The presence of a familial disease among royal members of 18th dynasty of the new kingdom who ruled in Egypt from the mid-16th to the early 11th centuries BC has been established, largely prompted by the bizarre body shape of Akhenaten (the iconoclastic pharaoh of this dynasty) and his family, as demonstrated in statues and artwork. It had been thought previously that this was an expression of a revolutionised artistic style that followed radical reforms by Akhenaten of Egyptian society, but recent studies on mummies confirmed the presence of a constellation of corresponding pathologies. Several illnesses have been suggested to solve this enigma; we propose Loeys-Dietz syndrome as a probable diagnosis for this genetic affliction within the royal family.

Loeys-Dietz syndrome (LDS) is an autosomal dominant inherited disorder of connective tissue that has been recently introduced as an important cause of familial aortic aneurysm. LDS is caused by heterozygous mutations in genes encoding transforming growth factor β receptors 1 and 2 (TGFBR1 and TGFBR2). Patients affected with this syndrome are characterised by specific clinical features not clear. The feminised appearance of Akhenaten was excluded by the pelvic bone shape. The study group also found evidence of Plasmodium falciparum infection in the mummies. They concluded that none of the presumed hypotheses about the familial disease was correct, but found a constellation of deformities in Tutankhamun and his family. They did not propose any specific diagnoses or syndromes that could explain repeated deformities and pathologies in the members of royal family.

We hypothesise that the 18th dynasty royal family of the new Egyptian kingdom might have suffered from Loeys-Dietz syndrome, which might solve the medical mystery of the 18th dynasty. We emphasise that previous theories regarding the royal family familial illness mainly originated from reliefs, sculptures and limited medical facts obtained from limited studies. Our postulation is based on pathological findings in a recent study on mummies.
without striking facial abnormalities are seen in type II LDS.

Skin manifestations

myopathic face.

high anterior hair line; hypoplastic supraorbital margins; and a

crowding.

are retrognathia, blue sclerae, highly arched palate and dental

and trigonocephaly is common.

Craniosynostosis in the forms of dolichocephaly, bracycephaly

eyes) and a cleft palate or a bifid uvula are characteristic of LDS.

prominent in type II LDS patients. Hypertelorism (wide-set

eyes) is less common in this syndrome.

Dolichostenomelia (long limbs, leading to an increase in the arm

ratio) is less common in this syndrome.

other craniofacial dysmorphology. In patients with LDS type 2, skin

abnormalities are prominent features, and they do not have major

craniofacial involvement. Diagnosis is confirmed by detection of

mutations in TGFBR1 and TGFBR2.6

LDS is characterised by 4 major categories of clinical features:

1. Cardiovascular system. The most important finding in

LDS patients is dilatation of the aorta at the level of the Valsalva

sinuses, while aneurysm of the ascending or descending aorta

is seen less frequently. Congenital heart diseases such as atrial

septal defect (ASD), bicuspid aortic valve and patent ductus

arteriosus (PDA) are also more prevalent in LDS patients.7 Mitral

d valve prolapse and regurgitation along with cardiomyopathy

secondary to coronary artery dysplasia have been reported in

these patients.8

2. Skeletal findings. Joint hyperlaxity, arachnodactyly, pectus

excavatum or carinatum, scoliosis and contractures of the feet

(talipes equinovarus) are seen in LDS patients, and are also

common in Marfan syndrome. Pes planus, spine instability

and spondylolisthesis are recurrent findings in this syndrome.6

Dolichostenomelia (long limbs, leading to an increase in the arm

span-to-height ratio and a decrease in the upper-to-lower segment

ratio) is less common in this syndrome.6

3. Facial dysmorphology. Abnormal facial features are

prominent in type II LDS patients. Hypertelorism (wide-set

eyes) and a cleft palate or a bifid uvula are characteristic of LDS.

Craniosynostosis in the forms of dolichocephaly, brachycephaly

and trigonocephaly is common.6 Other craniofacial features

are retrognathia, blue sclerae, highly arched palate and dental

crowding.8 In type II LDS patients, facial findings are not so

severe and include a tall, broad forehead; frontal bossing; a

high anterior hair line; hypoplastic supraorbital margins; and a

myopathic face.11

4. Skin findings. These patients have velvety and translucent skin

with easy bruising and delayed wound healing. Skin manifestations

without striking facial abnormalities are seen in type II LDS.6

Akhenaten: The apostate

Amenhotep IV, the strangest ruler of ancient Egypt, was the son

of Amenhotep III and his queen Tiye. Some Egyptologists have

considered him a criminally mad ruler, while others have admired

him as a great reformist. His radical and extensive reform of Egyptian

society influenced religion, art, politics and other aspects of Egyptian

life. He is probably the first and the only pharaoh who practised

monotheism and tried to propagate this doctrine in and around

the Egyptian territories. He changed his name to Akhenaten (he

who serves Aten) and began to replace images of Amon (the great

Egyptian god) and other statues of gods and goddesses with his

single god named Aten, whose image was a sun disk. When conflict

increased, he left Thebes (the ancient capital of Egypt) and moved to

a new region in Middle Egypt, near Amarna village in modern Egypt,

and built a new capital named Akhet-Aten (Horizons of the sun disk).

He forbade depicting any other god or goddess, and destroyed or

seized their temples, which led to a religious war within the country.

