

**Supplementary Table 1.** Summary of the literature reports regarding pathogenic variants (according to NM\_02470.4), height and vertebral fusion in *MYH3* related genetic syndromes  
Height z-scores reported here were recalculated using original data from the references using <https://www.who.int/childgrowth/standards/en/>.  
NA: not available, mo: months of age, y: years of age, \*several affected members from the same family are included

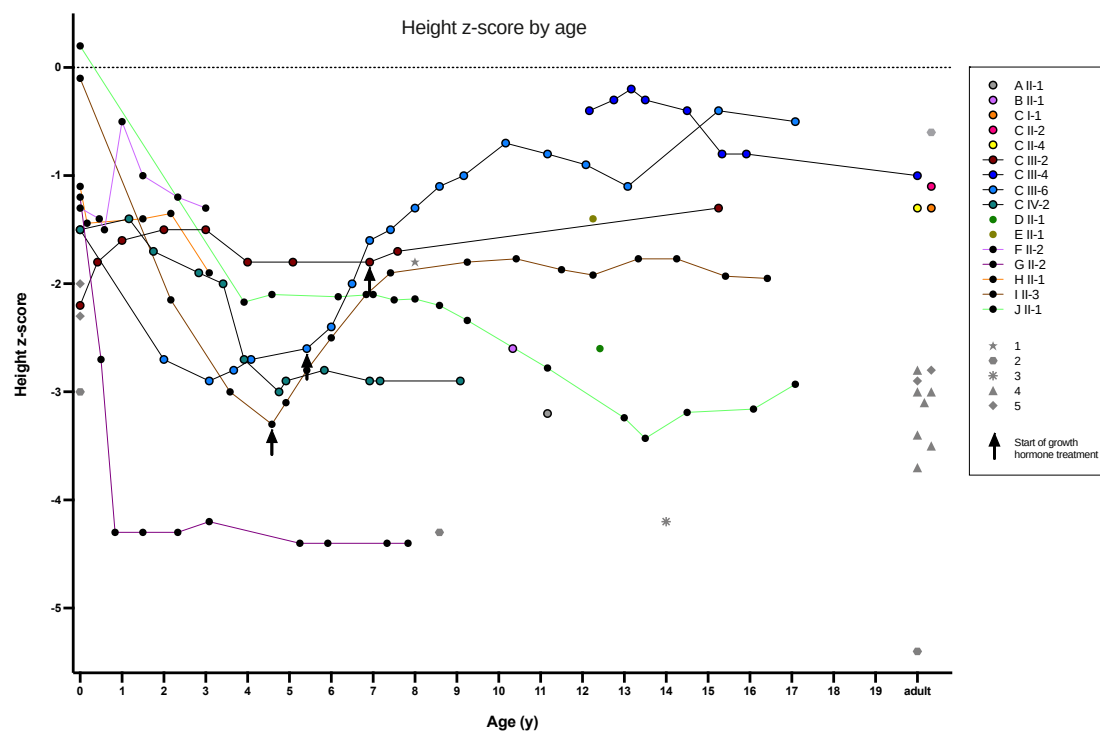
| Freeman-Sheldon syndrome, DA2A  |                                                                                                                                                                     |                                           |                                         |                                                                                                                      |                                                                                                             |                          |                          |
|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|
| Reference                       | Toydemir et al. 2006                                                                                                                                                | Tajsharghi et al. 2008                    | Al-Haggar et al. 2010                   | Beck et al. 2013                                                                                                     | Beck et al. 2014                                                                                            | Hague et al. 2015        | Ali et al. 2017          |
| Number of affected individuals* | 26                                                                                                                                                                  | 1                                         | 1                                       | 4                                                                                                                    | 15                                                                                                          | 1                        | 1                        |
| Pathogenic variants             | c.533C>T, p.(Thr178Ile)<br>c.1493A>G, p.(Glu498Gly)<br>c.1748A>C, p.(Tyr583Ser)<br>c.2014C>T, p.(Arg672Cys)<br>c.2015G>A, p.(Arg672His)<br>c.2474T>A, p.(Val825Asp) | c.533C>T, p.(Thr178Ile)                   | c.2014C>T, p.(Arg672Cys)                | c.737G>C, p.(Gly246Ala)<br>c.1019T>A, p.(Leu340Gln)<br>c.1397T>G, p.(Phe466Cys)<br>c.2503_2505delTTC, p. (Phe835del) | c.533C>T, p.(Thr178Ile)<br>c.1160A>G, p.(Tyr387Cys)<br>c.2014C>T, p.(Arg672Cys)<br>c.2015G>A, p.(Arg672His) | c.2015G>A, p.(Arg672His) | c.2015G>T, p.(Arg672Leu) |
| Height                          | NA                                                                                                                                                                  | Reported to have very short stature at 4y | Reported to have average height at 16mo | NA                                                                                                                   | NA                                                                                                          | NA                       | NA                       |
| Vertebral fusions               | NA                                                                                                                                                                  | NA                                        | NA                                      | NA                                                                                                                   | NA                                                                                                          | NA                       | NA                       |

