Growth charts in Cockayne syndrome type 1 and type 2

Sarah Baer[1], Nicolas Tuzin[2], Peter B. Kang[3] , Shehla Mohammed[4], Masaya Kubota[5], Yvette van Ierland[6], Tiffany Busa[7], Massimiliano Rossi[8], Godelieve Morel[9], Caroline Michot[10], Geneviève Baujat[10], Myriam Durand[11], Cathy Obringer[12], Nicolas Le May[12], Nadège Calmels[12,13], Vincent Laugel[1,12]

1. Service de Pédiatrie 1, Hôpital de Hautepierre, Hôpitaux Universitaires de Strasbourg, Strasbourg

2. Groupe Méthode en Recherche Clinique, Hôpitaux Universitaires de Strasbourg, Nouvel Hôpital Civil, Strasbourg, France.
3. Division of Pediatric Neurology, Department of Pediatrics, University of Florida College of Medicine, Gainesville, FL 32610, USA
4. South East Thames Regional Genetics Service, Guy's and St Thomas' Hospital, Great Maze Pond, London, SE1 9RT, UK
5. Division of Neurology, National Center for Child Health and Development, Tokyo, Japan
6. Erasmus University Medical Center, Department of Clinical Genetics, 3000 CA Rotterdam, The Netherlands
7. Hôpital de la Timone, Medical Genetics, Marseille, Provence-Alpes-Côte d'Azur, France
8. Centre de référence des anomalies du développement, Service de génétique, Hospices Civils de Lyon, & Centre de Recherche en Neurosciences de Lyon, Inserm U1028, UMR CNRS 5292, GENDEV Team, Lyon 1-Claude Bernard University, Bron, France
9. Service de Génétique Clinique, Centre de Référence Maladies Rares Centre Labellisé Anomalies du Développement-Ouest, Centre Hospitalier Universitaire de Rennes, 35033 Rennes, France
10. Service de génétique clinique, CRMR maladies osseuses constitutionnelles, INSERM UMR 1163, Université Paris-Descartes-Sorbonne Paris Cité, Institut Imagine, Hôpital Necker Enfants Malades, Paris, France
11. Centre d'Investigation Clinique INSERM-CIC 1434, CHRU de Strasbourg, F - 67091 Strasbourg, France.
12. Laboratoire de Génétique médicale, INSERM U1112, Institut de génétique médicale d'Alsace, Faculté de Médecine de Strasbourg, Hôpitaux Universitaires de Strasbourg, France.
13. Laboratoires de Diagnostic Génétique, Institut de génétique médicale d'Alsace, Nouvel Hôpital Civil, Hôpitaux Universitaires de Strasbourg, France.

Correspondance: Sarah Baer sarah.baer@chru-strasbourg.fr – Service de Pédiatrie 1 – 1 avenue Molière - 67082 STRASBOURG Cedex – France Tel : 03.88.11.67.68

CONFLICT OF INTEREST

The authors declare to have no conflict of interest

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ABSTRACT :

Cockayne syndrome (CS) is a multisystem degenerative disorder divided in 3 overlapping subtypes, with a continuous phenotypic spectrum : CS2 being the most severe form, CS1 the classical form and CS3 the late-onset form. Failure to thrive and growth difficulties are among the most consistent features of CS, leaving affected individuals vulnerable to numerous medical complications, including adverse effects of undernutrition, abrupt overhydration and overfeeding. There is thus a significant need for specific growth charts.

We retrospectively collected growth parameters from genetically-confirmed CS1 and CS2 patients, used the GAMLSS package to construct specific CS growth charts compared to healthy children from WHO and CDC databases.

Growth data were obtained from 88 CS patients with a total of 1626 individual growth data points. 49 patients were classified as CS1 and 39 as CS2 with confirmed mutations in *CSB/ERCC6, CSA/ERCC8* or *ERCC1* genes. Individuals with CS1 initially have normal growth parameters; microcephaly occurs from 2 months whereas onset of weight and height restrictions appear later, between 5 and 22 months. In CS2, growth parameters are already below standard references at birth or drop below the 5th percentile before 3 months. Microcephaly is the first parameter to show a delay, appearing around 2 months in CS1 and at birth in CS2. Height and head circumference are more severely affected in CS2 compared to CS1 whereas weight curves are similar in CS1 and CS2 patients.

These new growth charts will serve as a practical tool to improve the nutritional management of children with CS.

INTRODUCTION :

Cockayne syndrome (CS*; OMIM216400 & OMIM133540*) is a rare autosomal recessive disorder characterized by growth difficulties, neurological and sensorial impairments, intellectual disability and photosensitivity. The syndrome was first reported in 1936 by Sir Edward Cockayne[1] and the causative genes were described in the late 1990s.[2–4] CS is typically caused by mutations in *ERCC6/CSB* and *ERCC8/CSA* genes, whose protein products are involved in nucleotide excision repair (NER). After DNA damage induced by ultraviolet (UV) radiation, these two proteins are involved in the early steps of transcription-coupled repair of DNA lesions actually blocking elongating RNA polymerase, including UV-induced DNA damage.[5–7] More recently, mutations in other genes of the NER pathway including *ERCC1* have been linked to atypical CS phenotypes.[8] The ERCC1 protein is involved in a late step of both nucleotide excision repair and transcription-coupled repair as well as in interstrand crosslink repair and single strand annealing of double strand breaks.[9] Altogether more than 300 CS cases have been reported in the literature.[10]

The incidence in Western Europe and in Japan is estimated at 2.7 cases per million births.[11,12] CS is classically divided in 3 different subtypes depending on the severity and evolution of the disease[13] : CS2 is an early-onset form with lack of ambulation and a mean age of death around 6 years; CS1 is an intermediate subtype with onset in the first two years of life and usually ambulation for at least part of their course, with progressive neurodegeneration and a mean life-expectancy of 16 years; CS3 is the late onset form with onset at 3-4 years, ambulation into adulthood, and a life expectancy that can exceed 30 years.[11,14,15]

Growth restrictions are consistently seen in CS and are described as one of the major criteria for the diagnosis. Growth patterns vary greatly between individual CS patients and proportionally between subtypes.[13–16] Growth parameters in CS can be far below standard curves and standard growth charts are not suitable for monitoring the health and nutrition in these patients. Profound microcephaly is also a key feature of this syndrome. Beside the intrinsic growth restriction of the disease, patients with CS also present with neurological and gastrointestinal impairments which can impact growth when gastrointestinal reflux, recurrent vomiting or swallowing difficulties occur. Acute infectious events can also severely impair the feeding capacities and growth of CS children. Given the intrinsic and inevitable severe growth limitations in CS, it is particularly difficult to diagnose additional undernutrition or overfeeding in affected individuals, which could be very detrimental to their global health status and could be avoided or improved by appropriate nutritional monitoring and interventions. CS patients with undernutrition are at risk of anemia, fractures, asthenia, bleeding and many other complications in addition to their own syndrome. Conversely, in the experience of parents and caregivers, overfeeding in CS patients may lead to deteriorate their quality of life and cause discomfort.

Optimal nutritional management is currently hard to define in CS in the absence of appropriate growth charts. In this study, we aimed to present the first standardized normative curves for height, weight and occipital frontal circumference (OFC) in a large cohort of patients affected with CS1 and CS2 to help manage the growth and nutrition of these fragile individuals.

METHODS :

Patient population :

We retrospectively collected growth data from individuals with genetically-confirmed CS1 and CS2 in several established cohorts of CS patients in France, Japan, the UK, the Netherlands and the US. We excluded patients without molecular confirmation. This international multicenter survey was also supported by family support groups in France, the Netherlands and the UK. Both longitudinal and isolated growth data have been included in the survey. We also collected, whenever available, data about the type of nutrition (oral, enteral, nasogastric tube) and the time it was introduced. All data were registered in a password protected database.

