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Keloids in Rubinstein–Taybi syndrome: a clinical study

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Summary

Background Rubinstein–Taybi syndrome (RSTS) is a multiple congenital anomalies–intellectual disability syndrome. One of the complications is keloid formation. Keloids are proliferative fibrous growths resulting from excessive tissue response to skin trauma.

Objectives To describe the clinical characteristics of keloids in individuals with RSTS reported in the literature and in a cohort of personally evaluated individuals with RSTS.

Patients and methods We performed a literature search for descriptions of RSTS individuals with keloids. All known individuals with RSTS in the Netherlands filled out three dedicated questionnaires. All individuals with (possible) keloids were personally evaluated. A further series of individuals with RSTS from the U.K. was personally evaluated.

Results Reliable data were available for 62 of the 83 Dutch individuals with RSTS and showed 15 individuals with RSTS (24%) to have keloids. The 15 Dutch and 12 U.K. individuals with RSTS with keloids demonstrated that most patients have multiple keloids ($n > 1$: 82%; $n > 5$: 30%). Mean age of onset is 11·9 years. The majority of keloids are located on the shoulders and chest. The mean length × width of the largest keloid was 7·1 × 2·8 cm, and the mean thickness was 0·7 cm. All affected individuals complained of itching. Generally, treatment results were disappointing.

Conclusions Keloids occur in 24% of individuals with RSTS, either spontaneously or after a minor trauma, usually starting in early puberty. Management schedules have disappointing results. RSTS is a Mendelian disorder with a known molecular basis, and offers excellent opportunities to study the pathogenesis of keloids in general and to search for possible treatments.

What's already known about this topic?

- Individuals with Rubinstein–Taybi syndrome (RSTS) have an increased likelihood of developing keloid scars.
- RSTS is caused by mutations in the histone acetyltransferase genes, *CREBBP* or *EP300*.
- Keloids are proliferative fibrous growths and can cause extensive itching.

What does this study add?

- This study found that 24% of individuals with RSTS from a single country develop keloids.
- We describe age of onset, site, natural clinical course and reaction to various medical treatment schedules.
- RSTS is the most common Mendelian disorder in which keloids occur with a high frequency.

Rubinstein–Taybi syndrome (RSTS) is a multiple congenital anomalies–intellectual disability syndrome, characterized by broad thumbs and big toes, characteristic face, growth retardation and intellectual disability of variable degree. The syndrome has been observed in all ethnic groups. The birth prevalence is one in 100 000–125 000.[1,2] RSTS is almost always a *de novo* occurring entity. Ten per cent of individuals with RSTS have a microdeletion affecting chromosome band 16p13.3, in which the gene coding for cAMP response element-binding protein (CREB)-binding protein, *CREBBP*, is located; 50% carry a mutation in *CREBBP* itself and another 3% have a mutation in the gene coding for E1A-binding protein, *EP300*, located at chromosomal subdomain 22q13.2.[2] In the remaining individuals with RSTS no mutation can be detected despite a classical phenotype.

Individuals with RSTS have an increased lifetime risk of complications like glaucoma, visual problems and other ocular anomalies and behavioural problems.[3–5] They also have an increased risk of malignancies like leukaemia, neuroblastoma and meningioma.[6] These malignancies develop either in the first years of life or in midadulthood (30–45 years).

Another feature of RSTS is the development of keloids. The keloids occur either spontaneously or after relatively minor trauma. The keloids cause itching to a degree that may have a significant negative impact on life quality.[7] The frequency of keloid formation in RSTS is not well known and estimates vary from 5% to 57%.[5,6,8–13] One aim of the present study was to evaluate keloid formation in RSTS by performing a literature study of all publications describing individuals with RSTS with keloid formation. To obtain data on keloid prevalence, all RSTS individuals from a single country (the Netherlands) were evaluated. Finally, data from a similarly evaluated group of individuals with RSTS from the U.K. were added to obtain data of a sufficiently large group of individuals with RSTS who had keloids. Together, the studies provide clinical data from 27 individuals with RSTS with keloids.

