

Hypoparathyroidism, Dwarfism, Medullary Stenosis of Long Bones, and Eye Abnormalities (Kenny- Caffey Syndrome) and Hypoparathyroidism, Retardation, and Dysmorphism (Sanjad-Sakati) Syndrome

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20.1 Introduction

In 1966, Kenny and Linarelli described a mother and son who had severe short stature, thin long bones with narrow diaphyses, and episodes of hypocalcemia [1]. In 1967, Caffey described the radiographic features of the same patients [2]. The condition has since been known as Kenny-Caffey syndrome (KCS [MIM127000]) (see also Chap. 15). The inheritance of this disorder is autosomal dominant, and it was recently recognized to be allelic (i.e., caused by mutations in the same gene) to a lethal disorder, osteocranio-stenosis (OCS [MIM 602361]), characterized by gracile bones with thin diaphyses, premature closure of basal cranial sutures, and microphthalmia [3, 4]. Hypocalcemia due to hypoparathyroidism has been reported among patients with OCS who survived the perinatal period.

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The syndrome of hypoparathyroidism, retardation (of growth and mental development) with dysmorphic features, HRD syndrome, also known as Sanjad-Sakati syndrome has been described by Sanjad and Sakati in 1988 in an abstract followed by a detailed report 3 years later [5]. This syndrome has been described mostly in Arab patients and is inherited by the autosomal recessive mode. HRD syndrome shares several important clinical features with KCS, a fact that has caused some confusion in the literature. This syndrome has been classified by some authors as autosomal recessive KCS or KCS type 1 in contrast to KCS type 2, the autosomal dominant form.

The identification of the causative mutations for KCS/OCS and the HRD syndrome has clearly confirmed that KCS/OCS and the HRD syndrome are separate clinical and genetic disorders. KCS/OCS is caused by heterozygous mutations in the *FAM111A* gene, while HRD syndrome is caused by homozygous or compound heterozygous mutations in the *TBCE* gene as will be subsequently described.

The following clinical description of the clinical picture of KCS/OCS in this chapter will rely upon genetically diagnosed patients or sporadic patients from non-consanguineous, non-Arab families. Most of the currently described HRD patients were of Arab origin. Many were born to consanguineous families and carry a common single homozygous mutation in the *TBCE* gene.

20.2 HRD/Sanjad-Sakati Syndrome

20.2.1 Epidemiology

Most genetically diagnosed HRD patients have been of Middle Eastern (Arab) origin. In Saudi Arabia, estimated incidence varies from 1:40,000 to 1:100,000 live births. In Kuwait, the estimated incidence of the syndrome is 7–18 per 100,000 live births [6]. Based on the number of new cases and the total live births over the past 10 years, we estimated the incidence of HRD syndrome at 1 per 10,000 live births among the Bedouin in southern Israel (unpublished data).

20.2.2 Clinical Phenotype

The early literature on the HRD syndrome has been reviewed previously [7].

Growth retardation is seen in most of the patients. Both prenatal and postnatal growths are impaired [6–9]. In a recent study, all of the reported children suffered from intrauterine growth restriction (IUGR) with a resultant low birth weight and short birth length. Mean birth weight was $2,100 \pm 200$ g (-2.2 ± 0.25 SDS) in boys and $1,970 \pm 450$ g (-2.6 ± 0.7 SDS) in girls. Mean birth length was 44.7 ± 3.3 cm (-5.1 ± 1.27 SDS) in boys and 44.6 ± 2.75 cm (-4.7 ± 1.7 SDS) in girls. Analysis of growth in those patients by the infancy-childhood-puberty (ICP) growth model revealed that during the first year of life, linear growth followed a path of growth that, although very short, coincided with the first component (I) of the ICP model. However, further decrease in linear growth was observed during the second year of life. Growth analysis of the path of growth by the ICP model disclosed a markedly delayed appearance of the childhood component that normally occurs between 6 and 12 months of age, when the infancy component markedly decelerates. In HRD patients, the appearance of the C component occurred at the age of 17.6 ± 5.6 months in boys and 19.7 ± 6 months in girls. The latest available growth measurements, expressed as weight and

height SDs, in boys were -13.1 ± 3.8 and -8.7 ± 1 , respectively. In girls, the latest available weight and height SDs were -16.6 ± 4.4 and -9.5 ± 2.4 , respectively. BMI SDs or weight for length SDSs (in patients younger than 3 years) was below -2 in almost all the patients [10].