Patients with CS type 3 were excluded from the survey as not enough data were available to be able to draw reliable growth charts. Each measure at each age was counted as a single data point. As we hypothesized that patients from a given clinical subgroup behave follow similar growth patterns, we combined data points from different participants at the same ages, including longitudinal data from various individuals. We excluded outliers that deviated too far from the growth values of other patients (minimum +6SD compared to the Cockayne cohort), which could correspond to early intensive nutritional management or likely measurements errors. Our database was declared to the appropriate ethical and regulatory committees in accordance with French laws (CNIL, CPP). Subjects from the US were enrolled in an IRB-approved study at the University of Florida.

Growth chart calculation :

We used the package GAMLSS (Generalized Additive Models for Location, Scale and Shape) in R software to construct growth curves for height, weight, and OFC[17], with comparisons to

standard reference curves from the World Health Organization (WHO)[18] and the Centers for Disease Control and Prevention (CDC). The curves were constructed using a non-parametric regression model, with age-fitting of the curves for each gender and syndrome type. The estimated centiles by age and sex were converted back to Excel (*Microsoft Corporation, Redmond, Washington*) format to create charts for each anthropometric variable, including the WHO and CDC growth charts for healthy children.

RESULTS :

Data collection

We enrolled 88 participants with a clinical diagnosis of Cockayne syndrome who were categorized as having CS1 or CS2 (48 males and 40 females). All subjects had precise molecular diagnoses, with mutations in *ERCC1*, *ERCC6/CSB* or *ERCC8/CSA*.

In our cohort, 49 participants were classified as having CS1 (28 males and 21 females) and 39 patients were classified as having CS2 (20 males and 19 females). **(Figure 1)** Among the CS1 patients, 24 presented with mutations in *ERCC6/CSB* and 25 with mutations in *ERCC8/CSA*. The CS2 patients presented mainly with mutations in *ERCC6/CSB* (30 patients out of 39), 8 with mutations in *ERCC8/CSA* and one with mutation in *ERCC1*. All patients were born between 1985 and 2016.

A total of 722 weight measurements, 573 height measurements and 331 OFC measurements were analyzed. 18 different ethnic origins were represented in our cohort and we collected data from 16 countries (France, Nederland, United-Kingdom, Spain, Portugal, Finland, South Africa, Lebanon, Saudi Arabia, Iran, Tunisia, Turk, Belgium, Japan, India).

For 68 patients we had at least 2 measurements, and we had more than 4 measurements for 48 patients. We collected from 1 to 62 measurements per patient depending on the available data.

Due to limited growth data beyond certain ages we chose to construct growth charts until the age of 6 years for CS2 and 16 years for CS1, corresponding to the average age of death in previous studies.[15,19] These data are consistent with our results : in CS1 patients the mean age of death was 13.875 years [5-24] and 5.25 years in CS2 patients [4-7].

Growth parameters at birth

Birth weights were available for 61 CS patients (33 CS1 and 28 CS2, 29 females and 32 males). Birth lengths were available for 52 CS patients (30 CS1 and 22 CS2, 26 females and 26 males). Information on OFC at birth was available for 47 CS patients (24CS1 and 23 CS2, 24 females and 23 males).

Females with CS1 have a weight curve initially overlapping with the reference curve, whereas the weights of CS2 females start at approximately the 5th percentile with respect to the reference data. For height, females with CS2 start at approximately the 5th percentile with respect to the reference data, whereas those with CS1 have height curves similar to reference values at the beginning. The head circumferences of females with CS2 are below standard curves, whereas patients with CS1 have a head circumference that is close to the normal one. **(Figure 3)**

Males with CS2 start with a height slightly below the reference range while the weight and OFC are already under 5th percentile at birth. In males with CS1, weight, height and OFC are normal at birth. **(figure 5)**

Postnatal growth parameters (figures 2 and 4)

The mean number of longitudinal measurements per participant was approximately 7.4 data points each [1-62].

Weight:

Patients with CS2 presented with failure to thrive since birth, with weights below the 5th percentile by months 2 or 3 and final weights around 10 kg for girls and 11 kg for boys at 6 years. In CS1 patients, birthweights tend to be normal, but weights fall below the 5th percentile at approximately 9 months for boys and 17 months for girls. Final weights are approximately 14 kg for girls and 19 kg for boys at 16 years. CS patients grow steadily but extremely slowly during their whole life and we found no abrupt change in growth dynamics either in weight, height or OFC.

Height:

In CS2, height growth decelerates below the 5th percentile at the age of 2 months, with a final height of approximately 83.5cm for girls and 81 cm for boys at the age of 6 years.

In CS1, height is normal at birth, but growth decelerates below the 5th percentile by 22 months for girls and 5 months for boys, with final heights approximately 98 cm for girls and 130 cm for boys at 16 years. After 4 years of age, individuals with CS do not gain height perceptibly except for boys with CS1, whose growth remains constant but well below standard ranges.

OFC :

Children with CS2 were microcephalic from birth with a final OFC of 40 cm for boys and 39 cm for girls at 3 years.

In CS1 children, OFC was in the normal range at birth, but the mean curve drops below the standard by 2 months for boys and girls. The final OFC is 44 cm at 56 months for girls and 46 cm for boys at 73 months.

Different types of CS

Overall, individuals with CS2 are smaller than those with CS1 for both girls and boys, with a difference of 2 standard deviations. The weight curves for CS1 and CS2 are very similar. One of the main growth parameter differences between CS1 and CS2 involves OFC, with CS2 participants being more microcephalic than those CS1.

DISCUSSION:

Growth failure is a major problem in many neurodegenerative childhood diseases such as Cockayne syndrome (CS) and can be secondary to multiple etiologies. We developed these specific growth curves to improve the nutritional monitoring of children affected by CS and to help determine optimal nutritional regimens.

In the first description by Sir Edward Cockayne in 1936[1] and summarized by Isabelle Rapin in 2013[20] children with CS were initially described as "tiny, well proportioned, often attractive, delicate toddlers who are sociably interactive". Indeed, growth failure is a major CS criterion: in previously described cohorts it affects between 97 and 100% of patients[11,16,21]. This impairment is described as progressive as less than half of them presented with low birth weight (39% Calmels *et al.*[21] et 55% Baer *et al.*[10]). In the patients described herein, 12 children presented with IUGR (23%), which has recently been associated with reduced life expectancy.[10]

CS can be traditionally divided in different groups depending on the severity of the disease: CS1 with normal prenatal growth and onset of growth and developmental abnormalities by the age of 2 years, and CS2 with earlier growth failure, typically present at birth.[22] In our cohort and as reported before, CS2 patients were mostly mutated in *ERCC6/CSB* gene whereas CS1 were mutated in *ERCC8/CSA and ERCC6/CSB* genes.[23] We also reported a severe CS2 case who was associated with a rarely reported *ERCC1* mutation. Only four *ERCC1* mutated patients have been reported in the literature[10,24,25], the CS2 patient reported here, presented with severe encephalopathy and died at 5 years. Still there are no

clear-cut genotype/phenotype correlations between these genetic subtypes and *ERCC6/CSB*, *ERCC8/CSA* and *ERCC1* patients can present largely overlapping phenotypes .

In our charts, all CS1 patients have normal growth parameters at birth, with declines appearing between 2 and 22 months depending on the gender and the parameter. CS2 patients, as described previously, present with growth failure at birth or very early and at 3 months all growth parameters are below the 5th percentile. The most striking differences between CS1 and CS2 in our charts are the height and head circumference; CS1 and CS2 patients present with major delays in weight gain but there is no difference between these two groups.

The number of available data tends to decrease with age, corresponding to the short life expectancy associated with Cockaynes syndrome. We thus chose to stop the curves at the age of 6 years for CS2 and 16 years for CS1 in accordance with the average life expectancy reported in the literature[14,15,22]. For cranial parameters, in accordance with current practice and the amount of data available, we have stopped the curves at the age of 56 months for CS1 and 30 months for CS2.

