Supplementary File 1

Patient Summaries: This file provides clinical descriptions for all patients in the cohort. The clinical descriptions are based on the patient's prior medical history and/or physical examination by a trained pediatric specialist physician.

Patient P01

This patient is currently a 19 year old male born of a normal pregnancy at 41 weeks gestation with a birth weight of 2892 grams. He was growing at a normal growth rate along the 5th percentile until age 8 when he had an abrupt fall of in both weight gain and linear growth. An extensive evaluation for failure to thrive did not reveal an etiology. Growth hormone stimulation testing revealed marked growth hormone deficiency with a peak response to arginine of 2.5 ng/ml and to insulin of 1.5 ng/ml. A brain MRI was normal and there was no evidence of other pituitary hormone deficiencies. The patient displayed a robust response to recombinant growth hormone therapy. The patient had significantly decreased bone density (-4.5 SD below mean) and delayed bone age. The patient has nondysmorphic facial features. The patient's past medical history is significant for anxiety, ADHD, and depression requiring medical treatment, as well as a history of recurrent febrile seizures as a young child. On exam, there was a mild pectus carinatum with slight asymmetry. Family history was notable for febrile seizures, which were present in several cousins as well as the patient's sister. At enrollment, the patient was age 15 years 9 months and had a height of -3.17 SD.

Patient P02

This patient has been previously reported as noted in the main text. The male patient is currently 10 years old and was born after a normal pregnancy at 40 weeks gestation with a birth weight of 2977 grams. The patient had a congenital unilateral ptosis that was surgically corrected. Throughout childhood, the patient exhibited slow growth in height and weight, remaining below the 5th percentile in both. At age 4, a random growth hormone (GH) level was 2.85 ng/mL, and a GH stimulation test at age 5 revealed a peak response to arginine of 8.96 ng/mL and a peak response to glucagon of 6.37 ng/mL. Based on this moderate response to GH stimulation, the patient was initiated on recombinant GH therapy from age 5.5 years to age 10 years. There was no convincing evidence of a significant change in growth velocity after initiation of GH. On physical exam, the patient has ulnar bowing of the forearms, varus bowing of the lower legs, bilateral elbow contractures with decreased supination, pes planus, and hyperextension of the fingers, knees, shoulders, and wrists. Skin was soft, hair was of normal texture and distribution, and there was one scar on the forehead. The facial appearance was nondysmorphic and the patient did not have progeroid features. Testing of the *SHOX* and *RMRP* genes were normal, as were molecular tests for procollagen type 1. At enrollment, the patient was age 7 years 5 months and had a height of -3.87 SD.

Patient P03

The patient is currently a 10 year old male born with a dizygotic twin sister. The twin pregnancy was complicated by an incompentent cervix, premature labor, and hypertension. The fetuses stopped growing at 33 weeks with marked intrauterine growth restriction, and the patient and his twin were delivered by C-section at 37 weeks gestation and each weighed 1928 grams. The twin sister is healthy and of normal stature.

The patient displayed poor weight gain throughout childhood despite normal feeding. The patient reached appropriate developmental milestones. Physical exam showed normal facial features. There was a slight pectus carinatum. Dermatological exam reveals vitiligo, but no other abnormalities. Hormone levels were normal, except for low IGF-1 on several occasions with a normal peak growth hormone response of 11.7 ng/ml to stimulation testing with arginine and gulcagon. The patient was initiated on GH therapy for idiopathic short stature starting at age 7.5 for about 2 years, but was discontinued due to side effects of recurrent headaches. There was a mild transient increase in his growth velocity after

initiation of GH but no marked catch up growth. At enrollment, the patient was age 9 years 4 months and had a height of -3.48 SD.

Patient P04

The patient is currently a 17 year old female who was born at 40 weeks gestation with a birth weight of 2013 g. There was slightly delayed developmental milestones as an infant, but the patient is now cognitively normal and socially adjusted. The patient had short stature throughout childhood and was started on growth hormone at age 6 years for idiopathic short stature. Growth hormone stimulation testing with insulin produced a peak GH of 11.8 ng/ml. She continued on growth hormone until age 15 with a mild initial increase in growth velocity but no marked catch up growth. Due to a relatively early puberty, the patient was treated with a histrelin implant at 11 years 11 months in order to delay epiphyseal fusion and allow for additional growth. The patient was noted to have a markedly decreased bone density (-5 SD) during this therapy and at pubertal suppression was discontinued at the age of 14 years 11 months. Medical history is also significant for diffuse mild hypotonia as infant and mild left sided hemiparesis as infant, both of which resolved. MRI and EEG of the brain were normal except for a small pituitary stalk with an otherwise normal pituitary gland. At enrollment, the patient was age 14 years 1 month and had a height of -3.69 SD.