Global developmental delay is a universal feature of the syndrome. Although, many patients have moderate to severe mental retardation, some had mild to moderate mental retardation [7–9]. Speech skills have been reported as variable. Some patients' speech improved after attending speech therapy [9]. Several characteristic dysmorphic features have been described in patients with HRD syndrome (Fig. 20.1). Microcephaly, deep-set eyes, external ear malformations, depressed nasal bridge, thin upper lip, hooked small nose, micrognathia, and small hands and feet are consistent features of the syndrome. Prominent forehead, microphthalmia, and long philtrum have been reported as well [7–9]. Cryptorchidism and micropenis have been reported in some of the male patients. No fertility has been reported in patients with HRD. Dental abnormalities include microdontia and oligodontia, delayed teeth eruption, enamel hypoplasia, and severely carious teeth [7, 11, 12].

HRD patients display a variety of ocular findings, including microphthalmia, microcornea, keratitis, errors of refraction, strabismus, and retinal vascular tortuosity [13, 14]. Seizures due to hypocalcemia may appear as early as in the neonatal period and are a common feature of the syndrome [7, 9]. Significant neurological disabilities are rare [9].

The patients are susceptible to severe infections including life-threatening pneumococcal infections especially during infancy. The syndrome carries a high risk for mortality with a reported rate ranging between 25 and 55 % during infancy and early childhood. Recurrent infections and hypocalcemic seizures are the main reported causes of death in some infants [7, 10]. Chronic intestinal pseudo-obstruction has been also implicated as a cause of mortality in a child with the HRD syndrome [15]. Patients have been described as late as in their third decade of life.

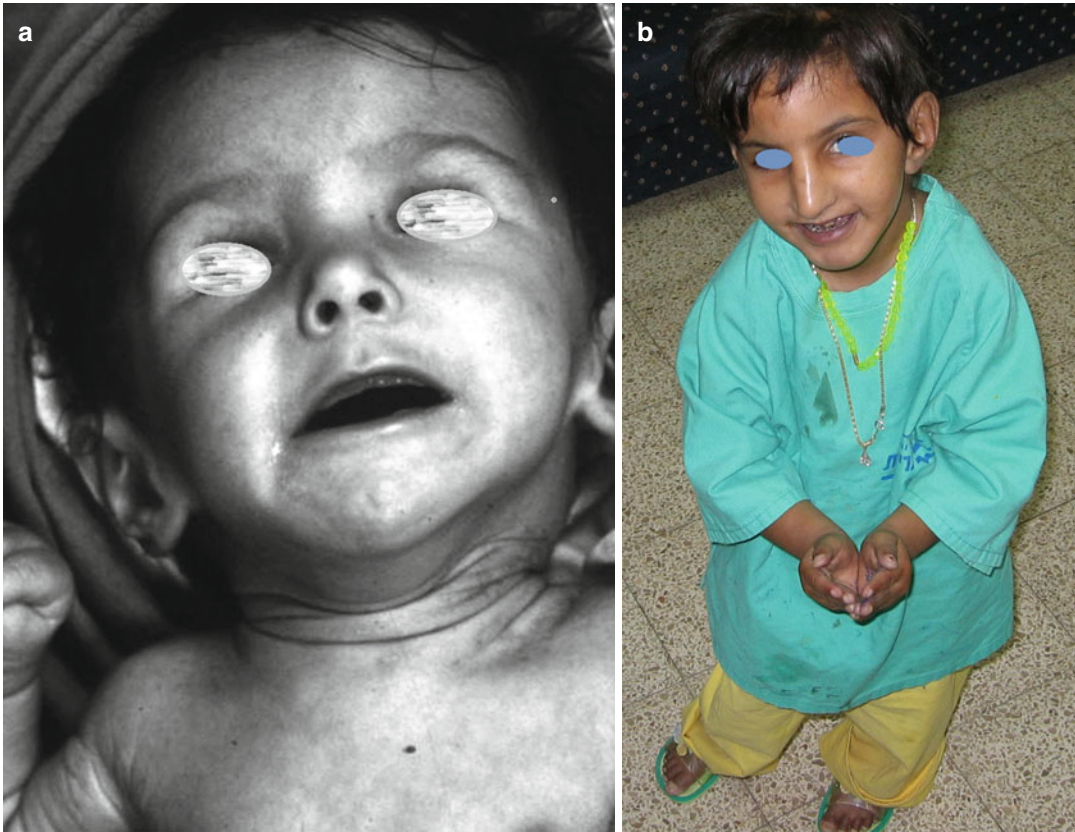


Fig. 20.1 HRD syndrome. (a) Facial dysmorphism. Note prominent forehead, small deep-set eyes, and depressed nasal bridge (Reproduced with permission from