Microcephaly is one of the key features of Cockayne syndrome. Progressive microcephaly has been considered to be one of the major or mandatory diagnostic criteria.[13,16,22] Microcephaly affects between 96% and 100% of patients with CS regardless of the different subtypes of the disease. When comparing the evolution of growth parameters in CS patients to healthy populations, microcephaly seems to be the first sign to appear : OFC is already below the 5th percentile at birth in CS2 patients and from the age of 2 months in CS1 patients. Microcephaly is also reported as the first clinical symptom in nearly 30% of CS

patients[10], it needs to be monitored accurately especially since early neurological examinations in newborn can be initially imprecise in these patients.

Growth failure in CS is known to be multifactorial, yet the precise contributions of various potential causes remains unclear. Thus, various investigators have tried to understand the pathophysiology of this major manifestation of CS. Endocrine function in CS patients has been described as normal: no deficiencies in growth hormone or thyroid stimulating hormone levels have been reported.[26] As CS is implicated in DNA repair pathway, growth hormone is not recommended for these patients, due to the potential risk of tumor growth. Metabolic dysfunction may contribute to growth failure in CS; some of the clinical manifestations of CS resemble those seen in mitochondrial disease, and CSB and CSA have been implicated in the regulation of oxidative stress.[26,27] Neurological impairments such as oral motor dysfunction may also play a role in CS growth failure.[22]

The present study has led to the development of the first growth charts tailored specifically for patients affected by CS. The evolution of CS is characterized by progressive neurological degeneration, affecting both the central and peripheral nervous systems often leading to limb hypertonia and spasticity, with more subtle signs of neuropathy. Some techniques have been developed to measure the height of children with contractures but have limitations. This can lead to potential underestimation of the height of severely affected children.

The collected data correspond to patients from 18 different countries and thus we expect that these growth charts are potentially applicable to a number of populations around the world. The reference WHO growth charts include data collected from more than 130

countries whereas the CDC growth charts include data only from the United States, thus there may be minor discordances among the various charts due to differences in the background populations.

As the data in our study were collected retrospectively and as CS is an extremely rare disease, it was not feasible to normalize our data based on variations in diet with the currently available data. We acknowledge that the various nutritional conditions of the patients included in the study may have been a confounding factor in the calculation of the growth charts. This was attenuated by the exclusion of the values that deviated too far from the data of the rest of the cohort (minimum +6SD higher than the rest of the cohort), which could correspond to early intensive nutritional management. Since no precise nutritional guidelines exist for CS, we also assumed that our global data were not altered by a systematic bias which would have been identical in all patients. We believe that our ability to produce separate growth curves based on CS subtype and gender is a major advantage of this study. We hope that future prospective studies, based on longitudinal cohorts and including extensive nutritional and metabolic assessments, will facilitate the normalization of longitudinal growth data based on factors such as daily mean caloric intake. Such prospective studies may also lead to even more precise knowledge and recommendations regarding optimal dietary regimens for these individuals.

The growth curves presented in the current study will assist clinicians in adjusting dietary regimens for patients with CS1 and CS2. In our experience, CS patients with undernutrition face many medical complications, but overfeeding patients, especially in acute settings, carries the risk of inducing neurological and general deterioration. We hope that these

curves will provide information that will help families, physicians, and dieticians adjust nutritional interventions, including gastrostomy feeding schedules. Future studies will help refine these charts. Growth parameter charts such as ours will also be useful for the design of future clinical trials.

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FIGURES:

Figure 1 : clinical and molecular description of included patients.

Figure 2 : Constructed growth charts for CS1 and CS2 patients in relation to the CDC reference charts (grey) for females CS patients (orange) : CS2 are represented with broken line and CS1 with unbroken line.

Figure 3 : Constructed growth charts for CS1 and CS2 patients from 0 to 3 years in relation to the CDC reference charts (grey) for females CS patients (orange) : CS2 are represented with broken line and CS1 with unbroken line.

Figure 4 : Constructed growth charts for CS1 and CS2 patients in relation to the CDC reference charts (grey) for male CS patients (blue) : CS2 are represented with broken line and CS1 with unbroken line.

Figure 5 : Constructed growth charts for CS1 and CS2 patients from 0 to 3 years in relation to the CDC reference charts (grey) for male CS patients (blue) : CS2 are represented with broken line and CS1 with unbroken line.

REFERENCES :

1. Cockayne EA. Dwarfism with retinal atrophy and deafness. *Arch Dis Child*. 1946;21(105):52-54. doi:10.1136/adc.21.105.52
2. Troelstra C, Odijk H, de Wit J, et al. Molecular cloning of the human DNA excision repair gene ERCC-6. *Mol Cell Biol*. 1990;10(11):5806-5813. doi:10.1128/mcb.10.11.5806
3. Mallery DL, Tanganelli B, Colella S, et al. Molecular analysis of mutations in the CSB (ERCC6) gene in patients with cockayne syndrome. *Am J Hum Genet*. 1998;62(1):77-85. doi:10.1086/301686
4. Henning KA, Li L, Iyer N, et al. The Cockayne syndrome group A gene encodes a WD repeat protein that interacts with CSB protein and a subunit of RNA polymerase II TFIIH. *Cell*. 1995;82(4):555-564. doi:10.1016/0092-8674(95)90028-4
5. Lans H, Hoeijmakers JHJ, Vermeulen W, Marteijn JA. The DNA damage response to transcription stress. *Nat Rev Mol Cell Biol*. 2019;20(12):766-784. doi:10.1038/s41580-019-0169-4
6. Proietti-de-santis L, Laugel V, Prantera G. *Chapter 7 - Cockayne Syndrome*. Elsevier Inc.; 2019. doi:10.1016/B978-0-12-813796-3.00007-9
7. Kolesnikova O, Radu L, Poterszman A. TFIIH: A multi-subunit complex at the cross-roads of transcription and DNA repair. *Adv Protein Chem Struct Biol*. 2019;115:21-67. doi:10.1016/bs.apcsb.2019.01.003
8. Ferri D, Orioli D, Botta E. Heterogeneity and overlaps in nucleotide excision repair (NER) disorders. *Clin Genet*. 2019:cge.13545. doi:10.1111/cge.13545
9. Marteijn JA, Lans H, Vermeulen W, Hoeijmakers JHJ. Understanding nucleotide excision repair and its roles in cancer and ageing. *Nat Rev Mol Cell Biol*.

2014;15(7):465-481. doi:10.1038/nrm3822

10. Baer S, Obringer C, Julia S, et al. Early-onset Nucleotide Excision Repair disorders with neurological impairment: clues for early diagnosis and prognostic counselling. doi:10.1111/cge.13798

11. Kubota M, Ohta S, Ando A, et al. Nationwide survey of Cockayne syndrome in Japan: Incidence, clinical course and prognosis. *Pediatr Int*. 2015;57(3):339-347. doi:10.1111/ped.12635

12. Kleijer WJ, Laugel V, Berneburg M, et al. Incidence of DNA repair deficiency disorders in western Europe: Xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy. *DNA Repair (Amst)*. 2008;7(5):744-750. doi:10.1016/j.dnarep.2008.01.014

13. Nance MA, Berry SA. Cockayne Syndrome: Review of 140 cases. *Am J Med Genet*. 1992;42(1):68-84. doi:10.1002/ajmg.1320420115

14. Natale V. A comprehensive description of the severity groups in Cockayne syndrome. *Am J Med Genet Part A*. 2011;155(5):1081-1095. doi:10.1002/ajmg.a.33933

15. Laugel V. Cockayne syndrome: The expanding clinical and mutational spectrum. *Mech Ageing Dev*. 2013;134(5-6):161-170. doi:10.1016/j.mad.2013.02.006

16. Wilson BT, Stark Z, Sutton RE, et al. The Cockayne Syndrome Natural History (CoSyNH) study: Clinical findings in 102 individuals and recommendations for care. *Genet Med*. 2016;18(5):483-493. doi:10.1038/gim.2015.110

17. Rigby RA, Stasinopoulos DM. Generalized additive models for location , scale and shape. 2005:507-554.

18. de Onis M, Blössner M. The World Health Organization Global Database on Child Growth and Malnutrition: Methodology and applications. *Int J Epidemiol*.

