Supplementary Table 1: Diagnostic criteria for patients with OI

OI type	Clinical features	Inheritance	Biochemical abnormality	Mutation
I	Normal stature, little or no deformity, blue sclerae, hearing loss	AD	50% reduction in type I collagen synthesis	*COL1A1*
II	Lethal; minimal calvarial mineralization, beaded ribs, compressed femurs, long bone deformity	AD	Structural alterations of type I collagen chains - overmodification	*COL1A1* *COL1A2*
III	Progressively deforming bones, DI, hearing loss, very short stature	AD	Structural alterations of type I collagen chains – overmodification (except *)	*COL1A1* COL1A2
IV	Normal sclerae in adult, mild/moderate deformity, variable short stature, DI, some hearing loss	AD	Structural alterations of type I collagen chains – overmodification (except *)	*COL1A1* *COL1A2*
V	Similar to type IV plus calcification of interosseus membrane of forearm, hyperplastic callus formation	AD	None described	*IFITM5**
VI	Similar to type IV with vertebral compression; mineralization defect	???	None described	*SERPINF1**
VII	Moderate to severe, with fractures at birth, early deformity and rhizomelia	AR	Overmodification	*CRTAP*

*Patients were reclassified into appropriate categories after gene discovery

Radiologic features

Type	Severity	Skull	Back	Extremities	Other
I	Mild	Wormian bones	Codfish vertebrae (adults)	Thin cortices	Osteopenia
II	Perinatal lethal	Undermineralization; plaques of calcification	Platyspondyly	Severely deformed; broad, crumpled, bent femurs	Small beaded ribs; findings are pathognomonic
III	Severe	Wormian bones	Codfish vertebrae; kyphoscoliosis	Flared metaphyses ("popcorn"-like appearance [childhood]), bowing, thin cortices	Thin ribs, severe osteoporosis
IV	Intermediate	± Wormian bones	Codfish vertebrae	Thin cortices	Protrusio acetabuli
V	Intermediate	?Wormian bones	?	Hypertrophic callus, usually of the femurs; mineralization of the interosseus membrane in the forearm	
VI	Intermediate	?Wormian bones	?	Similar to OI type IV	
VII	Intermediate	?Wormian bones	?	Similar to OI type IV	Rhizomelic shortening

Supplemental Material S1 – Manual of Operations on the performance of Spirometry in the OI LCRC

Spirometry is an effort-dependent test. It requires cooperation and understanding by the subject. Appropriate participant effort depends on instruction and communication with the technologist administering the test. Technologists should display a high level of motivation in regard to eliciting maximal effort from the subject. Physical and mental impairment may limit the participant's ability to adequately perform the test in an acceptable and reproducible manner.

Spirometry testing should only be completed by participants ≥ 6 years of age.

Before Test Administration

Equipment Preparation

• All spirometer components should be assembled according to the manufacturer's instructions (i.e., tubing, connectors, flow-sensors, valves, and adapters).
• A new in-line bacteria filter, disposable mouthpiece, or disinfected reusable mouthpiece should be in place; a clean or new flow-sensor should be used for flow-based spirometers. There is some risk of infection related to performance of spirometry. Cross-contamination between patient and technologist and between patients can occur if the use of gloves, hand washing, and equipment-decontamination procedures are not followed.
• Turn on the system to ensure adequate warm-up.
• Perform diagnostic spirometry only at ambient temperatures between 17 and 40° C (temperatures outside this range may cause problems for both volume-based and flowbased spirometers).
• Volume-displacement spirometers should be checked for leaks each day of use (application of at least 3 cmH2O to the system with the outlet occluded should result in a volume change of less than 30 mL/min). Leaks are the most commonly detected problem in volume-displacement spirometers.
• Flow-sensors should be checked for holes in the sensor, clogging, channel plugging, or excess moisture.
• Environmental data [i.e., internal spirometer temperature or ambient temperature, relative humidity (if applicable) and PB] from an accurate source representative of the laboratory should be entered before calibration checks.