Patients and methods

Literature

We performed a systematic literature search in PubMed allowing publications published between 1963 and 1 June 2013. The medical subject heading terms used were: 'Rubinstein–Taybi syndrome' together with 'keloid', 'scar' or 'itching'. We accepted as languages Dutch, English, French, German, Portuguese and Spanish. No other limits were used. Reference lists of articles identified as relevant were examined for other potentially relevant articles.

Patients

The families of all individuals with RSTS known to the support group in the Netherlands were invited to participate. In addition to these, the families of other individuals with RSTS who were known to the senior author (R.C.M.H.) but not known to the support group were contacted and invited. The parents or other legal representatives of individuals with RSTS who consented were sent questionnaires (see below). All individuals with RSTS who had keloids or possible keloids were personally evaluated by one of us. The diagnosis of RSTS was confirmed clinically for both the U.K. and Dutch patients by the senior author (R.C.M.H.), who has exceptional experience with RSTS.

Questionnaire study

The parents or legal representatives of all participating individuals with RSTS were sent three questionnaires: (i) a general questionnaire on the medical history, family history, signs and symptoms that are characteristic for RSTS, and on the investigations to detect the cause of RSTS; (ii) a questionnaire dedicated to keloid formation; and (iii) a questionnaire dedicated to itching (see Supporting Information). All questionnaires were developed specifically for this study. The itching questionnaire was adapted from previously published questionnaires.[14–16]

Clinical evaluations

All individuals with RSTS who possibly had keloids were invited to visit our clinic. If this was impractical, individuals were evaluated at home or during a meeting of the patient support group. Results from the questionnaires were discussed during the personal evaluation, and additional questions were asked in cases of ambiguity. Clinical investigations consisted of general physical examination and a specific evaluation of keloids using the standardized Patient and Observer Scar Assessment Scale.[17] The three dimensions of each keloid were measured with a ruler. Standardized photographs were taken of the keloid(s).

The data were analysed with SPSS (IBM, Armonk, NY, U.S.A.). The study was approved by the Medical Ethics Committee of the Academic Medical Center in Amsterdam. Written consent was obtained from parents or other legal representatives of all study participants.

Results

Literature

In performing a literature search, we were able to detect 37 patients with RSTS who had keloids.[6,8,10–13,18–23] For the patient characteristics see Table 1. In the available case reports, the authors provided very limited information about the keloid management. Siraganian *et al.* suggested a possible relationship between keloid formation and neoplasms in RSTS.[6] In a study group of 574 individuals with RSTS, they found 28 individuals who had keloids and 19 who had a neoplasm. Four individuals had both, pointing to a 21% risk for someone with RSTS, as well as cancer, to develop keloids compared with a 4% risk for those without cancer. As numbers were small, the study did not allow firm conclusions to be drawn.

As the description of literature cases was very frequently limited and often incomplete, we refrained from comparing the cases in the literature with the patients who participated in our study.

Questionnaires

Questionnaires and clinical evaluations were conducted in 15 patients with RSTS from the Netherlands and 12 from the U.K. General demographic data are provided in Table 2, and general characteristics fitting RSTS, including genetic data, are provided in Table 3 and illustrated in Figure 1. Results of molecular studies were available in all Dutch patients with RSTS. For patients from the U.K. with RSTS, these data were available in five individuals. Spontaneous keloids did not occur in family members of individuals with RSTS. Only one family member developed a keloid scar. Data about complaints resulting from the keloids (including itching) are provided in Table 4. Of the patients who complained of itching, 21% stated they continuously had feelings of itching, which were described as stinging, stabbing, burning, annoying and unbearable. The itching was almost exclusively located at the sites of their keloids. Itching did not precede keloid formation. The itching influenced the behaviour of affected individuals repeatedly, giving rise to feelings of depression, agitation, anxiety or decreased concentration.