2003;32(4):518-526. doi:10.1093/ije/dyg099

19. Vessoni AT, Chaves C, Guerra C, et al. Cockayne Syndrome : The many challenges and approaches to understand a multifaceted disease. 2020;1(suppl 1).

20. Rapin I. *Disorders of Nucleotide Excision Repair*. Vol 113. 1st ed. Elsevier B.V.; 2013. doi:10.1016/B978-0-444-59565-2.00032-0

21. Calmels N, Botta E, Jia N, et al. Functional and clinical relevance of novel mutations in a large cohort of patients with Cockayne syndrome. *J Med Genet*. 2018:jmedgenet-2017-104877. doi:10.1136/jmedgenet-2017-104877

22. Laugel V. Cockayne Syndrome. 2000 Dec 28 [Updated 2019 Aug 29]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.

23. Calmels N, Botta E, Jia N, et al. Functional and clinical relevance of novel mutations in a large cohort of patients with Cockayne syndrome. *J Med Genet*. 2018;55(5):329-343. doi:10.1136/jmedgenet-2017-104877

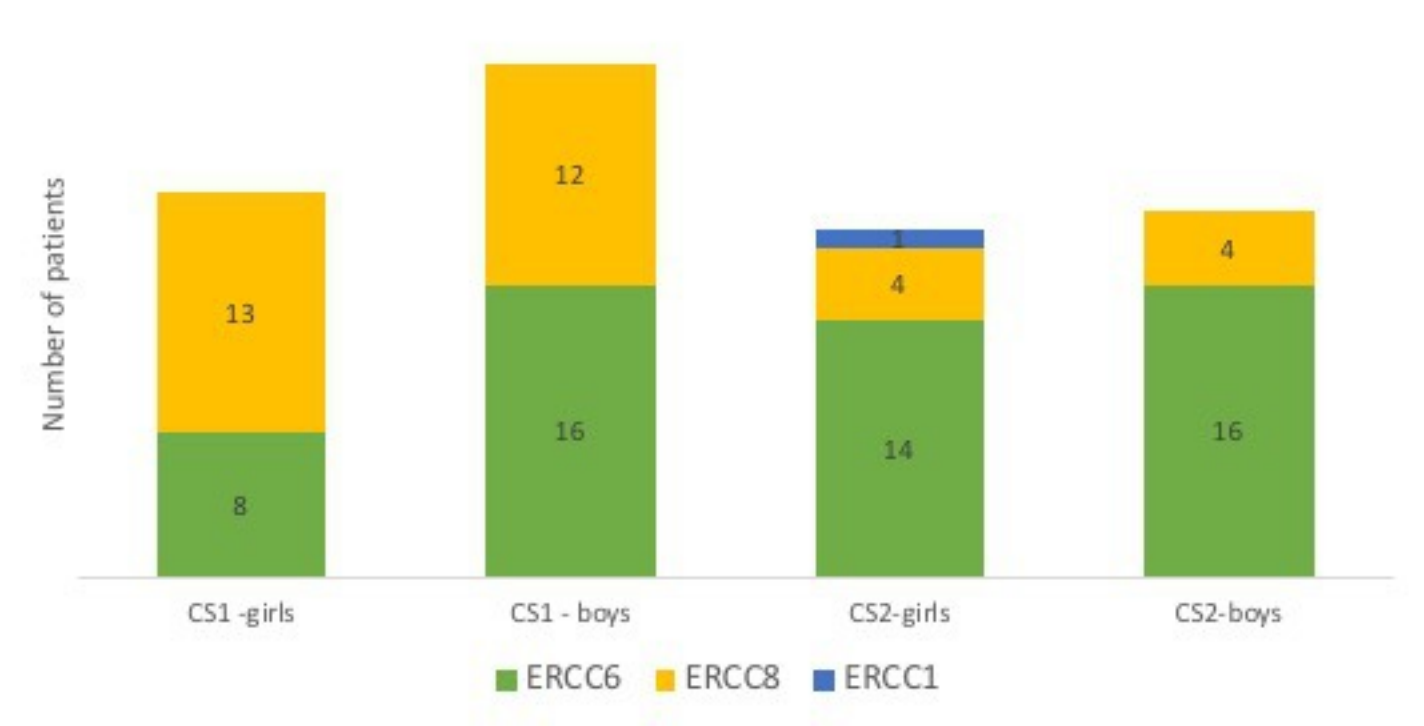
24. Kashiyama K, Nakazawa Y, Pilz DT, et al. Malfunction of nuclease ERCC1-XPF results in diverse clinical manifestations and causes Cockayne syndrome, xeroderma pigmentosum, and Fanconi anemia. *Am J Hum Genet*. 2013;92(5):807-819. doi:10.1016/j.ajhg.2013.04.007

25. Jaspers NGJ, Raams A, Silengo MC, et al. First reported patient with human ERCC1 deficiency has cerebro-oculo-facio- skeletal syndrome with a mild defect in nucleotide excision repair and severe developmental failure. *Am J Hum Genet*. 2007;80(3):457-466. doi:10.1086/512486

26. Karikkineth AC, Scheibye-Knudsen M, Fivenson E, Croteau DL, Bohr VA. Cockayne

syndrome: Clinical features, model systems and pathways. *Ageing Res Rev*. 2017;33:3-17. doi:10.1016/j.arr.2016.08.002

