***Supplementary material***

*Chmielewski P, Ponińska JK, Michalak E, et al. Cardiovascular involvement and prognosis in Loeys-Dietz syndrome. Kardiol Pol. 2023.*



**Table S1.** Identified variants in LDS-related genes, their types and pathogenicity according to American College of Medical Genetics and Genomics (Varsome 11.4).

| Gene | Transcript | Protein change | Type of variant | Pathogenicity |
|---|---|---|---|---|
| *TGFBR1* | NM_004612.4:c.605C>T | p.Ala202Val | missense | likely pathogenic |
| *TGFBR1* | NM_004612.4:c.844T>C | p.Tyr282His | missense | likely pathogenic |
| *TGFBR1* | NM_004612.4:c.934G>A | p.Gly312Ser | missense | pathogenic |
| *TGFBR1* | NM_004612.4:c.1042T>C [a] | p.Cys348Arg | missense | likely pathogenic |
| *TGFBR1* | NM_004612.4:c.1315G>A[a,b] | p.Glu439Lys | missense | unknown significance |
| *TGFBR2* | NM_003242.6:c.1144A>T[a] | p.Ser382Cys | missense | likely pathogenic |
| *TGFBR2* | NM_003242.6: c.1379G>A | p.Arg460His | missense | pathogenic |
| *TGFBR2* | NM_003242.6:c.1579G>A | p.Ala527Thr | missense | likely pathogenic |
| *TGFBR2* | NM_003242.6:c.1589C>T | p.Thr530Ile | missense | pathogenic |
| *SMAD3* | NM_005902.4:c.(206+1_207-1)_(658+1_659-1)del [a] | p.? | deletion of exons 2-5 | pathogenic |
| *SMAD3* | NM_005902.4:c.277C>T | p.Arg93Ter | nonsense | pathogenic |
| *SMAD3* | NM_005902.4:c.532+1G>T[a] | p.? | splicing | likely pathogenic |
| *SMAD3* | NM_005902.4:c.868A>T | p.Ile290Phe | missense | likely pathogenic |
| *SMAD3* | NM_005902.4:c.925_926del[a] | p.Ser309Ter | nonsense | likely pathogenic |
| *TGFB2* | NM_003238.3:c.194dupC | p.Glu66Glyfs Ter68 | frameshift | pathogenic |
| *TGFB2* | NM_001135599.3:c.430+3G>A[a,b] | p.? | splicing | unknown significance |
| *TGFB2* | NM_003238.3:c.1052C>T | p.Pro351Leu | missense | likely pathogenic[c] |

Legend: [a] novel; [b] excluded from the study; [c] classification taking into account phenotype concordance and co-segregation in the family; LDS, Loeys-Dietz syndrome; *TGFBR1*, transforming growth factor beta receptor 1 gene; *TGFBR2*, transforming growth factor beta receptor 2 gene, *SMAD3*, SMAD family member 3 gene; *TGFB2*, transforming growth factor-beta 2 gene

**Table S2.** Phenotypic characteristics at the time of genetic inquest according to LDS type

| | ***TGFBR1*** **n = 7** | ***TGFBR2*** **n = 15** | ***SMAD3*** **n = 7** | ***TGFB2*** **n = 5** | ***P*-value** |
|---|---|---|---|---|---|
| Age, years | 34 (25-54) | 29 (17-42) | 41 (19-47) | 34 (27-37) | 0.83 |
| Male sex | 5 (71%) | 6 (40%) | 6 (86%) | 2 (40%) | 0.16 |
| Probands | 4 (57%) | 4 (26%) | 5 (71%) | 2 (40%) | 0.23 |
| Cardiovascular involvement | 6 (86%) | 13 (87%) | 5 (71%) | 3 (60%) | 0.57 |
| Thoracic aortic dilatation | 5 (71%) | 12 (80%) | 5 (71%) | 2 (40%) | 0.42 |
| Aortic root, mm | 44 (34-47) | 38 (36-44) | 44 (37-48) | 33 (33-39) | 0.36 |
| Ascending aorta, mm | 33 (27-42) | 31 (27-41) | 40 (29- 61) | 26 (25-28) | 0.21 |
| Peripheral artery aneurysm (n=31) | 1 (17%) | 5 (36%) | 1 (17%) | 0 | 0.32 |
| Aortic TI (n= 25) | 2.07 (0.17) | 2.11 (0.31) | 2.09 (0.60) | 1.97 (0.25) | 0.86 |
| Aortic TI >1.95 | 4 (80%) | 7 (70%) | 3 (50%) | 3 (75%) | 0.73 |
| Vertebral TI (n=14) | 1.49 (0.33) | 1.55 (0.14) | 1.37 | 1.34 (0.19) | 0.48 |
| Internal carotid TI (n=14) | 1.17 (0.50) | 1.40 (0.13) | 1.12 | 1.23 (0.15) | 0.06 |
| Marfan systemic score, points | 1 (1-2) | 3 (2-6) | 0 (0-7) | 4 (3-6) | 0.11 |
| Marfan systemic score ≥7 points | 1 (14%) | 3 (20%) | 2 (29%) | 0 | 0.64 |
| Craniofacial anomalies | 3 (43%) | 9 (60%) | 2 (29%) | 2 (40%) | 0.56 |
| Skeletal findings | 3 (43%) | 14 (93%) | 4 (57%) | 5 (100%) | **0.02**[a] |
| Thorax deformities | 1 (14%) | 10 (67%) | 4 (57%) | 5 (100%) | **0.03**[b] |