Patient P05

The patient is currently an 18 year old female who was born of an uncomplicated pregnancy at 40 weeks gestation with a birth weight of 2211 grams. Medical history is significant for asthma. The patient has normal IGF-1 and IGFBP-3 levels. Bone age was consistent with chronological age. On exam, she had a mild thoracic scoliosis with no other significant dysmorphic features. Skeletal survey revealed a right sided hemivertabrae between T4/T6, with bifid spinous processes at C3 and T1. There are only 11 ribs on the right. Her X-rays were not consistent with any specific skeletal dysplasia. Genetic testing for Noonan's syndrome and Turner syndrome mosaicism was negative. The patient's father (5'1'') and brother (5'1'') both have short stature but do not have any known skeletal anomalies. The patient also has a step-brother (same mother) who is 6'2''. At enrollment, the patient was age 15 years 2 months and had a height of -3.15 SD.

Patient P06

The patient is currently a 12 year old female who was born of an uncomplicated pregnancy at 38 weeks gestation with a birth weight of 2400 grams. The patient reached appropriate developmental milestones. Facial appearance was nondysmorphic and the remainder of the physical exam was not remarkable. IGF-1 and IGFBP-3 levels were normal and a karyotype was normal. Bone age is about 1 year behind chronological age. The patient also has been diagnosed with anxiety disorder. The remainder of the medical history is unremarkable. At enrollment, the patient was age 9 years 1 months and had a height of -3.45 SD.

Patient P07

The patient is currently a 12 year old female and was twin A of a normal pregnancy at 39 weeks gestation. The patient was born at 2268 grams while her twin sister was born at 3827 grams. The patient had developmental delay most notable in her expressive language, while her twin sister did not demonstrate any delays. Medical history is notable for severe scoliosis, tethered cord, laryngomalacia, chronic constipation, and asymptomatic polycystic kidney disease. The patient has a history of hypothyroidism and relatively early puberty with breast development starting at age 9 years. She was started on pubertal suppression therapy with a histrelin implant in order to maximize growth potential. Growth hormone axis levels are normal. Physical exam reveals mildly dysmorphic facial appearance with a v-shaped nares, short philtrum, slightly beaked nose, and moderate scoliosis. Head circumference was normal. Prior genetic testing was all normal including a karyotype, FISH of 22q and 7q, fragile X

testing, and an extensive metabolic work up. At enrollment, the patient was age 9 years 3 months and had a height of -3.01 SD.

Patient P08

The patient is currently a 7 year old female who was born of an uncomplicated pregnancy at 39 weeks gestation with a birth weight of 2778 grams. She reached appropriate developmental milestones. The patient's medical history is significant for several episodes of pneumonia requiring hospitalization. She also has several severe food allergies, but is well-nourished. The patient has mild eczema. Her growth hormone and thyroid hormone axis levels are normal including a peak growth hormone of 11.0 ng/ml on stimulation testing with arginine and glucagon. Her bone age is slightly delayed (5 years at chronological age of 5 years 8 months by Gruelich and Pyle). Physical exam was unremarkable. The patient's parents and four sisters are all of normal stature. The patient has a paternal aunt and grandmother who have short stature at 4'10''. Karyotype and *SHOX* gene testing were normal. At enrollment, the patient was age 4 years 4 months and had a height of -3.90 SD.

Patient P09

The patient is currently a 14 year old male born of an uncomplicated pregnancy at 40 weeks gestation with a birth weight of 2268 grams. The patient reached appropriate developmental milestones. Medical history is unremarkable. Physical examination reveals an inverted triangular face with a normal head circumference. Facial appearance was otherwise nondysmorphic. Examination of the genitalia was normal with normal testicular size. The patient has gracile-appearing bones, but with normal limb length and a skeletal survey interpretation did not suggest any specific etiology. GH and thyroid hormone axes levels are normal. The patient was initiated on a trial of growth hormone at around age 12 but was withdrawn rapidly due to side effects. The parents are from the same town in India, and there is a distant relative with short stature. Fanconi's anemia chromosome breakage testing was negative. Russell-Silver Syndrome was suspected, but testing was negative. At enrollment, the patient was age 11 years 3 months and had a height of -3.18 SD.

Patient P10

The patient is currently an 11 year old female born of an uncomplicated pregnancy at 39 weeks gestation with a birth weight of 2778 grams. The patient reached appropriate developmental milestones. Her medical history is notable for mild chronic constipation and an episode of anemia. Physical examination is unremarkable. IGF-1 levels were mildly decreased (78 ng/mL; reference 88 to 474). GH stimulation testing was normal with a peak growth hormone level of 15.3 ng/ml after stimulation with arginine and glucagon. Thyroid function tests were normal. Bone age was markedly delayed (8-10/12 at chronological age of 11-7/12 by Greulich and Pyle). There is a family history of delayed puberty, but not short stature. At enrollment, the patient was age 11 years 8 months and had a height of -3.30 SD.