27. Cleaver JE, Lam ET, Revet I. Disorders of nucleotide excision repair: The genetic and molecular basis of heterogeneity. *Nat Rev Genet*. 2009;10(11):756-768. doi:10.1038/nrg2663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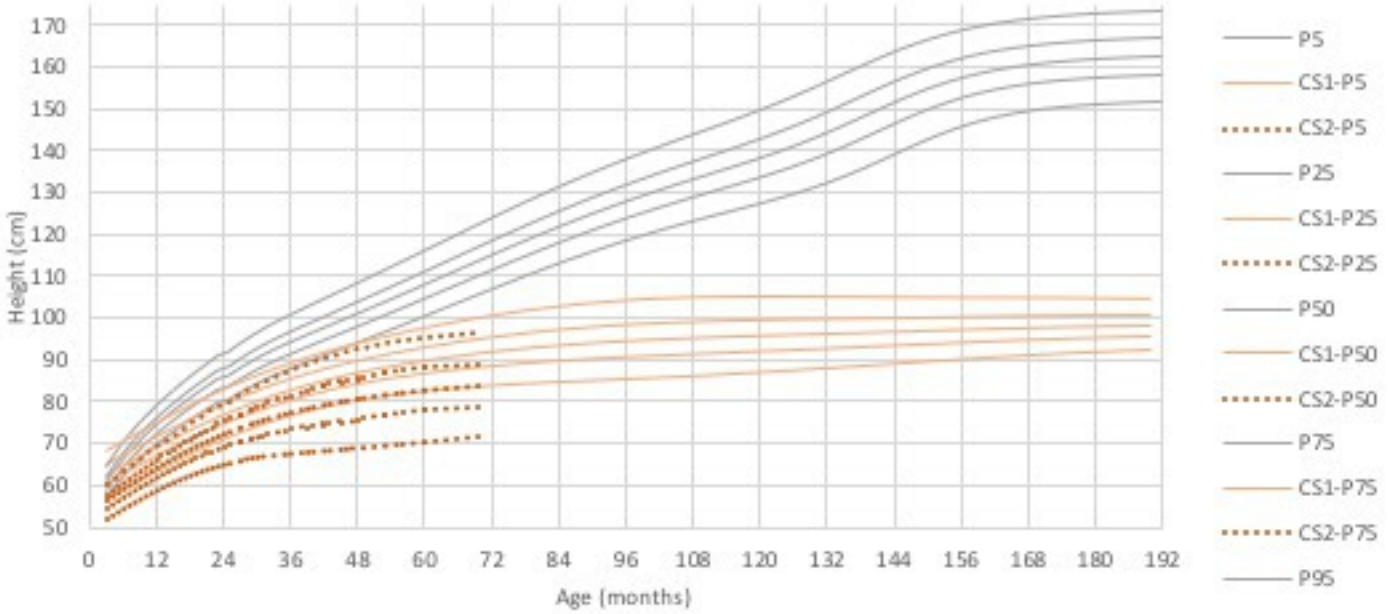
CS1 - boys
CS2-girls
CS2-boys
ERCC6
ERCC8
ERCC1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84
96
108
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132
