

Supplementary Table S1: Pathogenicity classification of all *SMAD2/3* and *TGFB2/3* variants described in this paper according to the ACMG guidelines. Evidence is provided by the criteria defined by Richards et al., 2015

| Gene | c-notation | p-notation | Effect | Evidence |
|--------------|---------------------------|------------------|-------------------------|----------------------------------|
| <i>SMAD2</i> | c.954T>A | p.Asn318Lys | Likely pathogenic (V) | PM2, PP3, PP2, PP1-M |
| <i>SMAD2</i> | c.1082A>C | p.Asn361Thr | Likely pathogenic (V) | PM2, PP3, PP2, PP1-M |
| <i>SMAD2</i> | c.1163A>G | p.Gln388Arg | Likely pathogenic (III) | PP3, PS3, PP2 |
| <i>SMAD2</i> | c.1190C>A | p.Ser397Tyr | Likely pathogenic (II) | PM2, PP3, PP2, PP1-S |
| <i>SMAD2</i> | c.1346T>C | p.Leu449Ser | Likely pathogenic (V) | PM2, PP3, PP2, PP1-M |
| <i>SMAD2</i> | c.1369G>A | p.Gly457Arg | Likely pathogenic (II) | PM2, PP3, PP2, PS2 |
| <i>SMAD2</i> | c.1400C>T | p.Ser467Leu | VUS | PM2, PP3, PP2 |
| <i>SMAD3</i> | c.2T>C | p.Met1Thr | Pathogenic (Ic) | PM2, PVS1, PP2 |
| <i>SMAD3</i> | c.3G>A | p.Met1Ile | Pathogenic (Ic) | PM2, PVS1, PP2 |
| <i>SMAD3</i> | c.221G>A | p.Arg74Gln | Likely pathogenic (V) | PM2, PM5, PP2, PP1, PP4 |
| <i>SMAD3</i> | c.266G>A | p.Cys89Tyr | Pathogenic (IIIb) | PM2, PP2, PP1-S, PP1-M, PP1, PP4 |
| <i>SMAD3</i> | c.269G>A | p.Arg90His | Likely pathogenic (V) | PM2, PP2, PP1, PP1-M, PP4 |
| <i>SMAD3</i> | c.281G>T | p.Trp94Leu | VUS | PM2, PP2, PP1, PP4 |
| <i>SMAD3</i> | c.290T>G | p.Leu97Arg | VUS | PM2, PP2, PP4 |
| <i>SMAD3</i> | c.300_301insAGGGCCGGCAGGC | p.His101Argfs*14 | Pathogenic (Ic) | PM2, PVS1, PP4 |
| <i>SMAD3</i> | c.313delG | p.Ala105Profs*11 | Pathogenic (Ic) | PM2, PVS1, PP4 |
| <i>SMAD3</i> | c.335C>T | p.Ala112Val | Likely pathogenic (V) | PM2, PP2, PP1-M, PP4 |
| <i>SMAD3</i> | c.370C>A | p.Pro124Thr | VUS | PM2, PP2, PP5, PP4 |
| <i>SMAD3</i> | c.374A>G | p.Tyr125Cys | Likely pathogenic (V) | PM2, PM5, PP2, PP4 |
| <i>SMAD3</i> | c.374A>C | p.Tyr125Ser | Likely pathogenic (V) | PM2, PM5, PP2, PP4 |
| <i>SMAD3</i> | c.401-6G>A | p.Val134Aspfs*33 | Pathogenic (Ia) | PM2, PVS1, PS1, PP4 |
| <i>SMAD3</i> | c.401_405dup | p.Pro136Phefs*52 | Pathogenic (Ic) | PM2, PVS1, PP4 |
| <i>SMAD3</i> | c.455delC | p.Pro152Hisfs*34 | Pathogenic (Ic) | PM2, PVS1, PP4 |
| <i>SMAD3</i> | c.511G>T | p.Glu171* | Pathogenic (Ic) | PM2, PVS1, PP4 |
| <i>SMAD3</i> | c.532+1G>C | | Pathogenic (Ic) | PM2, PVS1, PP4 |
| <i>SMAD3</i> | c.539_540insC | p.Pro180Thrfs*7 | Pathogenic (Ia) | PM2, PVS1, PS1, PP4 |
| <i>SMAD3</i> | c.546delT | p.Gly183Alafs*3 | Pathogenic (Ic) | PM2, PVS1, PP4 |