Patient P11

This patient has been previously reported as noted in the main text. The patient is currently a 21 year old male who was born without complications at 39 weeks gestation. The patient had a birth weight 1842 g (−3.7 SD) and length of 33 cm (−6.8 SD). He had difficulty feeding and subsequent poor growth, resulting in gastrostomy tube placement at age 17 months, which was removed at age 3 years. His head circumference was always large for his age (range +1.9 to +2.4 SD), but cognitive development was normal. The patient had an inverted triangular face with midface hypoplasia. Skeletal surveys revealed gracile-appearing bones. He was treated with growth hormone for a period of 5 years with a mild, transient increase in growth velocity. His history is also notable for significant scoliosis requiring surgical repair at age 14 years, delayed dentition, and tonsillectomy and tympanostomy tube placement as a

toddler for frequent otitis media. In addition, he had testicular maldescent and inguinal hernias requiring surgical repair. After his genetic diagnosis with 3M syndrome, evaluation revealed hypergonadotropic hypogonadism. Prior genetic testing of *PTPN11, SOS1, FGFR3, SHOX,* and molecular testing for Russell-Silver syndrome were negative. At enrollment, the patient was age 18 years 5 months and had a height of -4.07 SD.

Patient P12

The patient is currently an 11 year old female who was born of an uncomplicated pregnancy with a birth weight of 2637 grams. The patient reached appropriate developmental milestones. Medical history is significant for recurrent episodes of gastrointestinal pain, diarrhea, and vomiting throughout childhood and of unknown etiology. She had an extensive gastrointestinal work up including endoscopy and colonoscopy all of which were normal. She has had appropriate weight gain despite her abdominal complaints and her most recent BMI was at the 43rd percentile. Thyroid and growth hormone axes were normal including a normal response to growth hormone stimulation testing (peak growth hormone 11.2 ng/ml). Bone age was delayed (8-10/12 at chronological age of 10-9/12 by Greulich and Pyle). Physical exam is unremarkable. Facial appearance is non-dysmorphic. Karyotype and testing for *SHOX* were normal. Father was noted to have a delayed growth spurt, but currently measures 5'6''. At enrollment, the patient was age 8 years 8 months and had a height of -3.58 SD.

Patient P13

The patient is currently a 9 year old male born of an uncomplicated pregnancy at 40 weeks gestation and was appropriate for gestational age (3231 grams and 50.2 cm long). The patient reached appropriate developmental milestones. Medical history was unremarkable. IGF-1 and IGFBP-3 levels and thyroid hormone axis levels were normal. Bone age was mildly delayed (bone age was 7-0/12 months at age 8-3/12 by Gruelich and Pyle). Facial appearance was nondysmorphic. Skeletal survey was normal. At enrollment, the patient was age 7 years 7 months and had a height of -3.01 SD.

Patient P14

The patient is currently a 12 year old female born of an uncomplicated pregnancy at 40 weeks gestation with a birth weight of 3091 grams and length of 45.7 cm. She reached appropriate developmental milestones. The patient experienced failure to thrive in infancy requiring hospitalization at 6 months of age. Testing during the hospitalization revealed elevated liver enzymes which have self-resolved over time. Review of systems is notable for severe myopia but no other ophthalmological abnormalities. Facial appearance demonstrates a prominent forehead, a flat nasal bridge, and a curved and upturned nose. Skeletal survey was notable for bilateral coxa valga and mild medullary stenosis and cortical thickening of the long bones, particularly the femur. Head circumference at age 11-1/12 was 50.7 cm (6th percentile). Dental examination and history reveal soft enamel, five missing permanent teeth (all premolars), abnormal eruption pattern with delayed eruption of permanent teeth, and small permanent teeth. At enrollment, the patient was age 12 years and had a height of -5.99 SD.

GH, IGF-1, and IGF-BP3 levels, and GH stimulation tests were normal. She was started on GH at 3 ½ years of age and had a brisk response initially with a growth velocity of 7.5 cm/yr, 12.3 cm/yr, then 5.8 cm/yr at 6 month increments. Due to the slowing in her growth velocity, she was switched to IGF-1 at 5 ½ years of age. She experienced severe headaches, resulting in poor compliance and a poor growth response of 3 cm/y for 1 year. She was subsequently switched back to GH. Her GV then increased from the 25th to 95th percentile for her age until she was started on GnRH agonist therapy at 10 ½ years of age. In total, her height has increased from -5.99 SD to -3.38 SD. Her pubertal development started (Tanner II breasts) around 9 ½ years of age. This is likely familial as her mother also had early puberty. The patient had normal calcium and phosphate levels on three separate occasions including during infancy.

Family history was unremarkable, and the patient has three brothers, all of normal height. *SHOX* gene testing was normal and a chromosomal microarray revealed a 493 kb duplication on chromosome 4 also present in the mother.