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156
168
180
192
Age (months)
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CS1-P5
CS2-P5
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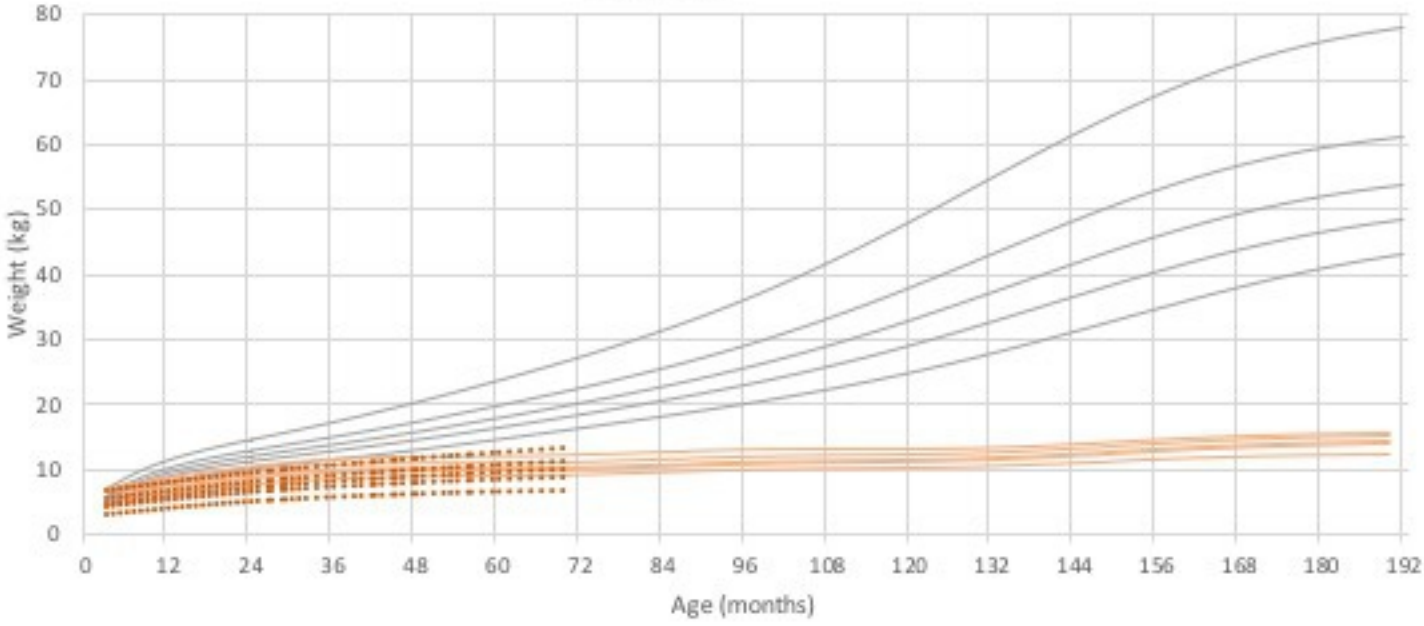
CS2-P75
P95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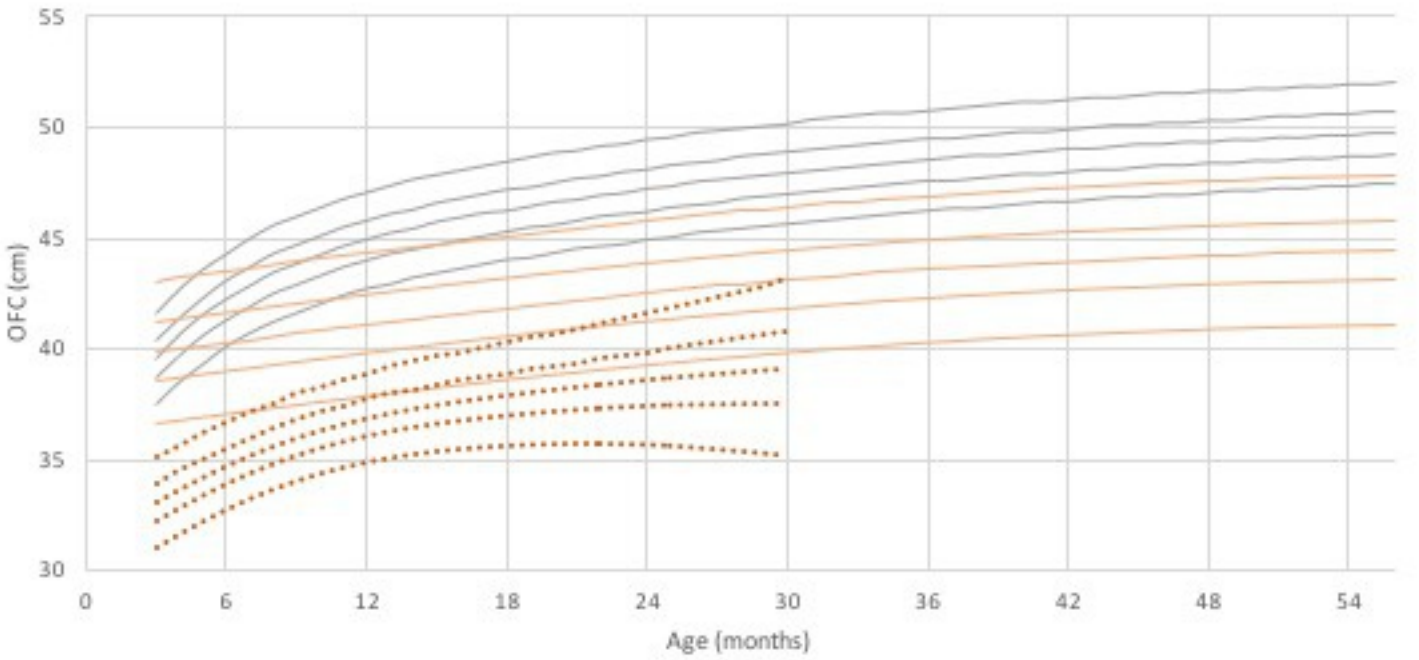
Age (months)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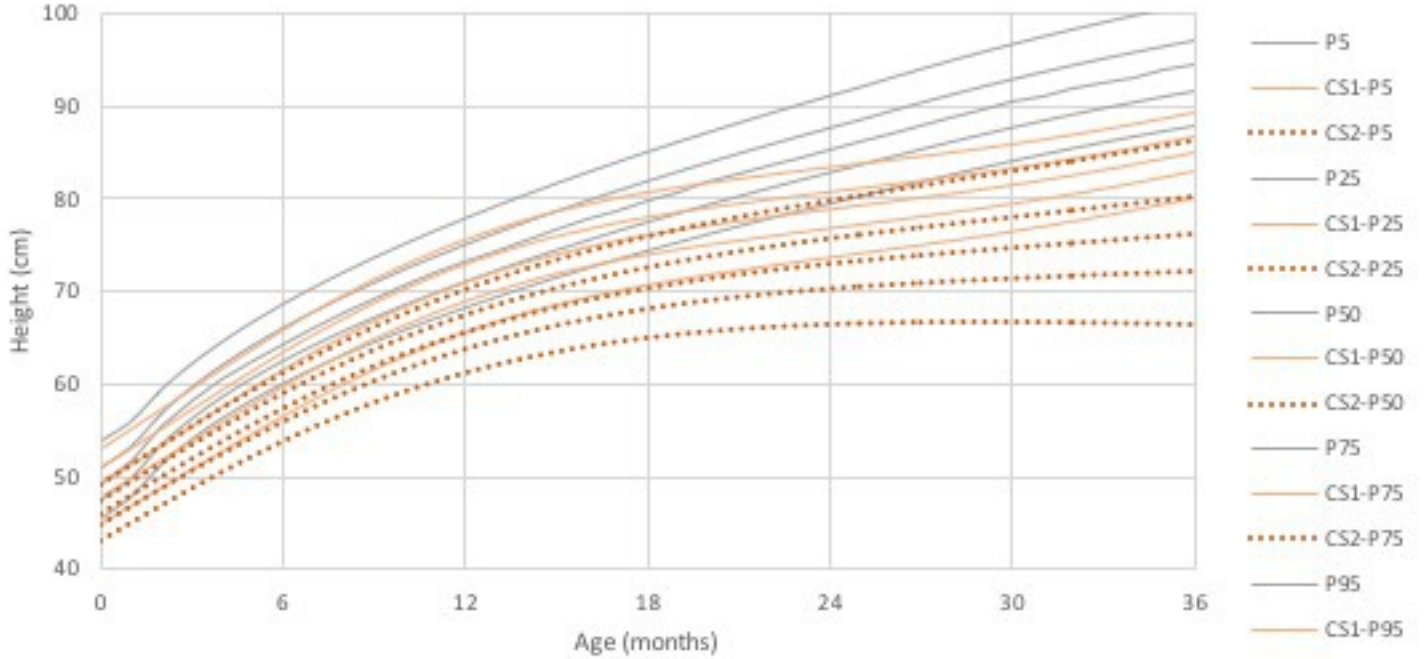