| | | | | | |
|---|---|---|---|---|---|
| Cutaneous manifestation | 4 (57%) | 11 (73%) | 3 (43%) | 2 (40%) | 0.44 |
| Skin striae | 3 (43%) | 5 (33%) | 1 (14%) | 1 (20%) | 0.65 |
| Hypertension | 3 (43%) | 7 (47%) | 3 (43%) | 0 | 0.16 |
| Smoking | 2 (29%) | 3 (20%) | 2 (29%) | 0 | 0.62 |

Legend: Number of subjects is expressed as n (%). Numerical variables are shown as mean (SD) or median and quartiles (IQR). TI, tortuosity index; [a] *TGFBR2* or *TGFB2* vs *TGFBR1* or *SMAD3*: p=0.004; [b] *TGFB2* vs *TGFBR1* or *TGFBR2* or *SMAD3*: *P* = 0.06

**Table S3.** Aortic events in the study cohort of patients with Loeys-Dietz syndrome

| Subject No. | Sex | Family status | Genetic variant | Age at event | Event description |
|---|---|---|---|---|---|
| #1 | M | Proband | *TGFBR1*:p.Ala202Val | 18 | elective Bentall surgery |
| | | | | 27 | elective Bentall re-surgery with aortic arch replacement due to graft bending and stenosis |
| #2 | F | Proband | *TGFBR1*:p.p.Tyr282His | 46 | A-type aortic dissection treated with supracoronary prosthesis implantation |
| | | | | 53 | elective Bentall surgery with aortic arch replacement |
| | | | | 54 | elective open surgical repair of descending aortic aneurysm |
| #3 | M | Proband | *TGFBR1*:p.Gly312Ser | 46 | A-type aortic dissection treated with implantation of supracoronary and arch prostheses |
| | | | | 49 | elective thoracic endovascular aortic repair |
| #4 | M | Proband | *TGFBR1*:p.Cys348Arg | 34 | elective David surgery |

| | | | | | |
|---|---|---|---|---|---|
| | | | | 37 | B-type aortic dissection treated with endovascular aortic stentgraft implantation |
| #5 | M | Proband | *TGFBR2*:p.Ser382Cys | 28 | A-type aortic dissection treated with Bentall surgery with hemiarch replacement |
| #6 | F | Proband | *TGFBR2*:p.Arg460His | 16 | A-type aortic dissection treated with David surgery |
| #7 | F | Relative | *TGFBR2*:p.Arg460His | 59 | A-type aortic dissection detected in its chronic phase, treated conservatively |
| #8 | M | Relative | *TGFBR2*:p.Arg460His | 36 | sudden death in a patient qualified for thoracic aortic aneurysm repair |
| #9 | M | Relative | *TGFBR2*:p.Arg460His | 32 | elective David surgery |
| #10 | F | Relative | *TGFBR2*:p.Arg460His | 27 | elective David surgery |
| #11 | F | Proband | *TGFBR2*:p.Ala527Thr | 40 | A-type aortic dissection treated with supracoronary prosthesis implantation |
| | | | | 42 | elective Bentall surgery with aortic arch replacement |
| | | | | 43 | elective open surgical repair of descending aortic aneurysm |
| #12 | F | Proband | *TGFBR2*:p.Thr530Ile | 7 | elective supracoronary prosthesis implantation |
| | | | | 11 | elective Bentall surgery |
| | | | | 15 | elective surgery for pseudoaneurysm at the aortic prosthesis suture |
| #13 | M | Proband | *SMAD3*: deletion of exons 2-5 | 57 | A-type aortic dissection treated with supracoronary prosthesis implantation |

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|---|---|---|---|---|---|
| | | | | 58 | elective Bentall surgery with aortic arch replacement |
| | | | | 59 | elective open surgical repair of descending aortic aneurysm |
| #14 | M | Proband | *SMAD3*:c.c.532+1G>T | 42 | A-type aortic dissection treated with supracoronary prosthesis implantation |
| #15 | M | Proband | *SMAD3*:p.Ile290Phe | 36 | A-type aortic dissection treated with supracoronary prosthesis implantation |
| #16 | F | Proband | *SMAD3*:p.Ser309Ter | 27 | elective supracoronary prosthesis implantation |
| | | | | 31 | elective Bentall surgery |

Legend: F, female; M, male; *TGFBR1*, transforming growth factor beta receptor 1 gene; *TGFBR2*, transforming growth factor beta receptor 2 gene; *SMAD3*, SMAD family member 3 gene