| <i>SMAD3</i> | c.584_585insTC | p.Gln195Hisfs*3 | Pathogenic (Ib) | PP4, PVS1, PM2, PM4 |
| <i>SMAD3</i> | c.652delA | p.Asn218Thrfs*23 | Pathogenic (Ib) | PM2, PVS1, PM4, PP1-M |
| <i>SMAD3</i> | c.668delC | p.Pro223Glnfs*18 | Pathogenic (Ic) | PM2, PVS1, PP4 |
| <i>SMAD3</i> | c.715G>A | p.Glu239Lys | Pathogenic (II) | PM2, PS1, PP2, PP1-S |
| <i>SMAD3</i> | c.728G>C | p.Arg243Pro | Likely pathogenic (II) | PM2, PP2, PP3, PP1-S, PP4 |
| <i>SMAD3</i> | c.733G>A | p.Gly245Arg | Likely pathogenic (VI) | PM2, PP3, PP5, PP4, PP2 |
| <i>SMAD3</i> | c.741_742delAT | p.Thr247Profs*61 | Pathogenic (Ic) | PM2, PVS1, PP4 |
| <i>SMAD3</i> | c.742T>C | p.Phe248Leu | Likely pathogenic (VI) | PM2, PP3, PP2, PP4, PP5 |
| <i>SMAD3</i> | c.748G>A | p.Ala250Thr | Likely pathogenic (II) | PM2, PP3, PP2, PP1-S |
| <i>SMAD3</i> | c.762delC | p.Met255* | Pathogenic (Id) | PM2, PVS1, PP4, PP5 |
| <i>SMAD3</i> | c.772G>C | p.Asp258His | Likely pathogenic (VI) | PM2, PP2, PP5, PP4, PP3 |
| <i>SMAD3</i> | c.782C>T | p.Thr261Ile | Pathogenic (IIIc) | PM2, PP3, PP2, PP5, PP1-S, PP4 |
| <i>SMAD3</i> | c.788C>T | p.Pro263Leu | VUS | PM2, PP3, PP2, PP4 |
| <i>SMAD3</i> | c.797C>A | p.Ser266* | Pathogenic (Ic) | PM2, PVS1, PP4 |
| <i>SMAD3</i> | c.803G>T | p.Arg268Leu | Likely pathogenic (II) | PM2, PS1, PP3, PP2, PP4 |
| <i>SMAD3</i> | c.836G>A | p.Arg279Lys | Likely pathogenic (VI) | PM2, PP3, PP2, PP1, PP4 |
| <i>SMAD3</i> | c.859C>T | p.Arg287Trp | Likely pathogenic (II) | PM2, PS1, PP3, PP2, PP4 |
| <i>SMAD3</i> | c.860G>A | p.Arg287Gln | Likely pathogenic (II) | PM2, PS1, PM5, PP3 |
| <i>SMAD3</i> | c.861delG | p.Arg288Aspfs*53 | Pathogenic (Id) | PM2, PVS1, PP3, PP2 |
| <i>SMAD3</i> | c.862_871+1dupAGACACATCGG | p.Arg292Aspfs*53 | Pathogenic (Ic) | PM2, PVS1, PP3 |
| <i>SMAD3</i> | c.887T>C | p.Leu296Pro | Likely pathogenic (V) | PM2, PP3, PP2, PP1-M |
| <i>SMAD3</i> | c.988A>G | p.Thr330Ala | Likely pathogenic (VI) | PM2, PP3, PP1, PP4, PP2 |
| <i>SMAD3</i> | c.1009+1G>A | | Pathogenic (Ic) | PM2, PVS1, PP3 |
| <i>SMAD3</i> | c.1009+2T>A | | Pathogenic (Ic) | PM2, PVS1, PP3 |
| <i>SMAD3</i> | c.1045G>C | p.Ala349Pro | Likely pathogenic (V) | PM2, PP3, PP2, PP1-M |
| <i>SMAD3</i> | c.1080dupT | p.Glu361* | Pathogenic (Ia) | PM2, PVS1, PP3, PS1 |
| <i>SMAD3</i> | c.1081G>T | p.Glu361* | Pathogenic (Ia) | PM2, PVS1, PS1 |
| <i>SMAD3</i> | c.1091A>G | p.Tyr364Cys | Likely pathogenic (VI) | PM2, PP3, PP2, PP1, PP4 |

| | | | | |
|--------------|----------------------------------------------------------------------------|--------------------|-------------------------|--------------------------------|
| SMAD3 | c.1102C>T | p.Arg368* | Pathogenic (Ia) | PM2, PVS1, PS1 |
