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1 **Traboulsi syndrome caused by mutations in *ASPH*: An autosomal recessive**  
2 **disorder with overlapping features of Marfan syndrome**

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10

11 **Abstract**

12 Traboulsi syndrome, otherwise known as facial dysmorphism, lens dislocation,  
13 anterior-segment abnormalities and spontaneous filtering blebs, is an autosomal  
14 recessive condition associated with characteristic ocular features including dislocated  
15 crystalline lenses, anterior segment abnormalities and in some individuals, non-  
16 traumatic conjunctival cysts. There is a distinctive facial appearance which includes  
17 flattened malar region with convex nasal ridge. Alterations in the aspartate beta-  
18 hydroxylase (*ASPH*) gene are known to be the cause of the condition.

19 We report seven further individuals from six unrelated families with characteristic  
20 ocular and facial features. Five individuals had aortic root dilatation, with childhood  
21 onset in some, and one undergoing aortic root repair aged 47 years for severe aortic  
22 regurgitation and aortic root dilatation. Interestingly, inguinal hernias were commonly  
23 reported. Although some skeletal features were seen, these were not consistent. One  
24 of the patients had mild deficiency of factor VII on clotting studies. The *ASPH* protein  
25 hydroxylates specific asparagine- and aspartate-residues in epidermal growth  
26 factor (EGF)-domain containing proteins including coagulation factors and associated  
27 genes including *FBN1*. We propose this as an explanation for the overlap in clinical

28 features with Marfan syndrome and conclude that Traboulsi syndrome is an important  
29 differential diagnosis. We strongly recommend echocardiography surveillance for  
30 patients with Traboulsi syndrome.

31

## 32 **Introduction**

33 Traboulsi syndrome, otherwise known as facial dysmorphism, lens dislocation,  
34 anterior-segment abnormalities and spontaneous filtering blebs (MIM: [601522](#)) is a  
35 rare genetic condition for which the genetic basis was described in 2014 (Patel et al.,  
36 2014). Until now, there have been limited cases reported in the literature. The  
37 condition was originally reported in a multiply consanguineous family from the Druze  
38 sect in Lebanon in 1995 (Shawaf et al., 1995). All affected individuals had ectopia  
39 lentis and facial dysmorphism. Progressive scleral thinning with spontaneous filtering  
40 blebs, peripheral irido-corneal adhesions, and glaucoma were also seen. Four  
41 individuals from an unrelated family from the same ethnic background were  
42 subsequently also reported. The family history was highly suggestive of an autosomal  
43 recessive inheritance pattern for this condition (Haddad et al., 2001). All affected  
44 individuals had lens dislocation, cataracts ± anterior chamber anomalies and a  
45 distinctive facial appearance with a convex nasal ridge, long face and dental crowding.  
46 Mansour et al. (2013) reported a 16 year old girl with similar features.

47 In 2014, Patel et al., confirmed the genetic basis for Traboulsi syndrome Patel et al.  
48 (2014). They identified two different homozygous mutations in the aspartate-β-  
49 hydroxylase gene (*ASPH*) in three families. Two of the families had been reported  
50 previously and carried the same mutation (Mansour et al., 2013; Haddad et al., 2001).  
51 They confirmed that *ASPH* is strongly expressed in the snout, limbs and eye (in  
52 particular the developing lens) of mouse embryos, which would provide an explanation  
53 for the clinical features associated with this condition. Since then further patients have  
54 been identified incidentally through exome sequencing studies in consanguineous  
55 families with congenital anomalies of the kidneys and urinary tract in a patient with  
56 lens dislocation and vesico-ureteric reflux (VUR) (Vivante et al., 2017), and through  
57 ophthalmic clinics (Siggs et al., 2019; Chandran et al., 2019; Kulkarni et al., 2019;  
58 Shanmugam et al., 2020; Van Hoorde et al., 2021; Senthil et al., 2021). These patients  
59 presented with characteristic facial and ocular features. These reports mainly focussed  
60 on the ocular phenotype and management. However, it is interesting to note that two  
61 of the patients reported by Senthil et al. (2021) had additional cardiac findings  
62 including one with mitral valve prolapse and mild mitral regurgitation and one with

63 severe aortic regurgitation requiring surgery that subsequently died of problems  
64 related to this. A 34 year old male was also reported by Lei et al. 2020. He had been  
65 previously diagnosed with Marfan syndrome in view of tall stature, thin body habitus  
66 and bilateral ectopia lentis. He presented to the respiratory clinic with lung bullae,  
67 recurrent left-sided spontaneous pneumothorax and was also found to have a  
68 ventricular septal defect. A molecular diagnosis of Traboulsi syndrome was later  
69 confirmed, and the authors questioned whether the additional features could be  
70 related to this diagnosis.

71 Herein, we report seven further individuals from six apparently unrelated families  
72 identified through genetics clinics with confirmed molecular diagnoses and features  
73 consistent with Traboulsi syndrome. These patients exhibited additional cardiac,  
74 musculoskeletal and haematological features thus expanding the phenotypic  
75 spectrum of Traboulsi syndrome and demonstrating considerable overlap with Marfan  
76 syndrome.

## 77 **Section snippets**

### 78 **Patient selection and methods**

79 All patients were referred to their regional clinical genetics service with ectopia lentis  
80 or anterior chamber anomalies, for investigation of an underlying syndromic genetic  
81 cause. Patient 1 was investigated by exome sequencing as part of the DDD study  
82 (Firth and Wright 2011) using the molecular methods and bioinformatics pipeline for  
83 exome analysis previously described (Wright et al., 2015). Confirmation of  
84 the *ASPH* variant was done using Sanger sequencing (Fig. 1B). Patients 2 & 3 had

### 85 **Clinical findings**

86 Fig. 1 shows the pedigrees of the 7 patients and their phenotypic data are summarized  
87 in Table 1, with further detailed clinical information provided as online supplementary  
88 file 1. The parents of 6 of the 7 patients were consanguineous and two patients had  
89 relatives with a similar phenotype, whose parents were also consanguineous. All of  
90 the patients presented initially with ocular features. This ranged from the incidental  
91 finding of lens dislocation in patient 4 whilst wishing to undergo

### 92 **Discussion**

93 Traboulsi syndrome is a rare autosomal recessive disorder with a primary eye  
94 phenotype of ectopia lentis, shallow anterior chambers with variable degree of angle  
95 closure by iridocorneal adhesions, patchy iris atrophy and spontaneous filtering  
96 conjunctival blebs, associated with facial dysmorphism (Shawaf S et al. Ophthalmic

97 Genet 1995; Haddad R et al. Am J Med Genet 2001; Mansour AM et al. Case Rep  
98 Ophthalmol 2013). The typical dysmorphic facial features of Traboulsi syndrome  
99 include

#### 100 **CRedit authorship contribution statement**

101 **Gabriela Jones:** Conceptualization, Writing – original draft, Data curation, Writing –  
102 review & editing, Funding acquisition. **Katie Johnson:** Writing – original draft, Data  
103 curation, Writing – review & editing, Funding acquisition. **Jacqueline Eason:** Writing  
104 – review & editing, Funding acquisition. **Mark Hamilton:** Writing – review & editing,  
105 Funding acquisition. **Deborah Osio:** Writing – review & editing. **Farah**  
106 **Kanani:** Writing – review & editing, Funding acquisition. **Julia Baptista:** Methodology

107

#### 108 **Declaration of competing interest**

109 The authors have no conflicts of interest to declare.

110

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119

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