Table 1 Overview of 37 individuals with Rubinstein–Taybi syndrome with keloids described in the literature

Sex	21 men/16 women
Mean age of onset (years)	20·4
Cause	
Spontaneous	10
After surgery	10
After vaccination	4
Other	17
Location	
Chest	18
Shoulders	8
Upper arms	12
Back	8
Number of keloids	
Single	6
Multiple	31
Ethnicity	
African	2
White	35

Table 2 General characteristics of 27 individuals with Rubinstein-Taybi syndrome who had keloids

	Total (n = 27)	The Netherlands (n = 15)	U.K. (n = 12)
Sex, n (%)			
Men	13 (48)	7	6
Women	14 (52)	8	6
Deceased, n (%)	5 (20)	5	0
Mean age (years)	33·0	38·5	27·0
Ethnicity, n (%)			
White	25 (93)	15	10
Asian	2 (7)	0	2
African	0 (0)	0	0
Mixed	0 (0)	0	0

Table 3 Characteristics of Rubinstein–Taybi syndrome (RSTS) in 27 individuals with RSTS who had keloids

Somatic manifestations	n (%)
Broad thumbs	29 (96)
Deviated thumbs	12 (44)
Broad big toe	25 (93)
Deviated big toe	9 (33)
Extra fingers/toes	4 (16)
Heart malformation	9 (36)
Kidney malformation	5 (20)
Undescended testes	9 (36)
Eye condition	18 (67)
Supple joints	17 (63)
Deviations palate	14 (56)
Deviations teeth	14 (56)
Haemangioma	8 (32)
Excessive hair	14 (56)
Cognition	
Intellectual disability	27 (100)
Genetic analyses	
CREBBP mutations	14 (50)
Microdeletion #16p13.3	2 (7)
Not performed[a]	7 (28)
No information	4 (15)

[a]Neither *CREBBP* nor *EP300* were evaluated.

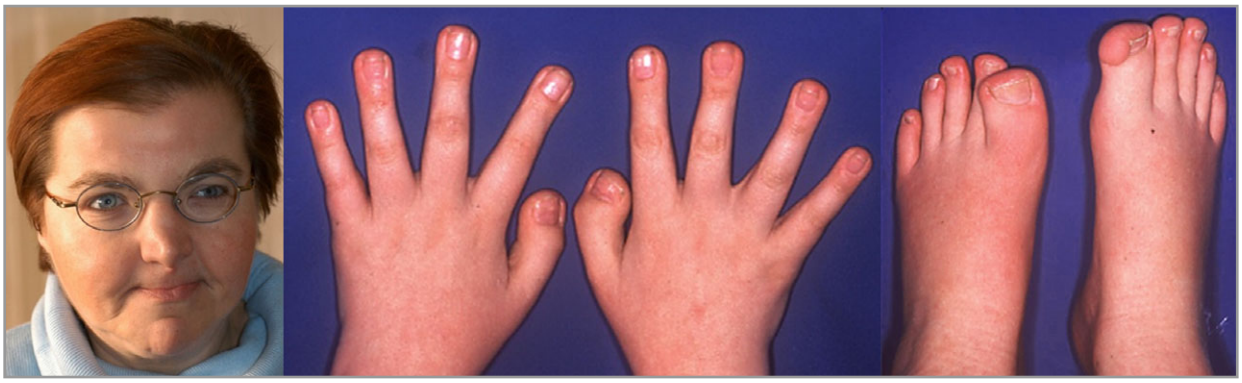

Fig 1. Characteristic face and distal limbs of an individual with Rubinstein–Taybi syndrome.