Hershkovitz et al. [7]) (b) A 14 years old patient with severe growth retardation and lack of pubertal signs

20.2.3 Biochemical and Radiological Findings

Hypocalcemia and hyperphosphatemia due to congenital permanent hypoparathyroidism are the hallmarks of HRD syndrome. Serum parathyroid hormone (PTH) levels are undetectable to very low in most of the patients [5, 6, 8, 10, 16–20]. Surprisingly, high PTH levels have been reported in two patients [17, 18]. Postmortem examinations of HRD patients have been seldom reported, but the absence of the parathyroid glands had been documented in one of the author's patient. Increased liver transaminases have been found in some patients without progression to chronic liver disease [17].

Partial growth hormone deficiency (GH <10 ng/ml) has been found following stimulation tests in

several patients [10, 17, 21–23]. Low serum IGF-I concentrations were found in all patients investigated in two studies [10, 22]. Normal immunoglobulin levels were found in all but one of the patients tested [7]. Normal T-cell responses to mitogens were observed in about ten patients studied [5, 16, 23], but reduced numbers of all T-cells subclasses were found in five patients reported by Richardson and Kirk 1990 [17]. Chemotactic migration, random migration, and phagocytosis of PMN from HRD patients were significantly lower than in PMN from healthy controls. Functional hyposplenism has been demonstrated in most of the studied patients [10].

Delayed bone age and osteopenia are common findings [17, 23], while medullary stenosis of the long bones, a common finding in the KCS syndrome, is infrequently observed in HRD patients

[8, 9]. Cranial MRI showed severe hypoplasia of the anterior pituitary and corpus callosum, with decreased white matter bulk in one study [22].

20.2.4 Diagnosis

The clinical signs of severe growth and mental retardation, typical dysmorphism, and congenital hypoparathyroidism are highly suggestive of the HRD syndrome, especially in Arab patients. The HRD syndrome should be differentiated from the KCS (see Table 20.1), the CHARGE association (coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies) and DiGeorge's syndrome.

20.2.5 Therapy

Early recognition and therapy of hypocalcemia is important. Humanized milk formulas containing low phosphorous, supplements with calcium salts, and administration of vitamin D analogs are effective in keeping serum calcium at the required low normal range. Hypercalciuria, which may cause nephrocalcinosis, should be treated by thiazides. Recombinant human PTH(1–34) may offer an advantage in the treatment of these patients, but it has not been tried on HRD patients. Since the recognition of the susceptibility of patients with HRD to serious bacterial infections, we recommend on daily prophylactic antibiotic therapy and prudent vaccination against pneumococci.

Table 20.1 Comparison between HRD/Sanjad-Sakati and Kenny-Caffey syndromes

| Feature | HRD/Sanjad-Sakati syndrome | Kenny-Caffey syndrome |
|------------------------------|--|--|
| Mode of inheritance | Autosomal recessive | Autosomal dominant |
| Ethnicity | Mostly Arabs | Pan ethnic |
| Growth | IUGR in most patients Extreme short stature | IUGR in less than 50 % Short stature |
| Mental development | Mental retardation | Normal mentality in most of the patients |
| Dysmorphic features | Microcephaly Deep-set eyes Micrognathia Dental anomalies Small hands and feet | Relative macrocephaly Delayed closure of the anterior fontanel Deep-set eyes Micrognathia Dental anomalies |
| Hypoparathyroidism | Universal Neonatal or early infantile onset | Common with variable age of onset |
| Other clinical complications | Susceptibility to severe bacterial infections High mortality Probably infertile | None in most patients Fertility has been reported in females only. |
| Laboratory findings | Hyposplenism Impaired PMN chemotaxis and phagocytosis Normal cell-mediated immunity Growth hormone deficiency | Hypomagnesemia Impaired T-cell function |
| Radiologic findings | Severe hypoplasia of anterior pituitary and corpus callosum. | Medullary stenosis and cortical thickening of the long bones |
| Molecular abnormality | Homozygous mutation in the tubulin-specific chaperone E gene (TBCE) | Heterozygous mutation in the FAM111A gene |

20.3 KCS/OCS

KCS is a rare disorder, and sporadic cases have been reported from various parts of the world in different ethnic groups [1, 24–30].