| SMAD3 | c.1141G>C | p.Gly381Arg | Likely pathogenic (V) | PM2, PP3, PP2, PP1-M |
| SMAD3 | c.1155-2A>G | | Pathogenic (Ic) | PM2, PVS1, PP3 |
| SMAD3 | c.1170_1179del | p.Ser391Alafs*7 | Pathogenic (Ic) | PM2, PVS1, PP3 |
| SMAD3 | c.1179_1180dupC | p.Cys394Leufs*4 | Pathogenic (Ic) | PM2, PP3, PVS1 |
| SMAD3 | c.1185G>C | p.Trp395Cys | VUS | PM2, PP3, PP2 |
| SMAD3 | c.1199T>C | p.Leu400Pro | VUS | PM2, PP3, PP2 |
| SMAD3 | c.1208C>T | p.Pro403Leu | Likely pathogenic (II) | PM2, PP3, PP2, PS2 |
| SMAD3 | c.1222G>C | p.Asp408His | Likely pathogenic (V) | PM2, PM5, PP3, PP2 |
| SMAD3 | c.1224C>A | p.Asp408Glu | Likely pathogenic (V) | PM2, PP3, PM5, PP2 |
| SMAD3 | c.1243G>C | p.Gly415Arg | Likely pathogenic (V) | PM2, PP3, PP2, PP1-M |
| SMAD3 | c.1247C>T | p.Ser416Phe | Likely pathogenic (V) | PM2, PP3, PP2, PP1-M |
| SMAD3 | c.1259G>A | p.Arg420His | VUS | PP3, PP2 |
| SMAD3 | c.1265C>T | p.Ser422Phe | Likely pathogenic (II) | PM2, PP3, PP2, PP1-S |
| SMAD3 | c.1267A>G | p.Ser423Gly | Likely pathogenic (V) | PM2, PP3, PP2, PP1-M |
| SMAD3 | c.1268G>A | p.Ser423Asn | Likely pathogenic (II) | PM2, PP3, PP2, PS2 |
| SMAD3 | c.1274C>T | p.Ser425Phe | VUS | PM2, PP3, PP2 |
| SMAD3 | Deletion from exon 2 onwards: Chr2.hg19: g.(67,408,242)_(67,603,013)del | | Pathogenic (Ic) | PVS1, PP3, PM2 |
| SMAD3 | Deletion 15q22.33 | | Pathogenic (Ic) | PM2, PVS1, PP3 |
| TGFB2 | c.236A>T | p.Gln79Leu | Likely pathogenic (VI) | PM2, PP3, PP2, PP1, PP4 |
| TGFB2 | c.244G>T | p.Ala82Ser | VUS | PM2, PP3, PP2, PP4 |
| TGFB2 | c.274G>T | p.Glu92* | Pathogenic (Ic) | PM2, PVS1, PP1 |
| TGFB2 | c.294_308delCTACGCCA AGGAGGT | p.Ala100_Tyr104del | Likely pathogenic (V) | PM2, PP3, PM4, PP1, PP4 |
| TGFB2 | c.297 >A | p.Tyr99* | Pathogenic (Id) | PM2, PVS1, PP3, PP1, PP4 |
| TGFB2 | c.304G>T | p.Glu102* | Pathogenic (Id) | PM2, PVS1, PP3, PP1, PP4 |
| TGFB2 | c.305_307delAGG | p.Glu102del | Likely pathogenic (V) | PM2, PM4, PP3, PP1, PP4 |
| TGFB2 | c.475C>T | p.Arg159* | Pathogenic (Ia) | PM2, PVS1, PS1, PP3, PP4 |
| TGFB2 | c.518_519 insT | p.Lys174Glufs*18 | Pathogenic (Id) | PM2, PVS1, PP3, PP4 |
| TGFB2 | c.577C>T | p.Arg193Trp | Likely pathogenic (III) | PP3, PP2, PP1-S, PP4 |
| TGFB2 | c.673G>T | p.Glu225* | Pathogenic (Id) | PM2, PVS1, PP3, PP4 |
| TGFB2 | c.687C>A | p.Cys229* | Pathogenic (Id) | PM2, PVS1, PP3, PP1, PP4 |
| TGFB2 | c.839-1G>A | p.Gly280Aspfs*41 | Pathogenic (Id) | PM2, PVS1, PP3, PP1, PP4 |
| TGFB2 | c.873_888dup | p.Asn297* | Pathogenic (Id) | PM2, PVS1, PP3, PP1, PP4 |
| TGFB2 | c.979C>T | p.Arg327Trp | Pathogenic (II) | PM2, PS1, PM5, PP3, PM1, PP1-S |