| Sheldon-Hall syndrome, DA2B3    |                                                                                                                                                                                                                                                                                           |                                                                   |                          |                                                                                |                          |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|--------------------------|--------------------------------------------------------------------------------|--------------------------|
| Reference                       | Toydemir et al. 2006                                                                                                                                                                                                                                                                      | Tajsharghi et al. 2008                                            | Alvarado et al. 2011     | Beck et al. 2013                                                               | Xu et. Al 2018           |
| Number of affected individuals* | 12                                                                                                                                                                                                                                                                                        | 3                                                                 | 6                        | 4                                                                              | 7                        |
| Pathogenic variants             | c.533C>T, p.(Thr178Ile)<br>c.782C>T, p.(Ser261Phe)<br>c.875C>G, p.(Ser292Cys)<br>c.1123G>A, p.(Glu375Lys)<br>c.1549G>T, p.(Asp517Tyr)<br>c.2306G>T, p.(Gly769Val)<br>c.2512A>G, p.(Lys838Glu)<br>c.2521_2523delCTC, p.Leu841del<br>c.4865A>C, p.(Asp1622Ala)<br>c.4910C>T, p.(Ala1637Val) | c.700G>A, p.(Ala234Thr)<br>c.1385A>G, p.(Asp462Gly)               | c.1309T>A, p.(Phe437Ile) | c.551G>C, p.(Gly184Ala)<br>c.700G>A, p.(Ala234Thr)<br>c.1512G>T, p.(Lys504Asn) | c.1160A>G, p.(Tyr387Cys) |
| Height                          | NA                                                                                                                                                                                                                                                                                        | Two patients with short stature but no numerical values available | NA                       | NA                                                                             | Reported to be normal    |
| Vertebral fusions               | NA                                                                                                                                                                                                                                                                                        | Scoliosis but vertebral fusions not mentioned                     | NA                       | NA                                                                             | NA                       |

| Contractures, pterygia and spondylocarpotarsal fusion syndrome 1A (CPSF1A) |                                                                                                                                                      |                                                                                                                            |                                                                                             |                                                                         |                                                                                  |                                                                                                                         |                                                                                                                                                               |
|----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reference                                                                  | Chong et al. 2015                                                                                                                                    | Carapito et al. 2016                                                                                                       | Zieba et al. 2016                                                                           | Takagi et al. 2018                                                      | Scala et al. 2018                                                                | Cameron-Christie et al. 2018                                                                                            | Zhang et al. 2020                                                                                                                                             |
| Number of affected individuals*                                            | 8                                                                                                                                                    | 4                                                                                                                          | 3                                                                                           | 1                                                                       | 1                                                                                | 4                                                                                                                       | 8 (and one fetus)                                                                                                                                             |
| Pathogenic variants                                                        | c.727_729del, p.(Ser243del)<br>c.3214_3216dup, p.(Asn1072dup)<br>c.3224A>C, p.(Gln1075Pro)                                                           | c.998C>G, p.(Thr333Arg)<br>c.4031T>C, p.(Leu1344Pro)                                                                       | c.727-729delTCC, p.(Ser243del)<br>c.1934T>G, p.(Phe645Cys)<br>c. 2699del, p.(Leu900Trpfs*9) | c.5198_5205dup, p.(Met1736fs*10)                                        | c.859T>G, p.(Phe287Val)                                                          | c.1986_1990delTTTAA, p.(Asn662Lysfs*15)<br>c.1581+1G>A, splice<br>c.[721A>G;724_725delinsAA], p.(Asn241Asp);[Ser242Asn] | c.3044_3047delinsTCAAATTTGTT<br>p.(Glu1015_Asp1016delinsValAsnLeuPhe)                                                                                         |
| Height                                                                     | Six patients are reported with short stature, one with normal stature and no data for one patient was available. Numerical values were not provided. | Family 1:<br>II-2: -4.3 at birth, -5.4 adult<br>III-1: -4.3 at 8y7m<br>Family 2:<br>I-2: -0.7 adult<br>II-1: -4.0 at birth | Affected individuals reported to have short stature. Numerical values were not provided.    | -3.0 at birth<br>-3.7 at 8y1mo<br>-4.2 at 14y1mo                        | -1.9 at 8y6mo                                                                    | NA                                                                                                                      | Affected family members:<br>-3.4, 72y<br>-3.7, 70y<br>-3.5, 51y<br>-3.1, 29y<br>-3.0, 69y<br>-3.0, 48y<br>-2.8, 46y<br>Unaffected family members (n=4): 0-0.5 |
| Vertebral fusions                                                          | Multiple<br>Large intrafamilial variability                                                                                                          | Multiple<br>Large intrafamilial variability                                                                                | Multiple                                                                                    | Multiple<br>Upward protrusion of odontoid causing basilar invagination. | Multiple cervical, thoracal and lumbar partial fusion.<br>Lunotriquetral fusion. | Multiple                                                                                                                | Multiple                                                                                                                                                      |