20.3.1 Clinical Phenotype

Larsen, reviewing 20 previously described patients, has reported short stature in most of them. The attained adult height was between 121 and 155 cm, in contrast to the extreme dwarfism observed in adult HRD patients (around 100 cm). Intrauterine growth restriction was observed in less than half of the patients unlike the 95–97 % presence of IUGR in HRD syndrome [26].

Most of the patients exhibited delayed closure of the anterior fontanel [26, 30]. The patients had typical facial appearance, including prominent forehead, deep-set eyes, beaked nose, thin upper lip, micrognathia, and external ear abnormalities [26, 28–30]. Microcephaly is a common feature in the HRD syndrome, while normal head circumference or even macrocephaly characterizes patients with KCS [12, 27, 28].

Most reported KCS patients had normal mental development [12, 26, 29, 30]. Ophthalmic abnormalities are common in patients with KCS. The various findings include reduced visual acuity; hyperopia; myopia; small corneal diameter; elevated, blurred margin of the optic nerve; tortuous blood vessels; glaucoma; and strabismus [12, 26, 29, 30]. Defective dentition, accompanied by oligodontia and severe carries is very common in the KCS [12, 26, 29].

Mother-to-son transmission was reported in the original description of the disorder [1] and some other women with KCS were reported to have unaffected children [26]. No cases of paternity were reported among males with the KCS. Micropenis, hypospadias, and small testes have been reported in some patients [26, 28, 29]. Except for hypocalcemia most of the patients with KCS do not suffer from life-threatening complications.

20.3.2 Biochemical and Radiological Findings

Hypoparathyroidism is often found among KCS patients but is not a universal phenomenon as it is in the HRD syndrome. The age of onset of hypocalcemia is variable, ranging from the neonatal period to adulthood [12, 26]. Interestingly, some patients have hypomagnesemia [30]. Absence of the parathyroid glands has been reported in a patient with the KCS [31]. Medullary stenosis with cortical thickening of the long bones is a hallmark feature of KCS, while infrequently described in HRD patients [2, 26, 27, 29, 30]. Delayed bone age is a common finding [26].

20.3.3 Osteocraniostenosis (OCS)

Osteocraniostenosis was delineated by Verloes et al. [3]. It has been recently recognized as allelic to the KCS. Osteocraniostenosis was lethal in the few reported cases in the neonatal period, but survival to 21 months of age has been reported [29, 32]. It is characterized by IUGR; spleen hypoplasia or aplasia; a striking bone dysplasia consisting of thin ribs and long, thin, straight, or curved tubular diaphyses, flared metaphyses, hypoplastic distal phalanges, and drumstick metacarpals; marked cranial hypomineralization, leading to wide fontanels and cloverleaf head shape; and intrauterine fractures [3, 4]. The facial appearance was variable, from mild anomaly to a striking combination of midface hypoplasia, short, upturned nose, short philtrum, and inverted V-shaped mouth. Hypocalcemia and hypoparathyroidism are recognized in surviving neonates [29].

20.4 Molecular Genetics and Pathogenesis of HRD and KCS/OCS Syndromes

20.4.1 HRD

20.4.1.1 Tubulin Folding and Assembly

Microtubules are polymerized from α/β -tubulin heterodimers [33]. Newly synthesized α - and β -tubulin polypeptides undergo a sequence of

folding steps catalyzed by chaperones. Initially, the tubulins are associated with the hexameric prefoldin complex that passes them on to the cytosolic chaperonin complex [34], and they are then further processed by tubulin-folding cofactors (the standard now seems to be TBCA-E or just cofactor) [35, 36]. In vitro folding assays suggest that in mammals α -tubulin binds to cofactors B and E, whereas β -tubulin binds to cofactors A and D. α -tubulin/TBCE and β -tubulin/TBCD are bound by TBCC, forming a super complex from which α/β -tubulin heterodimers are released by GTP hydrolysis of β -tubulin. The small G-protein Arl2 appears to play a regulatory role, binding to and sequestering cofactor D [37]. Budding yeast mutants lacking tubulin cofactor homologs have only conditional effects and are normally not lethal ([38] and references therein). In contrast, null mutations in fission yeast *TFC* genes cause abnormal cell shapes and mostly result in lethality [39–43]. Genetic analysis of tubulin cofactor function in fission yeast has led to a different model of tubulin folding: an essential pathway of α -tubulin folding involves, successively, cofactors B, E, and D, with the Arl2 homolog acting upstream of D, whereas a nonessential pathway of β -tubulin folding involves cofactor A passing β -tubulin on to cofactor D to associate with α -tubulin [40–42]. Results in the plant *Arabidopsis* suggest that cofactors C–E and Arl2 are stringently required for microtubule formation, similar to the requirements for in vitro assays using purified mammalian cofactors [44]. *PFI*, the ortholog of the vertebrate *Tbce* in *Arabidopsis*, is necessary for continuous microtubule organization, mitotic division, and cytokinesis but do not mediate cell cycle progression [45, 46]. Vesicle trafficking to the division plane during cytokinesis but not to the cell surface during interphase was impaired [45].

