keloids occur in 24% of individuals with RTS, are unavoidable, and can have major impact on the quality of life; no management strategy is universally successful and treatment needs individual adaptation.

Strength of recommendation: ***A+++***

R29

In 17% of individuals with RTS pilomatricomas occur which can be removed completely in case of discomfort for the individual.

Strength of recommendation: ***A+++***

R30

Individuals with RTS, and especially those with distal limb malformations, should avoid nail care habits and shoes that may cause ingrown nails. Treatment is as in the general population.

Strength of recommendation: ***A++/B+***

R31

Every individual with RTS should be evaluated at diagnosis by renal ultrasound and by obtaining blood pressure measurement.

Strength of recommendation: ***A+++***

R32

Renal malformations or hypertension in a child with RTS warrants consultation of a pediatric nephrologist and/or pediatric urologist.

Strength of recommendation: ***A+++***

R33

The position of testes should be evaluated at diagnosis by physical exam in every male with RTS.

Strength of recommendation: ***A+++***

R34

Hypermenorrhagia or metrorrhagia in females with RTS can be effectively treated with hormonal contraceptives.

Strength of recommendation: ***A++/B+***

R35

Surgery to correct radially deviated thumbs in someone with RTS is sometimes indicated, which can best be determined when hand function can be reliably assessed, often at 3-4 years of age or thereafter. Surgery should be performed preferably by a surgeon familiar with the procedure in individuals with RTS.
Strength of recommendation: ***A+++***

R36
Regular evaluation of motor skills including gait analysis is indicated for individuals with RTS. If gait is disturbed, patellar instability and aseptic hip joint inflammation should be considered in particular.
Strength of recommendation: ***A+++***

R37
The spine curvature should be checked in late childhood and puberty in everyone with RTS. Management of scoliosis follows that in the general population.
Strength of recommendation: ***A+++***

R38
In individuals with RTS with recurrent fractures, bone density studies to check for osteoporosis are indicated.
Strength of recommendation: ***A+++***

R39
In every newborn or child with RTS the palate should be closely examined at diagnosis by inspection and palpation.
Strength of recommendation: ***A+++***

R40
Specific attention should be paid to talon cusps in everyone with RTS, especially in the permanent dentition. Treatment is indicated if interfering with occlusion, mouth closure or causing caries.
Strength of recommendation: ***A+++***

R41
Practicing daily oral hygiene is strongly recommended in individuals with RTS. Regular professional dental assessment should take place preferably by a special needs dentist.

Detailed dental assessment and treatment may be facilitated if performed under sedation or anesthesia.
Strength of recommendation: ***A+++***

R42
If a child with RTS has unexplained recurrent infections a baseline immune workup should be performed. If this yields abnormal results, consultation with an immunologist is indicated.
Strength of recommendation: ***A+++***

R43
Vaccination in individuals with RTS should be performed as in the general population, and cause the typical level of protection.
Strength of recommendation: ***A+++***

R44
Oncologic surveillance of individuals with RTS should follow national healthcare standards without need for additional surveillance.
Strength of recommendation: ***A+++***

R45
Cerebral MRI usually does not contribute to regular clinical care in individuals with RTS and should be limited to those with a neurological indication.
Strength of recommendation: ***A+++***

R46
If individuals with RTS develop epileptic seizures, treatment and surveillance should follow national standards of care.
Strength of recommendation: ***A+++***

R47
Early assessment of developmental functioning of children with RTS allows adequate and timely access to dedicated services that contribute to optimal developmental outcomes.
Strength of recommendation: ***A+++***

R48
Early intervention to develop communication, both in the preverbal and verbal stage, facilitates social interactions in children with RTS.

Strength of recommendation: ***A+++***

R49

Regular developmental assessment over the life-span facilitates care in individuals with RTS.
Strength of recommendation: ***A+++***

R50

Optimal care for individuals with RTS involves screening for anxiety using a questionnaire validated for individuals with intellectual disability. Interventions for anxiety should follow best practice guidance for individuals with intellectual disability.
Strength of recommendation: ***A+++***

R51

Individuals with RTS may benefit from a thorough assessment of autism characteristics and access to support designed for people on the autism spectrum.
Strength of recommendation: ***A+++***

R52

Individuals with RTS may benefit from learning appropriate skills to manage complex social situations, understand others' intentions, and reduce impulsivity.
Strength of recommendation: ***A+++***

R53

The common disorders of adulthood (hypertension, diabetes mellitus, cardiovascular problems) occur at low frequency in individuals with RTS and should be managed as in the general population.
Strength of recommendation: ***A+++***

R54

Sexual education including contraception and family counselling adapted to the developmental level of the adolescent or adult with RTS should be provided.
Strength of recommendation: ***A+++***

R55

Parents and caregivers should be informed that an overall specific cure for the physical, developmental and behavioural characteristics of RTS does not exist; congenital anomalies cannot be completely corrected after birth.

Strength of recommendation: ***A+++***

R56

Future research is needed to focus on disease pathogenesis and subsequent development of therapeutics that may ameliorate postnatal characteristics of RTS.

Strength of recommendation: ***A+++***