Calibration Check (verification)

A calibration check is different from calibration and is the procedure used to validate that the device is within calibration limits (e.g. +3% of true). If the device fails its calibration check, then a new calibration procedure or equipment maintenance is required (refer to device user manual).

• A 3 L syringe should be used for calibration checks of spirometers; the syringe should have an accuracy of ±15 mL or ±0.5% of full scale (15 mL for a 3 L syringe), whichever is greater. The syringe should be checked at least annually to include a leak

check and, if appropriate, to ensure the adjustable stop has not moved. A dropped or damaged syringe should be considered out of calibration until it is checked.
• Calibration checks (verification) should be performed at least once for each day of testing.
• Calibration checks should produce a measured value within 3.5% of the syringe volume (i.e., ±0.105 L for a 3 L syringe). Flow-sensing spirometers that measure flow at the mouth may require separate correction factors for inspiratory and expiratory volumes.
• For flow-based spirometers, the 3 L syringe should be discharged at least three times to give a range of flows varying between 0.5 and 12 L/sec. The volume achieved at each of these flows should meet the accuracy requirement of ±3.5%. For devices with disposable flow sensors, a new and different sensor, taken from those that might be used for patient tests, should be tested each day.
• The calibration syringe should be maintained at the same temperature and humidity as the spirometer.

Participant Preparation
The participant should wear loose fitting clothing so their chest expansion is not restricted. The participant may want to remove belts, vests or any other clothing that might restrict chest expansion. Well fitting false teeth should not be removed. The participant should refrain from smoking at least 2 hours before the test and should refrain from taking short acting inhaled or oral bronchodilators at least 4 hours before the test.

Administering the Test
1. Measure the participant's height without shoes, in centimeters to the nearest cm and weight without shoes, in kg to the nearest kg and record the participant's age in years on the day of testing.
If the subject is unable to stand, or has marked spinal deformity (e.g. kyphoscoliosis), an arm span measurement may be used to estimate standing height. Have the subject stretch his/her arms in opposite directions and obtain the maximal distance between the tips of the middle fingers. (For Caucasian men, height = arm span/1.03, for African American men height = arm span/1.06, and for women height = arm span/1.01)
2. Have the participant sit down in a chair (preferably a chair with arms and no wheels) making sure they are sitting up straight with legs uncrossed and both feet on the floor.
3. Ask the participant if they have recently smoked and if so when. Record.
4. Ask the participant the time of their last meal. Record
5. Ask the participant about his/her current use of pulmonary medications, dosage, and number of hours taken before the start of testing. Record.
6. Demonstrate the test to the participant including the correct posture, position of the nose clips and mouthpiece and forced expiration. Explain to the participant that he/she will breath normally and then when instructed will take a BIG breath in and then BLAST the air out and keep blowing, blowing, blowing, blowing until they can not blow anymore.
7. Instruct the participant to place the mouth piece in his/her mouth and place the nose

clips on his/her nose. Ensure a tight mouth seal is maintained throughout each test maneuver and there are no obstructions (e.g. tongue and teeth) at the mouth piece.
8. Instruct the participant to breathe normally.
9. After 3 tidal breaths tell the participant to “take a BIG breath in” and then “BLAST it out”
10. Enthusiastically encourage the participant to keep blowing air out until they can’t blow anymore by saying “go, go, go, go, keep going, keep going, keep going.”
11. Observe the participant for any signs of distress and check the computer display duringthe test to help ensure maximal effort. Stop the procedure, if the participant feels “dizzy” since syncope could follow due to prolonged interruption of venous return to the thorax.
12. After the first maneuver is finished, praise the participant for good effort. Let her/him remove the mouth piece and nose plugs. Go over the test with the participant and let her/him know what they did well with and if there is anything that they could improve on. If needed demonstrate the proper procedures again.
13. When the participant is ready, re-peat the test until three acceptable spirograms have been obtained OR a maximum of 8 tests have been performed OR the participant can no longer continue.