Amarna artistic style

Sculptors in ancient Egypt showed kings and royalty in an idealised

fashion, and did not show physical defects. But in the new art style

that was a consequence of Akhenaten’s reforms, artists were free to

depict reality, such as an unattractive body, and even exaggerate these

features (as cartoonists tend to do).12 Therefore, it is possible that

Akhenaten really had an elongated face, underdeveloped thorax with

gynaecomastia and a prominent abdomen, and current statues and

sculptures are exaggerated forms of this unusual appearance.

Is Akhenaten’s religion a key to his disease?

Aten was the name of Akhenaten’s god that was reflected as a sun

disk. The sun was the symbol of Aten, whose temples had no roof

so that sunshine could play directly onto the altar. Akhenaten spent

time worshiping Aten, naked, in sunlight, to receive his bliss (Fig. 3).

One might also think that Akhenaten had an illusion that was alleviated by exposure to sunshine.

Can Loewy-Dietz syndrome justify the pathologies in Akhenaten and his family?

Different syndromes and diseases have been hypothesised to explain

a probable underlying disease in Akhenaten, Tutankhamun and

Fig. 3. Akhenaten’s family worshipping Aten (the sun image).
18th dynasty royalty. Marfan syndrome was suspected owing to the marfanoid features of Akhenaten and his family in statues. Recently, however, Marfan syndrome and similar diseases were excluded as none of the royalty fulfilled Marfan criteria. However, the latter study confirmed the presence of a group of pathologies in royal members of the 18th dynasty. LDS is a clinical continuum and should be suspected in patients with Marfan-like features not fulfilling Ghent criteria.15

Hawass et al. found repeatedly in the royal family, not only clinical features of LDS, but also scoliosis, club foot, incisional hernia, cleft palate, retrorhynatism, dental crowding and highly arched palate.4 No mummy showed dolichostenomalia, whilst in LDS, in contrast to Marfan syndrome, dolichostenomalia is not frequent. According to their findings, Akhenaten and Tutankhamun had brachycephaly, which can occur in LDS patients (Table 1).

Cardiac pathologies in LDS, such as ASD and cardiomyopathy, are prevalent, and both can induce pulmonary hypertension and right-sided heart failure.14 Patients with right-sided heart failure will develop liver congestion that can progress to cirrhosis over time. Patients with right-sided heart failure even without cirrhosis may have ascites, gynaecomastia and peripheral oedema. Therefore the unusual shape of Akhenaten in statues and paintings of a prominent abdomen and large breasts could be due to ascites and gynaecomastia, which are seen in cirrhosis secondary to right-sided heart failure in the context of LDS; this can be a reason for gynaecomastia if proved to be present.

Vitamin D deficiency has been described in patients with LDS.15 Diffuse musculoskeletal pain and even myopathy, chronic fatigue and depression can occur in patients with hypovitaminosis D.16 Exposure to sunlight is the main source of vitamin D, and treatment of vitamin D deficiency with sun exposure has been reported.17 TGFBR gene polymorphism is associated with bone mineral density and bone turnover, and osteopenia/osteoporosis may also occur in LDS.18 Furthermore, patients with LDS suffer from some skin manifestations as described above. TGF-β signalling pathway in the cells is initiated by binding of the ligand to the TGFBR2 and subsequent phosphorylation of TGFBR1. Activated TGFBR1/TGFBR2 complex mediates transcription of multiple genes via its downstream Smad signalling proteins. Mutations in TGFBR1/TGFBR2 as seen in LDS enhance the TGF-β signalling pathway and increase transcription of multiple downstream genes and proteins.19 Quan et al. showed that solar ultraviolet irradiation reduces collagen in human skin which is mediated by blocking TGFBR2/Smad signalling.20 This finding was also confirmed in other studies.

The foregoing findings may provide reasons to justify the association between Akhenaten’s disease and his religious reforms. Akhenaten might have suffered from chronic musculoskeletal pain owing to vitamin D deficiency and osteoporosis secondary to LDS, and sunshine exposure might have relieved his pain. Furthermore, the diseased TGF-β signalling pathway was down-regulated by his sunshine worshiping of Aten. In this way, he indeed received physical and spiritual beneficence from his god, which strengthened his faith in Aten despite considerable political, religious and social pressures.

Both types of LDS are generally believed to be two sides of a clinical spectrum. Therefore, an affected individual could have no striking facial appearance. Developmental delay has been reported to occur in a small minority of patients with LDS, but most have normal intellectual ability. Only 25% of these patients have an affected parent, and 75% of patients developed de novo mutations. So it would not be unusual if Akhenaten, with the more severe form of the syndrome, had apparently normal parents or children. Another possibility is that Tutankhamun was more severely affected than his father Akhenaten, which may be explained by homozygocity for the TGFBR mutation, because of the consanguinity.

The main cause of early mortality (mean age 26.1 years) in LDS is dissection of a dilated aorta. Although confirmation of aortic aneurysm in the remaining mummies is not possible, neither Akhenaten and Tutankhamun nor other relatives were more than 50 years old, as determined by DNA studies. Lastly: a related syndrome with aortic aneurysm and early-onset osteoarthritis was recently found to be caused by mutations in the SMAD3 gene. This gene encodes some proteins that are involved in the TGFβ pathway. Patients with this condition also presented with bifid uvula/clert palate, hypertelorism and skin abnormalities.20

**Conclusion**

Based on the foregoing findings, the possibility of Loey-Dietz syndrome or an abnormality in the SMAD3 gene should be considered as the underlying disease of this Egyptian royal family. Mutations in **TGFBR1** and **TGFBR2** or SMAD3 from DNA of remaining mummies can clarify one of the mysteries of Egyptian history.


