Supplementary Table 1. Phenotypic characteristics of patients and their *NOTCH2* mutations (reference sequence: NM_024408.3).

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	Female	Male	Male	Male	Female
Age at first assessment (years)	14.7	6.7	15.3	10.4	9.1
Calendar Year	2010	2002	2008	1998	2015
Height in cm (z-score)†	139.1 (-3.5)	118.0 (-0.4)	161.2 (-1.3)	124.8 (-2.4)	125.3 (-1.4)
Weight in kg (z-score)†	57.0 (0.5)	21.5 (-0.28)	51.9 (-0.6)	29.6 (-0.7)	23.8 (-1.27)
BMI in kg/m^2 (z-score)†	29.5 (1.8)	15.6 (0.0)	20.0 (0.0)	19.0 (0.8)	15.2 (-0.6)
Mutation	c.6902T>A	c.6662_6663delTG	c.6787C>T	N/A	c.6724_6725delAG
Protein	p.Leu2301*	p.Val2221Glufs*22	p.Gln2263*	N/A	p.Ser2242*
Mobility					
Normal		+	+		+
Wheelchair-bound	+				
Craniofacial Findings					
Synophrys	+	+		+	
Midfacial flattening	+	+		+	
Downslanted palpebral fissures	+	+		+	+
Hypertelorism	+	+	+	+	+
Wide nose	+	+		+	
Long philtrum	+	+		+	+
Thin lips	+	+		+	+
Low set ears		+	+	+	+
Retro/micrognathia	+	+	+	+	+
High narrow/cleft palate	+	+	+	+	+
Down turned mouth	+	+		+	
Pale skin	+				
Large head circumference	+	+		+	+
Prominent eyes	+	+			
Abnormal dentition					
Irregular wide-spaced teeth	+	+			
Loss of teeth	+	+	+	+	
Short roots of permanent teeth		+			
Malocclusion				+	
Hypoplastic distal phalanges	+	+	+	+	
Broad thumbs	+	+			
Single palmar creases	+				
Hyperconvex nails	+	+			
Hearing impairment	+	+	+	+	
Coarse voice	+	+		+	
Coarse hair	+	+			
Coarse/dry skin	+	+			
Congenital heart defect (VSD)				+	
Upper airway obstruction				+	
Developmental delay			+		
GI malrotation		+			
Endocrine Features					
Short stature	+			+	
Delayed puberty	+				
Hypospadias		+		+	
Renal comorbidities					
Polycystic kidneys	+			+	

† Z-scores calculated using LMS parameters from National health and nutrition survey (NHANES), CDC/National Center for Health Statistics. https://www.cdc.gov/growthcharts/percentile_data_files.htm
Flegal KM, Cole TJ. Construction of LMS parameters for the Centers for Disease Control and Prevention 2000 growth charts. Natl Health Stat Report. 2013;(63):1-3.

Supplementary Table 2. Radiographic findings of 5 children with HCS (whole observation period).

	Radiographic findings				
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
HEAD					
Wormian Bones	+	+	+		+
Platybasia	+			+	
Basilar invagination	+			+	+
Bathrocephaly					+
Scaphocephalus	+			+	
Open skull sutures	+				+
Chiari malformation	+			+	
Dilatation of ventricles	+	+		+	
Thin corpus callosum	+				
Thin superior cerebellar peduncles	+				
Arachnoid cyst posterior fossa with defect in occipital bone		+			
Tympanic bone incompletely formed		+			
Irregular temporomandibular joint		+			
SPINE					
Vertebral fractures*	+		+	+	+
Syringomyelia	+			+	
Spondylolisthesis		+			
Scoliosis- kyphosis	+	+	+	+	
Sclerosis of anterior vertebral endplates	+	+	+		
Osteoporosis/osteopenia*	+	+	+	+	+
LIMBS					
Fracture of long bones*	+	+	+	+	
Acroosteolysis hands and feet	+	+	+	+	+
Fibular bowing (serpentine fibulae)		+		+	+
Hip acetabular dysplasia	+				
Hip protrusio	+			+	
Loss of normal femoral epiphysis	+				
Valgus deformity at the knees		+			
Abnormal ankle mortise		+			
Accessory naviculae					+
Metatarsus varus and adductus					+
Hallus valgus		+			
Bilateral radial dislocation			+		

* Osteoporosis was diagnosed by the responsible clinician based on diagnostic criteria valid at the time. P1,2,3,5 would have met the 2013 ISCD diagnostic criteria before treatment and patient 4 during treatment. For ISCD criteria, see

Crabtree NJ, Arabi A, Bachrach LK, Fewtrell M, El-Hajj Fuleihan G, Kecskemethy HH, Jaworski M, Gordon CM; International Society for Clinical Densidometry. Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD Pediatric Official Positions. J Clin Densitom 2014;17(2):225-42.