End of Test Criteria

Individual spirograms are “acceptable” if:
1. They are free from artifacts
    a. Cough or glottis closure during the first second of exhalation
    b. Glottis closure that influences the measurement
    c. Early termination or cut-off
    d. Effort that is not maximal throughout (variable effort)
    e. Leak at the mouth
    f. Obstructed mouthpiece
2. They have good starts (volume <5% of FVC or 0.15 L, whichever is greater)
3. They show satisfactory exhalation – (expiratory time duration of ≥6 seconds for individuals over 10 years of age OR ≥3 seconds for individuals under 10 years of age, OR a plateau in the volume-time curve with evidence of a continuously forced expiratory effort, where a plateau is defined as no change in volume for at least one second)

After three acceptable spirograms have been obtained, apply the following tests:
1. The two largest values of FVC must be within 0.150 L of each other
2. The two largest values of FEV1 must be within 0.150 L of each other
If both of these criteria are met the test session may be concluded
If both of these criteria are not met, continue testing until
1. Both of the criteria are met with the additional acceptable spirograms
OR
2. A total of eight tests have been performed
OR
3. The participant cannot or should not continue

Supplementary Figure Legends

Supplementary Figure 1: FEV1/FVC ratio in type in type I collagen-related OI. Each dot represents observed FEV1/FVC ratio from the baseline visit of a single participant. The lines represent the LOESS regression lines for each OI type.

Supplementary Figure 2: Height Z-scores in type I collagen-related OI. Each dot represents measured height Z-scores from the baseline visit of a single participant. The lines represent the LOESS regression lines for each OI type. As expected, the height in OI type III> OI type IV> OI type I.

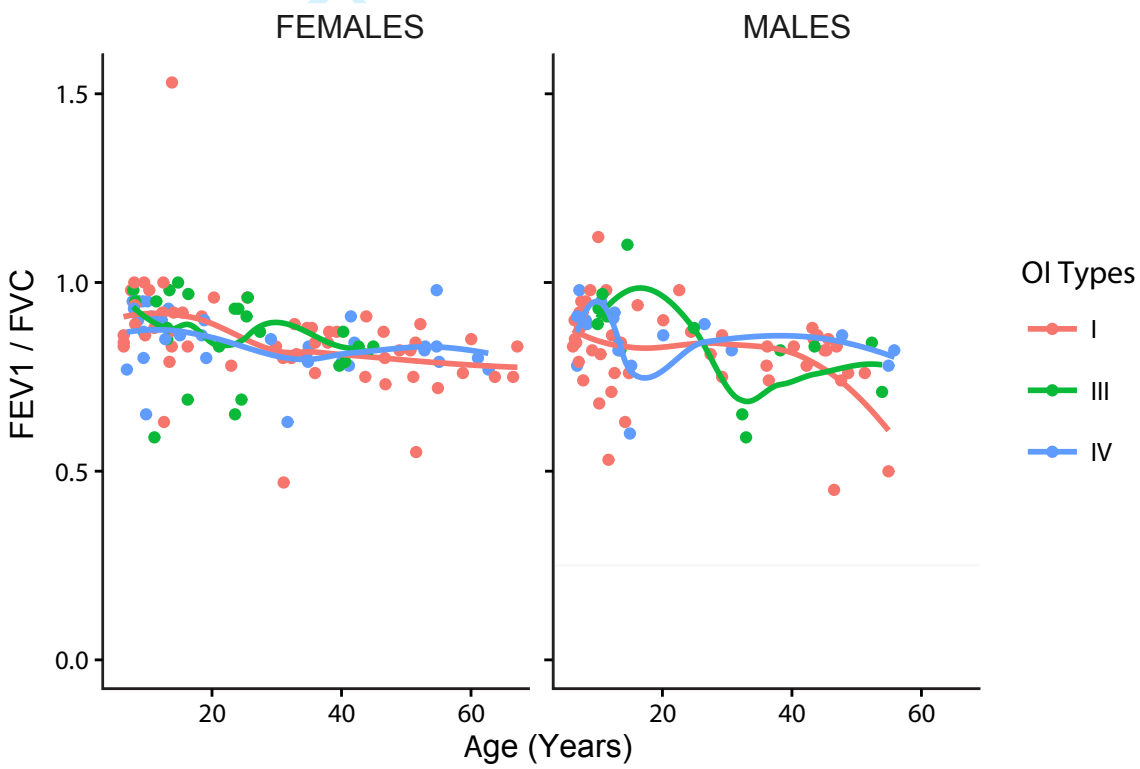
Supplementary Figure 3: Percent predicted FVC and FEV_1 in type I collagen-related OI. Each dot represents measured percent predicted values for a single participant. The lines represent the LOESS regression lines for each OI type. Percent predicted values were calculated as (observed values/predicted value) x100. In spite of significantly lower FVC and FEV_1, the percent predicted values in OI type III and IV are normal or even higher than normal highlighting that the normalization may underestimate the pulmonary involvement in OI.