Age (months)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Age (months)
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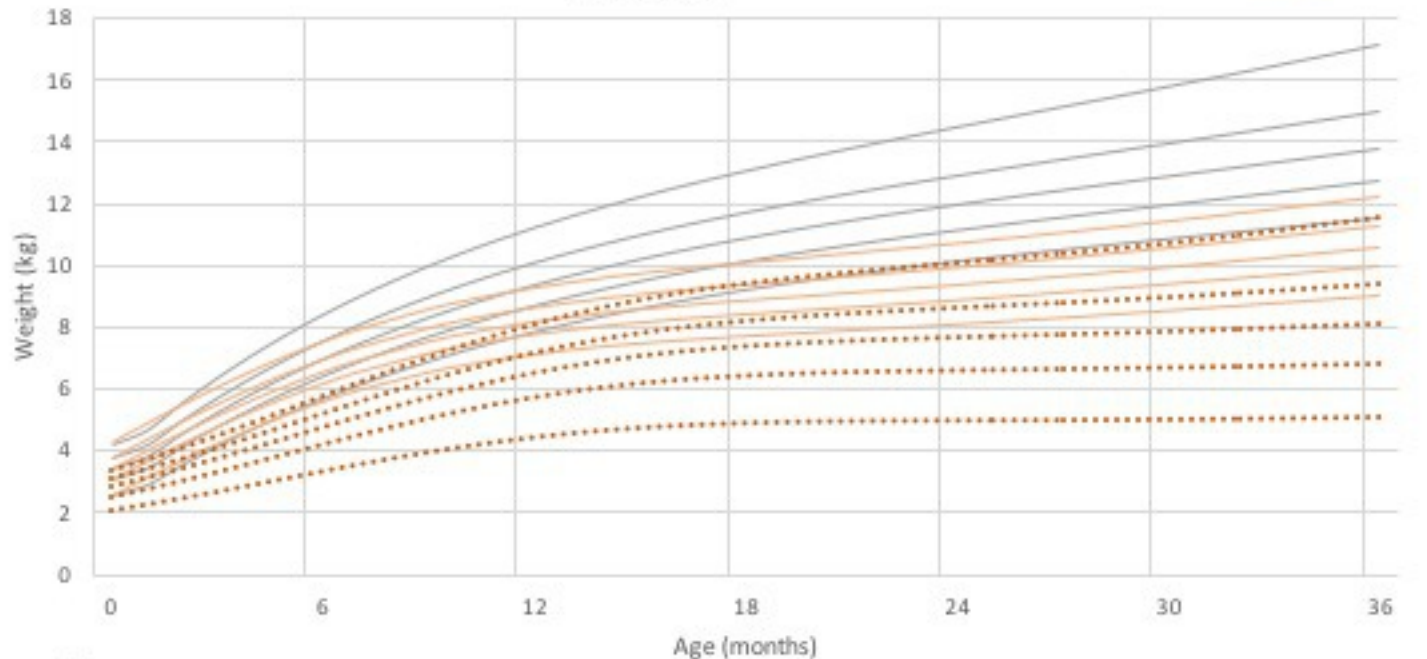
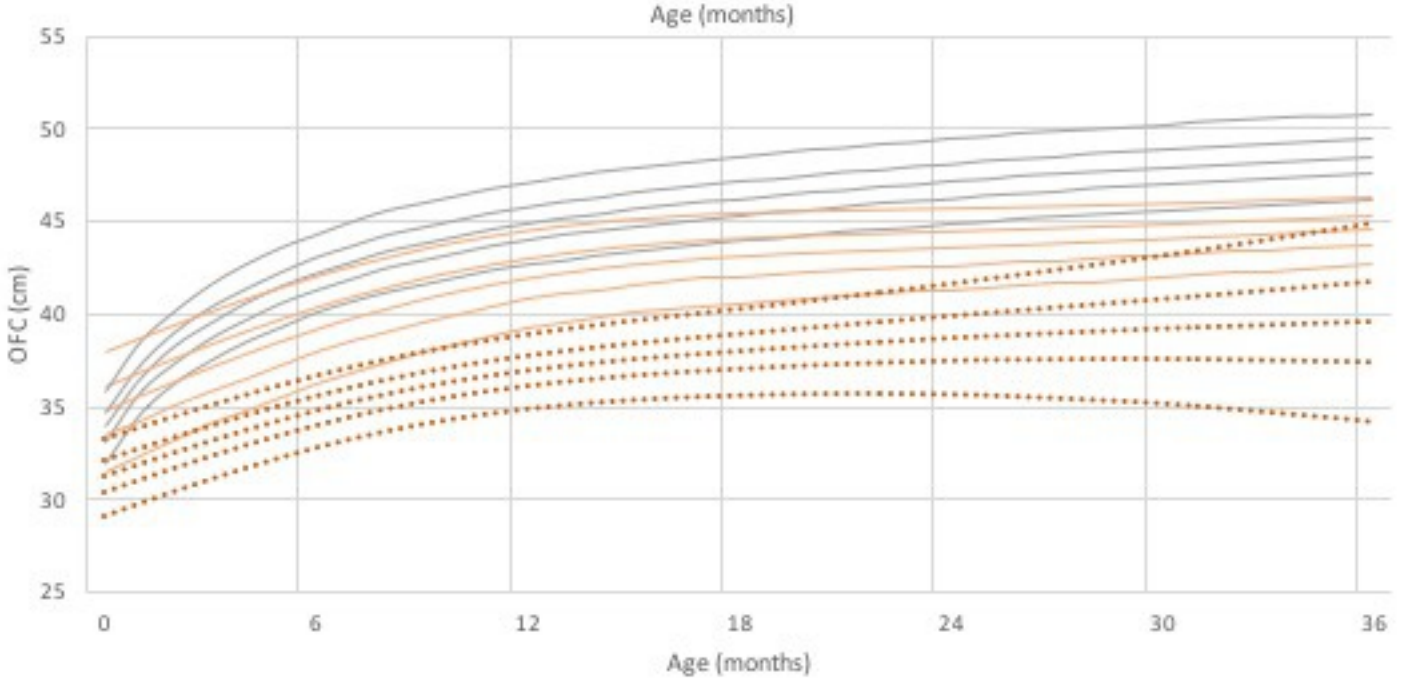
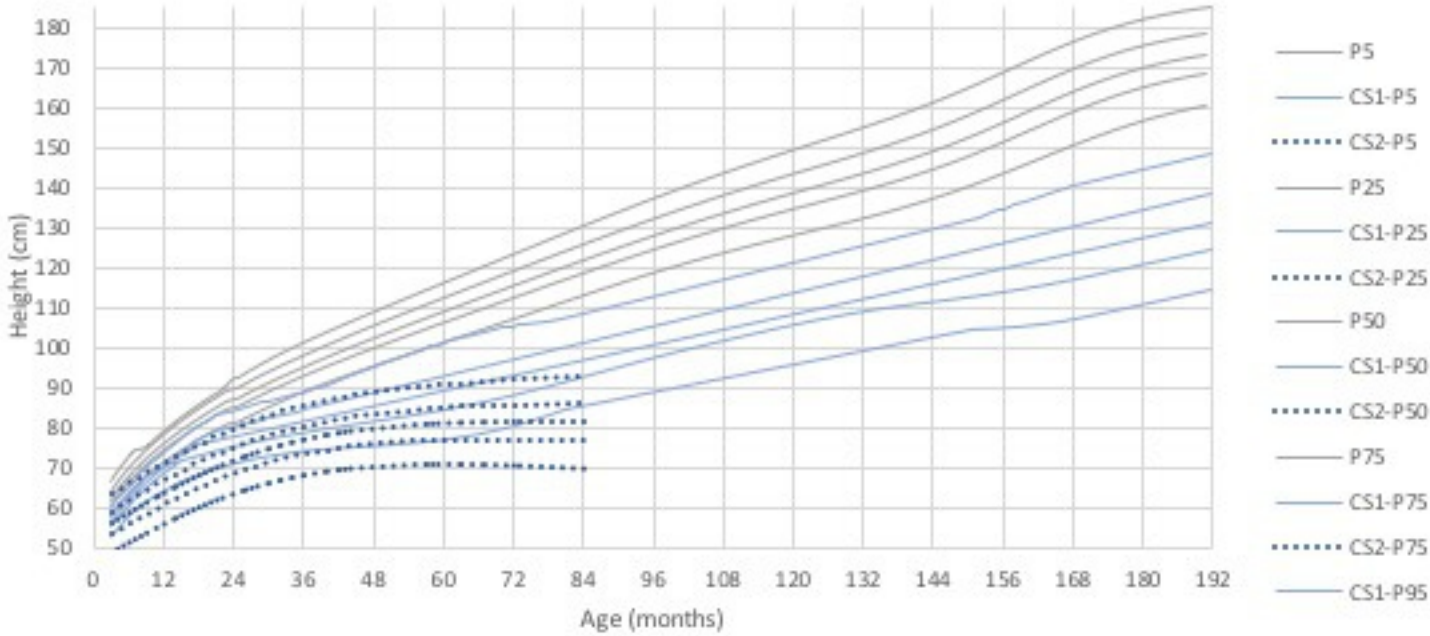
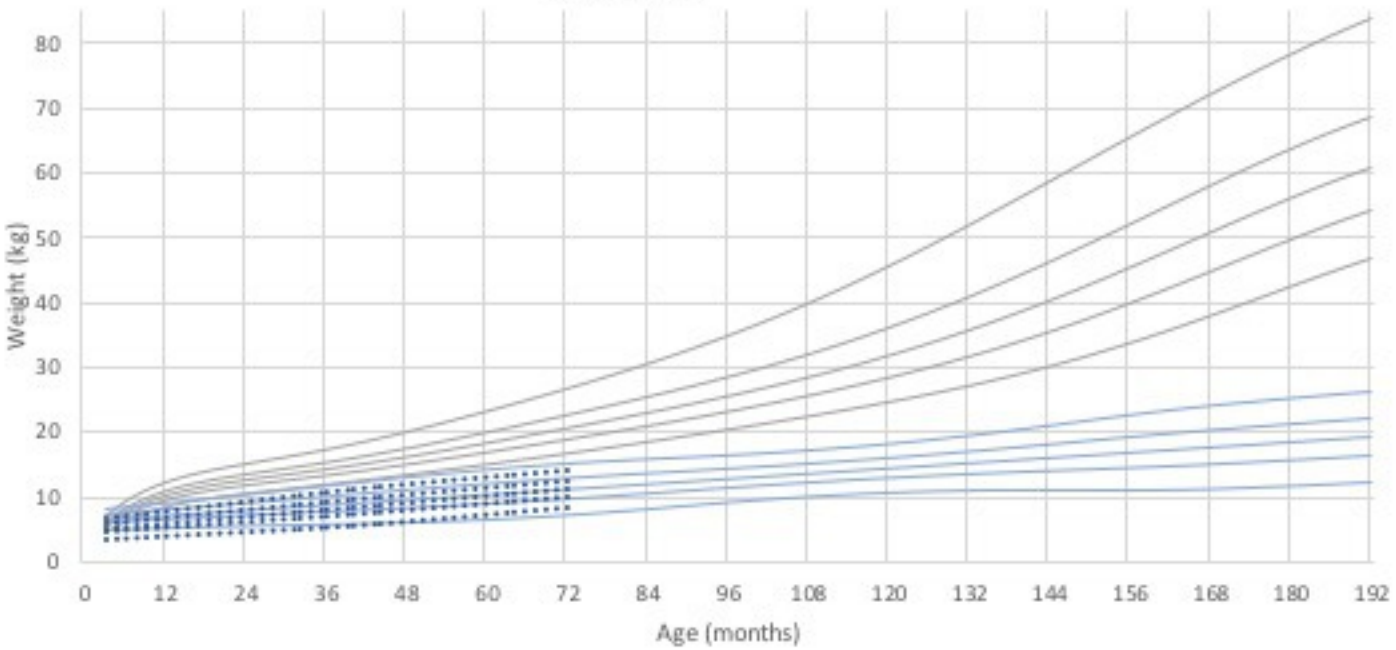
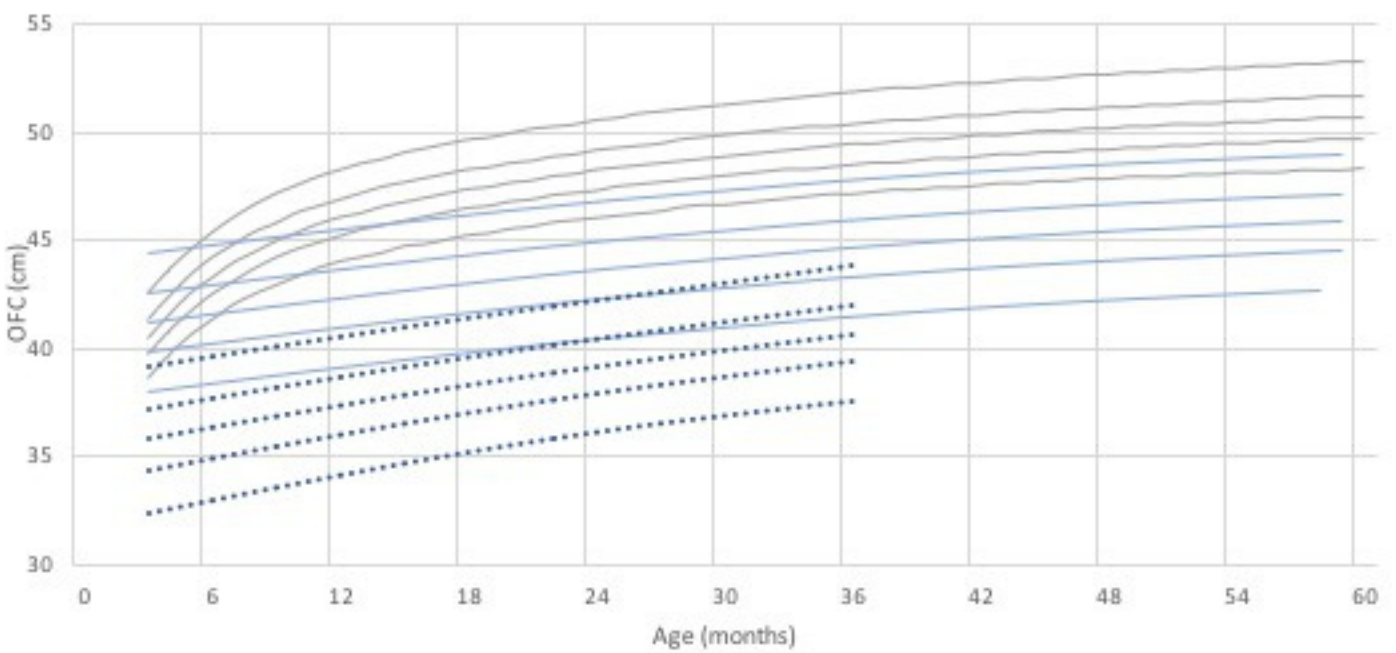
CS1-P5
CS2-P5
P25
CS1-P25
CS2-P25
P50
CS1-P50
CS2-P50
P75
CS1-P75
CS2-P75
P95
CS1-P95