Coincident with the discovery that mutations in *TBCE* cause recessive HRD, a missense mutation in murine *Tbce* (W527G) inherited in homozygosity was described in a mouse model of peripheral motor neuropathy, *pnn* [47, 48]. The W527G mutation destabilized the chaperone, resulting in diminished protein levels [48]. The

original *pnn* mice had low birth weight, decreased brain size, and hypogonadism, reminiscent of the human trait, but no hypoparathyroidism was noted and no report of continued low weight or size [49]. Since mice that lack parathyroid glands have PTH serum levels identical to those of wild-type mice, as do parathyroidectomized wild-type animals, are viable and fertile and have only a mildly abnormal bone phenotype [50], it is possible that the parathyroid defect has been overlooked. Although many embryonic cell lines enabling creation of a mouse in which *TBCE* is deleted are available [51], there are no reports of such a mouse model. In agreement with no existence of a mouse null for *TBCE* *Drosophila*, *tbce* nulls are embryonic lethal, requiring tissue-specific knockdown for the study of the effects of absence of *TBCE*. Tissue-specific knockdown and overexpression of *tbce* in neuromusculature resulted in disrupted and increased microtubules, respectively. Alterations in *TBCE* expression also affected neuromuscular synapses [52]. No other phenotype was observed in *Drosophila*.

As in mice and *Drosophila*, complete absence of *TBCE* function was not reported in human. The common homozygous mutation: a deletion of four amino acid deletion (del52-55) leaves tubulin GAP-enhancing activities (unpublished results), while the cryptic out-of-frame translational initiation caused by a heterozygous mutation of the *TBCE* gene, rescues tubulin formation in a compound heterozygous HRD patient carrying a second nonsense mutation [53].

Our studies on the effect of a homozygous four amino acid deletion of *TBCE*(del52-55) in patients' cells demonstrated that lymphoblastoid cells showed aberrant microtubule polarity and the microtubules arrays are not centered on centrosomes in disease cells. This effect was more pronounced in fibroblasts than in keratinocytes. Thus, the cellular phenotype may be tissue specific despite ubiquitous transcriptional *TBCE* expression. Organization of the Golgi complex in patients' fibroblasts was diffuse and surrounded the nucleus, in contrast to its compact and localization near one side of the nucleus in control cells. The distribution of late endosomes which, like the Golgi complex, is microtubule dependent

revealed an abnormally diffuse pattern in the whole cell in contrast to the predominantly perinuclear pattern observed in control cells [54].

The specific absence of parathyroid glands, with accompanying normal development of the thyroid and other branchial pouch derivatives, is an intriguing and unexpected aspect of a derangement in tubulin physiology [55]. The interplay between the known factors involved in the parathyroid development and the *TBCE* and/or microtubule cytoskeleton remains to be elucidated by future studies.

20.4.2 KCS/OC

The mutation causing the dominant form of the *KCS2* was recently identified by the power of exome sequencing. Interestingly, the same missense mutation, R569H in the gene *FAM111A* (NM_001142519.1), occurring de novo was detected in heterozygosity in five patients studied by a Swiss group [29] and in four Japanese patients [30]. *FAM111A* encodes a previously uncharacterized protein consisting of 611 amino acids. The carboxy-terminal half of the protein has homology to trypsin-like peptidases, and the catalytic triad specific to such peptidases is conserved [56], but its possible proteolytic activity was not studied. Similarly to *TBCE*, the transcriptional expression of *FAM111A* is ubiquitous according to the human protein atlas [57]. It is expressed in the parathyroid gland and bone, but the expression levels are similar to those in other tissues. A recent report showed that *FAM111A* functions as a host range restriction factor and is required for viral replication and gene expression by specifically interacting with Simian Virus 40 large T antigen (LT) [56]. In addition, *FAM111A* mRNA and protein levels have been shown to be regulated in a cell cycle-dependent manner with the lowest expression during the G0 or quiescent phase and peak expression during the G2/M phase [56]. Another recent report revealed that variants in the region including *FAM111A* and *FAM111B* were associated with prostate cancer [58]. However, the clinical course of disease in *KCS2* patients