Table 4 Complaints associated with keloids in 27 individuals with Rubinstein–Taybi syndrome

Complaint	n (%)
Itching	24 (89)
Pain	5 (19)
Restriction in movements	2 (7)
Infection	4 (15)
Difficulties falling asleep	7 (27)
Waking up during the night	3 (11)
Differences in behaviour	10 (37)

Clinical evaluations

The major characteristics of the keloids are provided in Table 5. The localizations are depicted in Figure 2. Examples of the keloid formation in the present group are available in Figure 3. Only five patients had a single keloid, all the others had several. We found no differences in general or RSTS manifestations between patients with a single keloid and those with several keloids. Most keloids are located in the sternal (63%) and the shoulder (41%) areas. Treatment results were usually disappointing, but in two individuals itching was reduced to a limited extend. Treatment had no effect on keloid growth. Several biopsies representative of keloid lesions were evaluated by a single pathologist (D.d.J.). These showed a normal, nonatrophic epidermis, and extensive deposition of randomly and horizontally oriented broad, acellular, hyalinized collagen bands extending from upper reticular dermis into the subcutaneous fat. In the periphery of the lesions, the presence of more cellular components with fibroblast and histiocyte proliferations varied. No prominent vertical vascular proliferations were seen, which further distinguished these lesions from hypertrophic scars.

Discussion

Keloids are proliferative fibrous growths of the skin that result from an excessive tissue response to trauma. Sometimes such traumas are minimal or unnoticed (i.e. constituting a potential cause of spontaneous keloid formation). Keloids are unique to humans.[24] They grow continuously and invasively beyond the confines of the original wound, in contrast to hypertrophic scars, which stay within the boundaries of the original wound and after a period of continuous growth, slowly regress. Histologically, keloids contain type I and III collagen fibres, which lie in haphazardly connected loose sheets randomly oriented to the epithelial surface.[25] The keloid-derived fibroblasts show excessive extracellular matrix production and proliferation, altered apoptosis, growth factor response and cytokine production.[26] The management of keloid scars remains difficult and multiple treatments have been advocated with varying degrees of success and high recurrence rates.[27] An International Advisory Panel has developed consensus guidelines.[28]

Keloids occur in all ethnic groups, but are more common in individuals of African and Asian descent. Individuals with dark skin have a 15 times higher chance of developing keloids compared with individuals who have light skin.[29] Keloids occur most frequently in individuals aged 11–30 years. Puberty and pregnancy are known to be associated with an increased frequency of keloid development, which has been interpreted to be hormone related.[30,31] In addition to skin trauma (surgery, insect bites, burns, piercings, vaccination, scratching), genetic predisposition plays a major role in keloid development.[32,33] But even in individuals with a genetic predisposition to develop keloids, significant injury may or may not lead to keloid formation, so pathogenesis and means of prevention remain largely unknown. The evidence for genetic susceptibility to keloid formation is best demonstrated by its variable occurrence in various ethnicities and within families, and its prevalence in twins.[34] A small number of congenital disorders also exhibit keloids as a feature. The most commonly associated syndromes are RSTS and Goeminne syndrome and, less frequently, Ehlers–Danlos syndrome type IV. Goeminne syndrome is characterized by marked keloid formation, congenital torticollis, naevi and varicosities starting in early puberty.[35] The keloid formation starts in infancy, without evidence of preceding trauma, and spreads all over the body. Intelligence is normal. Only two families have been reported worldwide, the gene is unknown but it is likely to be an X-linked inherited disorder. RSTS is the only Mendelian

Table 5 Characteristics of keloids in 27 individuals with Rubinstein–Taybi syndrome

Age at first keloid (years)	
Mean	11·9
Median	15·4
Number of keloids	
1	5 (18%)
1–5	14 (52%)
> 5	8 (30%)
Cause	
Surgery	13
Spontaneous	8
Trauma	2
Other	4
Size of largest keloid	
Length × width (range)	7·1 (2–20) × 2·8 (1·5–20) cm
Thickness (range)	0·7 (0·4–1·2) cm
Locations (> 1 keloid)	
Sternal	17
Shoulders	11
Lower back	6
Upper arm	8
Leg	6
Lower jawline	1
Treatment	8 patients, 11 keloids
Steroid injection	4
Lotion	5
Laser therapy	1
Pressure therapy	1

