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

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Abstract

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

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

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

Introduction

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

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

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

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

Section snippets

Patient selection and methods

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

Clinical findings

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

Discussion

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

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

CRediT authorship contribution statement

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

Declaration of competing interest

The authors have no conflicts of interest to declare.

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References

Hugo H Abarca Barriga, Nathaly Caballero, Milana Trubnykova, Maria Del Carmen Castro-Mujica, Jorge E La Serna-Infantes, Flor Vasquez, Raoul C Hennekam. **A novel ASPH variant extends the phenotype of Shawaf-Traboulsi syndrome**. Am. J. Med. Genet. A, 11 (2018), pp. 2494-2500

P. Chandran, P. Chermakani, P. Venkataraman, S.P. Thilagar, G.V. Raman. **A novel 5 bp homozygous deletion mutation in ASPH gene associates with Traboulsi syndrome**. Ophthalmic Genet., 40 (2019), pp. 185-187

J.E. Dinchuk, R.J. Focht, J.A. Kelley, N.L. Henderson, N.I. Zolotarjova, R. Wynn, N.T. Neff, J. Link, R.M. Huber, T.C. Burn, M.J. Rupar, M.R. Cunningham, B.H. Selling, J. Ma, A.A. Stern, G.F. Hollis, R.B. Stein, P.A. Friedman **Absence of post-translational aspartyl beta-hydroxylation of epidermal growth factor domains in mice leads to developmental defects and an increased incidence of intestinal neoplasia**. J. Biol. Chem., 277 (2002), pp. 12970-12977

H.V. Firth, C.F. Wright, DDD Study. **The deciphering developmental disorders (DDD) study**. Dev. Med. Child Neurol., 53 (2011), pp. 702-703

R. Haddad, S. Uwuydat, R. Dakroub, E.I. Traboulsi. **Confirmation of the autosomal recessive syndrome of ectopia lentis and distinctive craniofacial appearance**. Am. J. Med. Genet., 99 (2001), pp. 185-189

Browser, W.J. Kent, C.W. Sugnet, T.S. Furey, K.M. Roskin, T.H. Pringle, A.M. Zahler, D. Haussler. **The human genome browser at UCSC**. Genome Res., 12 (2002), pp. 996-1006

N. Kulkarni, I.C. Lloyd, J. Ashworth, S. Biswas, G.C.M. Black, N.I.H.R. BioResource Consortium, J. Clayton-Smith. **Traboulsi syndrome due to ASPH mutation: an under-recognised cause of ectopia lentis**. Clin. Dysmorphol., 28 (2019), pp. 184-189

C. Lei, T. Guo, S. Ding, L. Liao, H. Peng, Z. Tan, H. Luo. **Whole-exome sequencing identified a novel homozygous ASPH frameshift variant causing Traboulsi syndrome in a Chinese family**. Mol. Genet. Genomic Med., 9 (2020), p. e1553

B.L. Loeys, H.C. Dietz, A.C. Braverman, B.L. Callewert, J. De Backer, R.B. Devereux, Y. Hilhorst-Hofstee, G. Jondeau, L. Faivre, D.M. Milewicz, R.E. Pyeritz, P.D. Sponseller, P. Wordsworth, A.M. De Paepe. **The revised Ghent nosology for Marfan syndrome**. J. Med. Genet., 47 (2010), pp. 476-485

A.M. Mansour, M.H. Younis, R.H. Dakroub. **Anterior segment imaging and treatment of a case with syndrome of ectopia lentis, spontaneous filtering blebs, and craniofacial dysmorphism**. Case Rep. Ophthal., 4 (2013), pp. 84-90

N. Patel, A.O. Khan, A. Mansour, J.Y. Mohamed, A. Al Assiri, R. Haddad, X. Jia, Y. Xiong, A. Megarbane, E.I. Traboulsi, F.S. Alkuraya. **Mutations in ASPH cause facial dysmorphism, lens dislocation, anterior-segment abnormalities, and spontaneous filtering blebs, or Traboulsi syndrome**. Am. J. Hum. Genet., 94 (2014), pp. 755-759

I. Pfeffer, L. Brewitz, T. Krojer, S.A. Jensen, G.T. Kochan, N.J. Kershaw, L.A. Hewitson Ks< McNeill, H. Kramer, M. Munzel, R.J. Hopkinson, U. Oppermann, P.A. Handford, M.A. DcDonough, C.J. Schofield. **Aspartate/asparagine-β-hydroxylase crystal**

structures reveal an unexpected epidermal growth factor-like domain substrate disulfide pattern. Nat. Commun., 28 (2019), p. 4901

S. Senthil, S. Sharma, S. Vishwakarma, I. Kaur. **A novel mutation in the aspartate beta-hydroxylase (ASPH) gene is associated with a rare form of Traboulsi syndrome**. Ophthalmic Genet., 42 (2021), pp. 28-34

P.M. Shanmugam, P. Sagar, V.K. Konana, S. Simakurthy, R. Ramanjulu, A. Sheema r, K.C.D. Mishra. **Recurrent unintentional filtering blebs after vitrectomy**. Indian J. Ophthalmol., 68 (2020), pp. 660-662

S. Shawaf, B. Noureddin, A. Khouri, E. Traboulsi. **A family with a syndrome of ectopia lentis, spontaneous filtering blebs, and craniofacial dysmorphism**. Ophthalmic Genet., 16 (1995), pp. 163-169

O. Siggs, E. Souzeau, J.E. Craig. **Loss of ciliary zonule protein hydroxylation and lens stability as a predicted consequence of biallelic ASPH variation**. Ophthalmic Genet., 40 (2019), pp. 12-16

T. Van Hoorde, F. Nerinckx, E. Kreps, D. Roels, P. Huyghe, M. Van Heetvelde, H. Verdin, E. De Baere, I. Balikova, B.P. Leroy. **Expanding the clinical spectrum and management of Traboulsi syndrome: report on two siblings homozygous for a novel pathogenic variant in ASPH**.Ophthalmic Genet., 42 (2021), pp. 493-499

A. Vivante, D.-Y. Hwang, S. Kuhl, J. Chen, S. Shril, J. Schulz, A. van der Ven, G. Daouk, N.A. Soliman, A.S. Kumar, P. Senguttuvan, E.O. Kehinde, V. Tasic, F. Hildebrandt. **Exome sequencing discerns syndromes in patients from consanguineous families with congenital anomalies of the kidneys and urinary tract**. J. Am. Soc. Nephrol., 27 (2017), pp. 69-75

C.F. Wright, T.W. Fitzgerald, W.D. Jones, S. Clayton, J.F. McRae, M. van Kogelenberg, D.A. King, K. Ambridge, D.M. Barrett, T. Bayzetinova, A.P. Bevan, E. Bragin, E.A. Chatzimichali, S. Gribble, P. Jones, N. Krishnappa, L.E. Mason, R. Mille r, K.I. Morley, V. Parthiban, E. Prigmore, D. Rajan, A. Sifrim, G.J. Swaminathan, A.R. Tivey, A. Middleton, M. Parker, N.P. Carter, J.C. Barrett, M.E. Hurles, D.R. FitzPatri ck, H.V. Firth, DDD study. **Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data** Lancet, 385 (2015), pp. 1305-1314