Supplementary Figure 4: Pearson correlation between measured height and arm span calculated height in OI types I, III, and IV

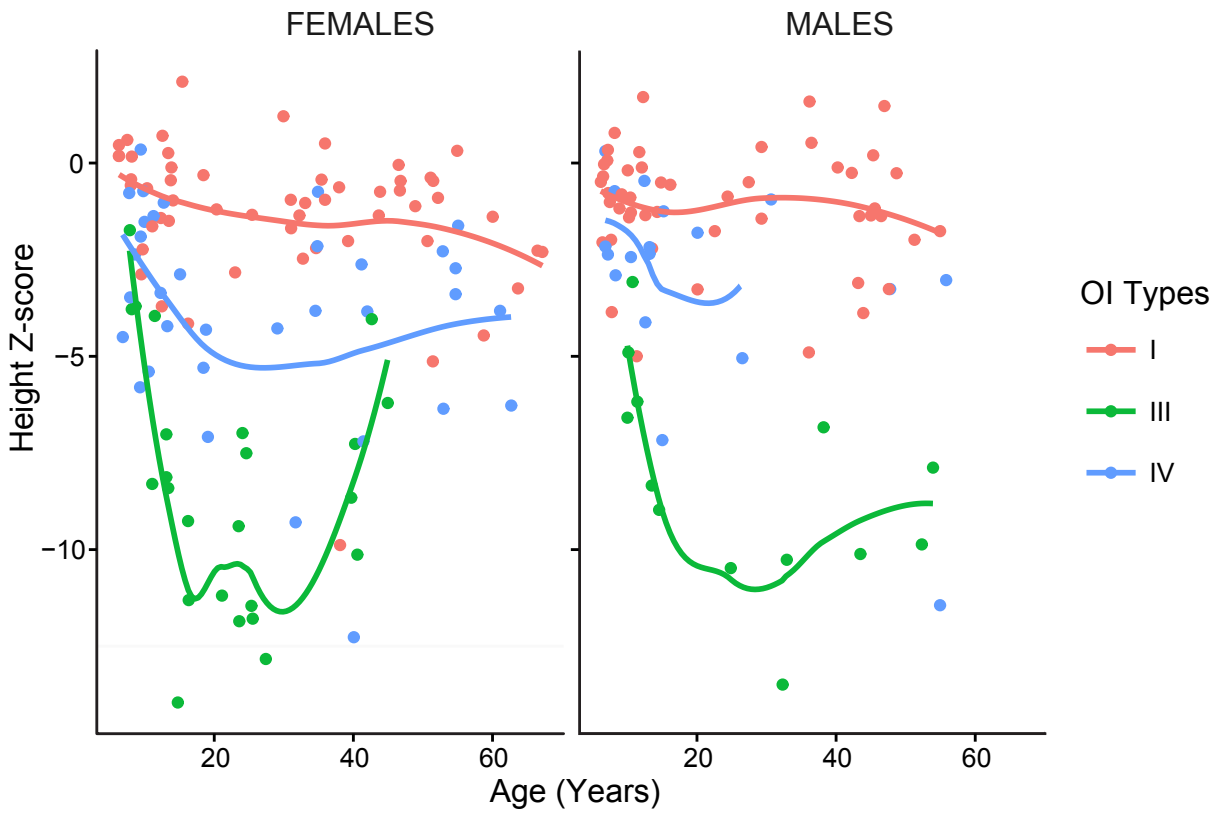
Arm span calculated height and measured height have a higher correlation in OI type I than in OI types III and IV.