| Contractures, pterygia, and spondylocarpotarsal fusion syndrome 1B |                                                                                                                                                                                                                                            |                                                                                                                                                                                                                          |
|--------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reference                                                          | Cameron-Christie et al. 2018                                                                                                                                                                                                               | Hakonen et al. 2020                                                                                                                                                                                                      |
| Number of affected individuals*                                    | 6                                                                                                                                                                                                                                          | 4                                                                                                                                                                                                                        |
| Pathogenic variants                                                | c.4647+1G>A, splice<br>c.-9+1G>A, splice<br><br>c.141T>G, p.(Tyr47*)<br>c.-9+1G>A, splice<br><br>c.1141+131_3256del, (6 kb intragenic deletion beginning within intron 12 and continuing to part way through exon 26)<br>c.-9+1G>A, splice | c.1053C>G, p.(Tyr351*)<br>c.-9+1G>A, splice<br><br>c.3102+5G>C, splice<br>c.-9+1G>A, splice                                                                                                                              |
| Height                                                             | NA                                                                                                                                                                                                                                         | Family A<br>pat 1: -1.1 at birth, -2.8 as adult<br>pat 2: -1.4 at birth, -2.9 adult,<br>Family B:<br>pat 1: -2.3 at birth<br>pat 2: -2.1 at birth.<br>Family B reported to have short stature at 6y and 3y respectively. |
| Vertebral fusions                                                  | Multiple                                                                                                                                                                                                                                   | Multiple                                                                                                                                                                                                                 |

**Supplementary Figure 1.** Growth of individuals with *MYH3*-associated skeletal fusion syndromes (#618469, #178110) in this and comparison with height/length data from previous studies. Please note variable short stature in patients with both autosomal dominant and autosomal recessive *MYH3*-associated skeletal fusion syndromes.



Height data were retrospectively collected from patients and journals and z-scores were calculated using WHO growth standards (<https://www.who.int/tools/child-growth-standards/software>). Note, that individuals with autosomal dominant and autosomal recessive *MYH3*-associated skeletal fusion syndromes have different and overlapping degrees of short stature. C:III-3, C:III-6 and I:2-1 were treated with growth hormone from age of 5 y 6 mo, 7 y and 4 y 8 mo respectively (indicated by black arrows).

Data from the individuals in the study with dominant and recessive *MYH3*-associated skeletal disorders, is shown using filled-in circles with black borders and filled-in circles without borders respectively. Data of the individuals with several data points are joined with a line, whereas data of the individuals where a single data point is available, is depicted only with filled-in symbols. Height z-scores of individuals from previous reports<sup>1-5</sup> are depicted in grey symbols and were calculated from data retrieved from the references listed below and numbered accordingly in grey in the sidebar.