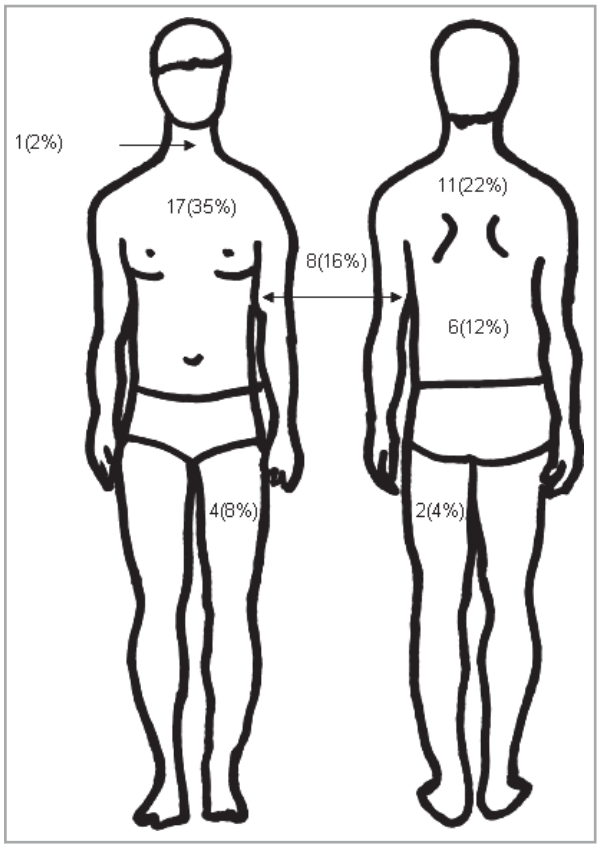

Fig 2. Schematic representation of the distribution of keloids over the total body in 27 individuals with Rubinstein–Taybi syndrome.

entity of known cause in which keloid formation occurs with significant frequency. Studying keloids in individuals with RSTS may shed light on keloid pathogenesis in general, which motivated us to carry out the present study.

The individuals with RSTS presented in this study are identical to individuals with RSTS in general with respect to phenotype, growth, development and molecular background.[2] They were all of white extraction, except two with an Asian ethnicity. None had an African background. There is no unusual ethnic distribution explaining the frequency of keloids.