| TGFB2 | c.980G>A | p.Arg327Gln | Pathogenic (IIIa) | PM2, PS1, PM5, PP3, PM1, PP1 |
| TGFB2 | c.988C>T | p.Arg330Cys | Pathogenic (IIIb) | PM2, PS1, PP3, PM1, PP1 |
| TGFB2 | c.1000delG | p.Ala334Arg*fs25 | Pathogenic (Ic) | PM2, PVS1, PP3 |
| TGFB2 | c.1021_1025delTACAA | p.Tyr341Cysfs*25 | Pathogenic (Id) | PM2, PVS1, PP3, PP1 |
| TGFB2 | c.1042C>T | p.Arg348Cys | Likely pathogenic (V) | PM2, PP3, PP2, PP1-M |
| TGFB2 | c.1097C>A | p.Pro366His | Likely pathogenic (V) | PM2, PP3, PP2, PP1-M |
| TGFB2 | c.1106_1110delACAAT | p.Tyr369Cysfs*26 | Pathogenic (Ia) | PM2, PVS1, PP3, PP1-S |
| TGFB2 | c.1125delT | p.Gly376Glufs*17 | Pathogenic (Ic) | PM2, PVS1, PP3 |
| TGFB2 | c.1165dupA | p.Ser389Lysfs*8 | Pathogenic (Ib) | PM2, PVS1, PP3, PP1-M |
| TGFB2 | c.1170+1G>A | | Pathogenic (Id) | PM2, PVS1, PP3, PP1 |
| TGFB2 | c.1234G>C | p.Asp412His | VUS | PM2, PP3, PP2, PP4 |
| TGFB2 | Entire gene Chr1.hg19: g.(215,588,712)_(222,145,072)del | | Pathogenic (Ia) | PM2, PVS1, PS2 |
| TGFB2 | Entire gene Chr1.hg19: g.(216,672,181)_(220,202,575)del | | Pathogenic (Ia) | PM2, PVS1, PS2 |
| TGFB2 | Entire gene Chr1.hg19: g.(214,271,966)_(219,506,825)del | | Pathogenic (Ia) | PM2, PVS1, PP3, PS2 |
| TGFB2 | Entire gene Chr1.hg19: g.(215,713,272)_(218,899,968)del | | Pathogenic (Ia) | PM2, PVS1, PS2 |
| TGFB3 | c.106A>T | p.Lys36* | Pathogenic (Ic) | PM2, PVS1, PP3 |
| TGFB3 | c.437delT | p.Leu146Hisfs*68 | Pathogenic (Ic) | PM2, PVS1, PP3 |
| TGFB3 | c.704delA | p.Asn235Metfs*11 | Pathogenic (Id) | PM2, PVS1, PP3, PP1 |
| TGFB3 | c.754+2T>C | p.Glu216_Lys251del | Pathogenic (Id) | PM2, PVS1, PP3, PP1 |
| TGFB3 | c.787G>C | p.Asp263His | Likely pathogenic (II) | PM2, PP3, PS1, PP2, PP1 |

| | | | | |
|--------------|------------|------------------|------------------------|------------------------------|
| TGFB3 | c.796C>T | p.Arg266Cys | VUS | PM2, PP3, PP1 |
| TGFB3 | c.898C>T | p.Arg300Trp | Pathogenic (IIIb) | PM2, PP3, PS1, PP2, PP1-M |
| TGFB3 | c.899G>A | p.Arg300Gln | Pathogenic (IIIa) | PM2, PS1, PP3, PM5, PM1 |
| TGFB3 | c.898C>G | p.Arg300Gly | Likely pathogenic (IV) | PM2, PM5, PP3, PM1, PP2, PP1 |
| TGFB3 | c.965T>C | p.Ile322Thr | Likely pathogenic (V) | PP3, PP2, PM1, PP1-M, PP1 |
| TGFB3 | c.979G>T | p.Asp327Tyr | Likely pathogenic (V) | PP3, PP2, PM1, PP1-M, PP1 |
| TGFB3 | c.1095C>A | p.Tyr365* | Pathogenic (Ia) | PM2, PVS1, PP3, PM1, PS2 |
| TGFB3 | c.1157delT | p.Leu386Argfs*21 | Pathogenic (Ic) | PM2, PVS1, PP3 |
| TGFB3 | c.1202T>C | p.Leu401Pro | Likely pathogenic (IV) | PM2, PM5, PP3, PM1, PP2 |
| TGFB3 | c.1226G>A | p.Cys409Tyr | Pathogenic (IIIb) | PM2, PP3, PM1, PP2, PS3 |

VUS = Variant of Unknown Significance