revealed neither increased viral infections nor carcinogenesis up to early adulthood. Again, in similarity to *TBCE*, the de novo mutation (R569H) would not significantly affect the function of *FAM111A* as suggested by in silico analyses. Additionally, the mutant *FAM111A* mRNA was expressed similarly to the wild type in peripheral blood cells. This raises the question of how this mutation causes *KCS2*. One hypothesis is that this mutation does not cause loss of function of the protein but rather modulates its peptidase activity for a particular target peptide in a mutant-specific way. Another possibility is that *FAM111A* functions with some physiological partner(s) and the disease occurs as a result of specific modulation of this putative network. In agreement with the suggestion that the amino acid changed by the mutation interacts with other partners is exposed on the protein surface as indicated by molecular modeling. Since other LT-interacting proteins, such as RB, p53, FBXW7, and CDC73, are involved in gene transcription and are bona fide tumor suppressors, *FAM111A* is localized in the nucleus and its expression is cell-cycle dependent; it was suggested that *FAM111A* might be involved in the regulation of gene transcription [29]. *KCS1* and *KCS2* share distinctive phenotypic features.

FAM111A is important for skeletal development, the dysmorphic features, and primary hypoparathyroidism but not for intrauterine growth and mental development.

The autosomal recessive Kenny-Caffey syndrome [59] (AR-KCS; MIM244460), HRD [16] (MIM241410), or Sanjad-Sakati syndrome (SSS) [5] is caused by mutations in the tubulin-specific chaperone E gene, *TBCE* (Fig. 20.2) [54]. Presently, the only known function for *TBCE* is to serve as a chaperone of α -tubulin.

Conclusion

The partly phenotypic overlap between *KCS* and *HRD* syndromes might indicate a functional relationship between *FAM111A* and *TBCE*. It is tempting to speculate that the two proteins might be interlinked in a common regulatory pathway. It could also be that one of the candidate partner proteins of *FAM111A*

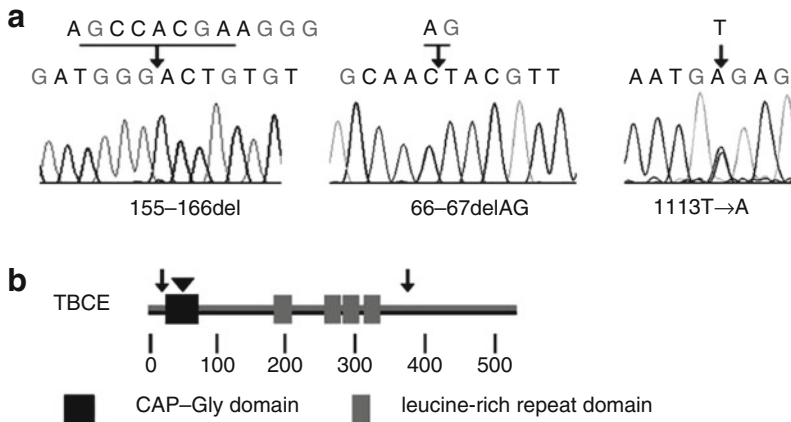


Fig. 20.2 *TBCE* mutation analysis. (a) Sequence traces from affected individuals. All affected Middle Eastern subjects evaluated were homozygous with respect to the 155–166del mutation, and a Belgian individual with HRD was compoundly heterozygous with respect to 66–67delAG and 1113 T→A (mutation positions are relative to +1 at the initiation ATG). The mutated sequences are shown above the electropherograms, with the positions of dele-

tion or point mutations indicated by arrows and wild-type sequences given above the arrows. (b) Mutations in *TBCE* relative to the CAP-Gly and leucine-rich repeat domains. Positions of truncating mutations (Val23fs48X, Cys371X) are indicated by arrows, and the in-frame deletion (del52–55) is indicated by an arrowhead. Approximate amino acid positions are indicated below the cartoon (Reproduced with permission from Hershkovitz et al. [7])

is *TBCE*. The identification of mutations in these two genes as causative of KCS and HRD syndromes provides novel tools for the study of the pathophysiological mechanisms of these pathologies.

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