Supplementary Figure 5: Predicted FVC and FEV_1 values calculated using reference population data generated by Hankinson et al with either measured height (blue) and arm span calculated height (red). Blue and red dots represent predicted FVC and FEV_1 for a single participant with measured and arm span calculated heights, respectively. The lines represent the LOESS regression lines.

Supplementary figure 1



Supplementary figure 2



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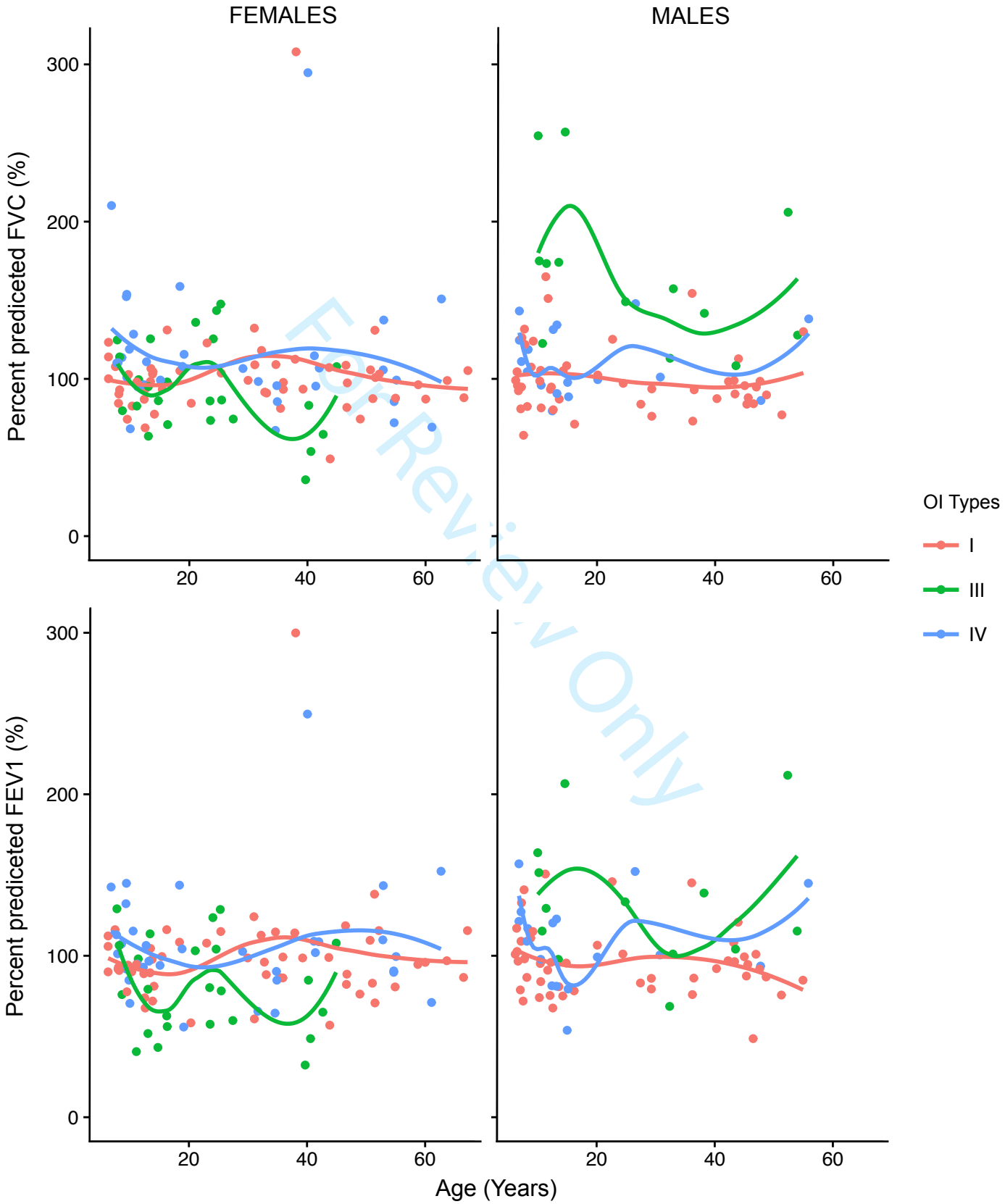