- 1 Scala, M. *et al.* A novel pathogenic *MYH3* mutation in a child with Sheldon-Hall syndrome and vertebral fusions. *Am J Med Genet A* **176**, 663-667, doi:10.1002/ajmg.a.38593 (2018).
- 2 Carapito, R. *et al.* Protein-altering *MYH3* variants are associated with a spectrum of phenotypes extending to spondylarcarpotarsal synostosis syndrome. *Eur J Hum Genet* **24**, 1746-1751, doi:10.1038/ejhg.2016.84 (2016).
- 3 Takagi, M. *et al.* A novel truncating mutation in *MYH3* causes spondylarcarpotarsal synostosis syndrome with basilar invagination. *J Hum Genet* **63**, 1277-1281, doi:10.1038/s10038-018-0513-0 (2018).
- 4 Zhang, J. *et al.* Identification of a novel pathogenic variant in the *MYH3* gene in a five-generation family with CPSFS1A (Contractures, Pterygia, and Spondylarcarpotarsal Fusion Syndrome 1A). *Mol Genet Genomic Med* **8**, e1440, doi:10.1002/mgg3.1440 (2020).
- 5 Hakonen, A. H. *et al.* Recessive *MYH3* variants cause "Contractures, pterygia, and variable skeletal fusions syndrome 1B" mimicking Escobar variant multiple pterygium syndrome. *Am J Med Genet A* **182**, 2605-2610, doi:10.1002/ajmg.a.61836 (2020).

# **Complete author list of the Deciphering Disorders Involving Scoliosis and Comorbidities (DISCO) study**

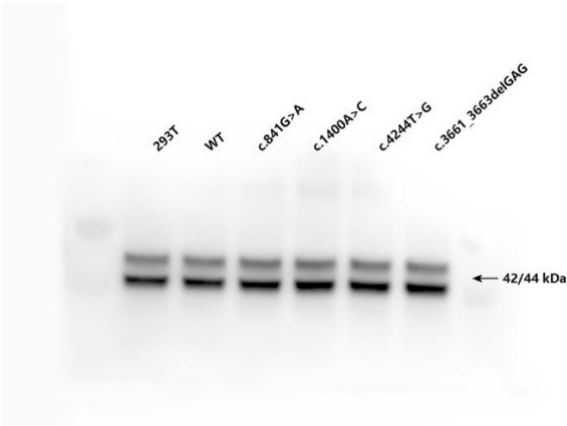
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Full gel image of Western blots in Figure 4a



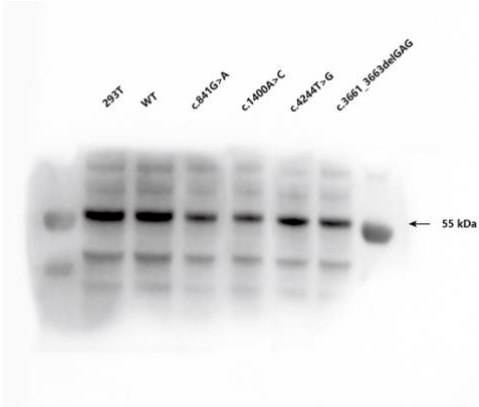
MYH3-EGFP



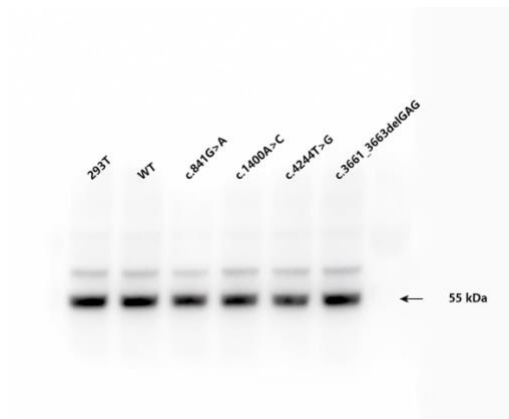
p-ERK1/2



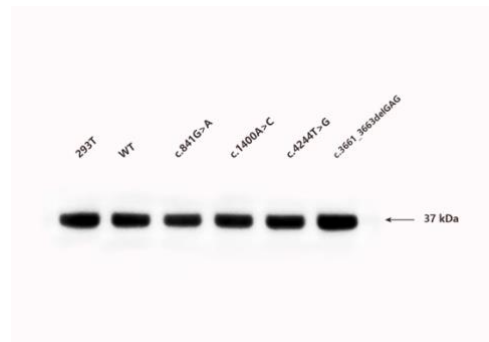
p-p38



p-SMAD3



SMAD3



GAPDH