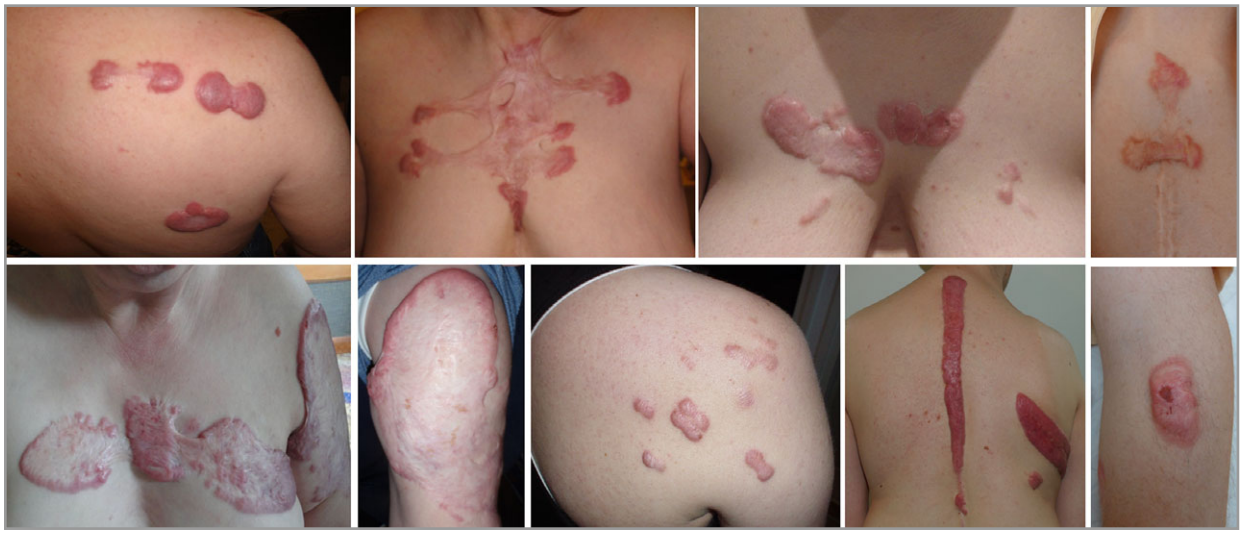

Fig 3. Examples of keloid formation in the presented individuals with Rubinstein–Taybi syndrome. All developed apparently spontaneously except upper row panel right (after surgery for fracture) and lower row panel 4 (after scoliosis surgery).

The mean age of keloid onset in the present study group (11·9 years) is lower than the mean age in the general population (women 22·3 years; men 22·8 years).[24] This can probably be explained by the increased likelihood of developing keloids in individuals with RSTS. Half of the patients with RSTS presented in this study developed keloids after surgery. Keloids developed in the other individuals with RSTS without known trauma (spontaneously) or after a minor trauma. No one in the study group had any piercings. Eighty-two per cent of RSTS individuals had more than one keloid. In individuals without RSTS, the occurrence of multiple keloids is strongly linked to a family history of keloids. In the present RSTS study group, only one relative reported a (single) keloid, again suggesting that RSTS is the main aetiological factor in keloid formation for this cohort.

In the general population, keloids occur more frequently on the chest, shoulders, upper back and ears.[33] The ear is likely to be the most common site for developing keloids. There is no good explanation for this distribution over the body, except for the occurrence of keloids on the earlobes after piercings.[33] In the present RSTS group, keloids were located mainly on the chest, shoulders and upper back. There were no keloids on the ears and, indeed, no individual with RSTS from this group had an ear piercing.

In the general population, the main problems patients experience in relation to keloids are the aesthetic disfigurement, impaired function owing to restricted skin and joint mobility, pain and itching.[36] In the present RSTS study, itching was very common and significantly affected patients' lives on a daily basis, sometimes leading to sleep problems. Pain and frequent infections were much less common. We evaluated whether itching also was frequent in RSTS individuals without keloids (n = 37) but this was not the case (data not shown). The results are in agreement with the opinion of the 125 families with a child who has RSTS gathered at the Third RSTS World Conference (May 2011). When asked to indicate the most important issue for future research, they responded that the treatment of keloids in individuals with RSTS should obtain primary priority. Aesthetic appearance was only a minor concern for the patients and their families.

The present RSTS study group received a limited number of treatments for their keloids. This is possibly related to the invasiveness of first-line therapy (recurrent painful injections), which is difficult to administer to patients with an intellectual disability. The few strategies that were followed had little effect.

RSTS is caused by mutations in *CREBBP* and *EP300*.[2] Both genes are coactivators in the Sma and Mad-related protein/Transforming growth factor-β signalling pathway, which has been suggested to play a key role in keloid development.[37] Elucidating the mechanisms involved in keloid pathogenesis will form a basis for better therapy, and potentially highlight novel treatment strategies. RSTS is a well-recognized human developmental disorder with a 24% risk of keloid formation. As the molecular pathology is known in most cases, and established animal and *in vitro* molecular models exist, RSTS forms an excellent model to study aetiology and pathogenesis of keloids. Such studies have recently been initiated by the authors of this study.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Data S1. Clinical Questionnaire.
Data S2. Itching scale.
Data S3. POSAS Observer Scale.
Data S4. Keloid Questionnaire.