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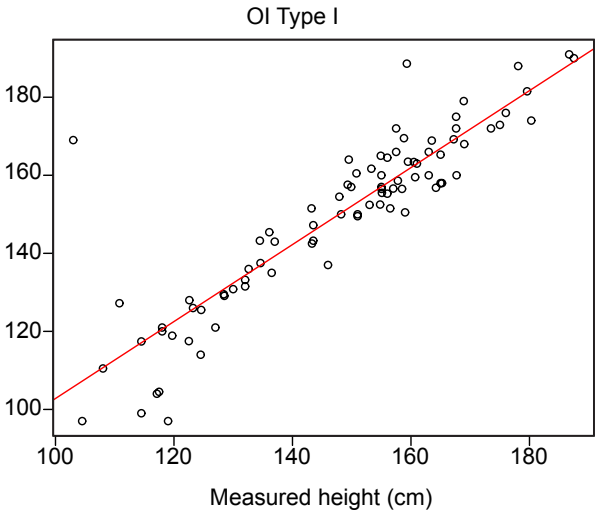

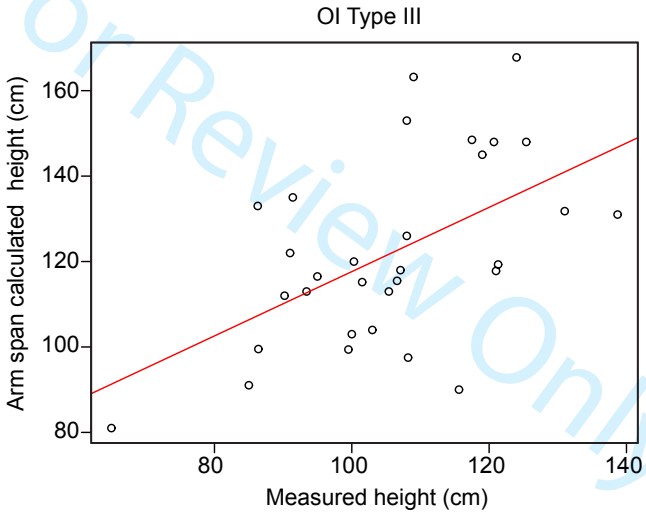

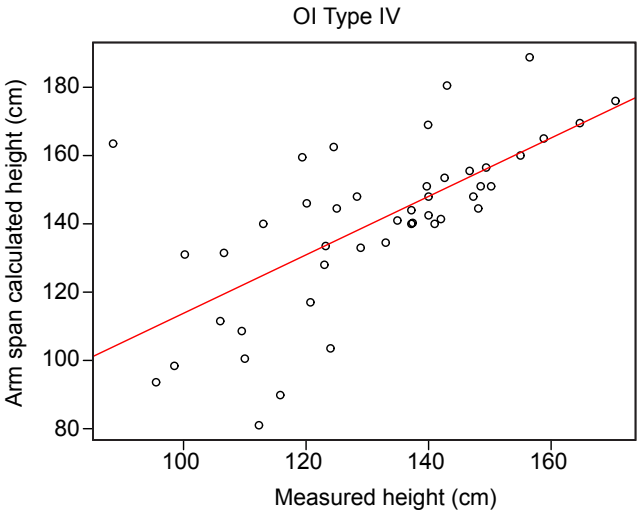

Supplementary figure 5