| Gene Symbol | Gene Name                  | Transcript ID            | Transcript Variant | Protein Variant   | ACMG Classification | dbSNP         | 1000 Genomes Frequency | ExAC Frequency | gnomAD Frequency | PolyPhen2 Score | CADD score | Phylo p-value |
|-------------|----------------------------|--------------------------|---------------------|-------------------|---------------------|---------------|-------------------------|----------------|------------------|----------------|------------|---------------|
| PKP1        | Plakophilin-1             | NM_001005337.2; NM_000299.3 | c.846+1G>A          | Pathogenic        | 780771517          | N/A          | 0.001                   | 0              | N/A              | 25.3          | 9.53x10^-6 |               |
| KCNE3       | Potassium voltage gated channel subfamily E regulatory subunit 3 | NM_005472.4 | c.248G>A            | p.R83H            | Pathogenic         | 17215437     | 0.1                     | 0.297          | 0.293            | Benign         | 17.94      | N/A           |
| CPS1        | Carbamoyl-Phosphate Synthase 1 | NM_001122633.2; NM_001875.4; NM_001122634.3 | c.1054C>T; c.2425C>T; c.2407C>T | p.R809C; p.R803C; p.R352C | Likely Pathogenic | 201716417   | N/A                     | 0.001          | 0.001            | Probably Damaging | 35         | 1.25 x 10^-3 |
| GARS        | Glycyl-t-RNA Synthetase   | NM_001316772.1; NM_002047.3 | c.1009C>T; c.1171C>T | p.R337C; p.R391C  | Likely Pathogenic  | 370057212   | N/A                     | 0.003          | 0.003            | Benign         | 35         | 6.52 x 10^-4 |
| APTX        | Aprataxin                 | NM_001195250.1; NM_001195251.1; NM_001195249.1; NM_001195254.1; NR_036557.1; NR_036577.1; NR_036578.1; NR_036579.1; NR_036576.1; NM_001195249.1; NM_001195254.1; NR_036557.1 | p.L194M; p.L262M; p.L248M; p.L190M; p.L208M | Likely Pathogenic | 141195622  | N/A                     | 0.138          | 0.135            | Benign         | < 10       | N/A           |
| CRX         | Cone-Rod Homeobox         | NM_000554.5 | c.425A>G            | p.Y142C           | Likely Pathogenic  | 61748442     | 0.02                    | 0.041          | 0.051            | Probably Damaging | N/A        | N/A           |

**Supplementary Table S1.** Pathogenic and likely pathogenic variants identified in our index late-onset FOP patient.
| PDB ID | ALK receptor kinase structural model | Arg NE → backbone O | Arg NH1 → backbone O | Arg NH2 → backbone O |
|--------|-------------------------------------|---------------------|---------------------|---------------------|
| ----   | BMPRIA receptor kinase structure-based (BMPRIB) 3D-homology model | Arg 443 NE Leu 321 O 2.05 Å | Arg 443 NH1 Glu 451 O 2.86 Å | Arg 443 NH2 Leu 321 O 3.15 Å |
| 3MDY chain A | BMPRIB receptor kinase in complex with FKBP12 | Arg 413 NE Leu 291 O 1.83 Å | Arg 413 NH1 Glu 421 O 2.75 Å | Arg 413 NH2 Leu 291 O 3.14 Å |
| 3MDY chain C | BMPRIB receptor kinase in complex with FKBP12 | Arg 413 NE Leu 291 O 1.88 Å | Arg 413 NH1 Glu 421 O 2.81 Å | Arg 413 NH2 Leu 291 O 3.14 Å |
| 3H9R   | ALK2 receptor kinase in complex with FKBP12 | Arg 417 NE Leu 295 O 1.89 Å | Arg 417 NH1 Glu 425 O 2.85 Å | Arg 417 NH2 Leu 295 O 3.28 Å |
| 3MY0 chain A | ALK1 receptor kinase (w/o helix-GS loop-helix) | Arg 411 NE Leu 289 O 1.64 Å | Arg 411 NH1 Glu 419 O 3.00 Å | Arg 411 NH2 (Gln) 290 O 3.11 Å |

**Supplementary Table S2.** Structure-based identification and calculated lengths for conserved H-bonds forming a trivalent network stabilizing the C-lobe scaffold of all four human activin receptor-like kinases.
Supplementary Table S3. Numerical values for the number of fish per phenotype, reported for each figure.