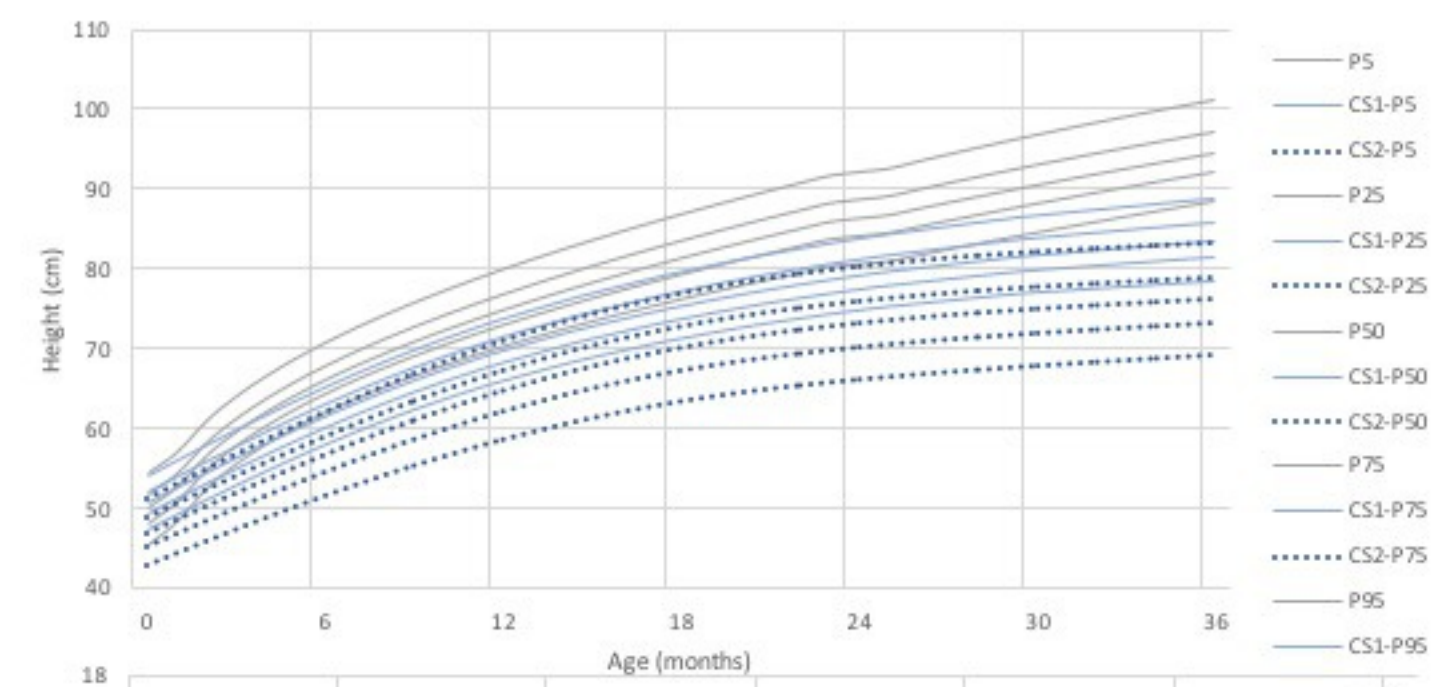

Weight (kg)
18
16
14
12
10
8
6
4
2
0
0
6
12
18
24
30
36
Age (months)

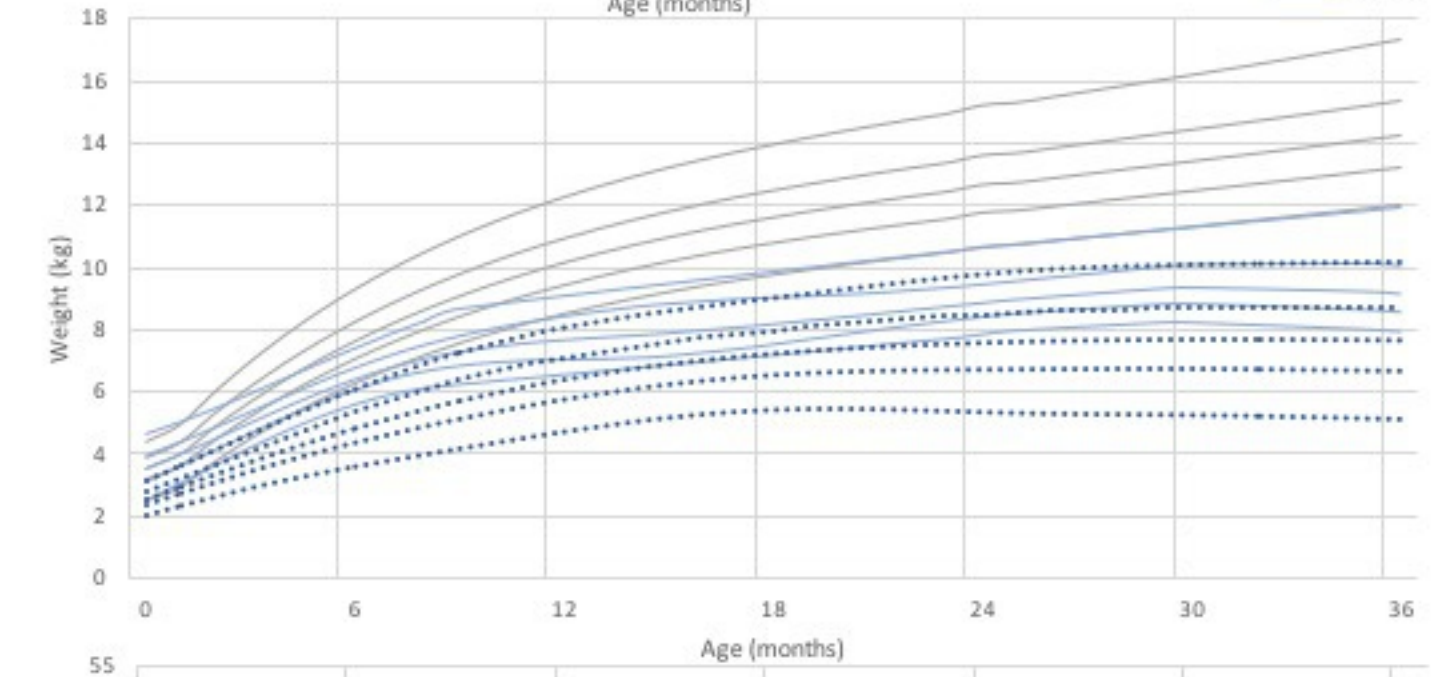

OFC (cm)
55
50
45
40
35
30
25
0
6
12
18
24
30
36
Age (months)

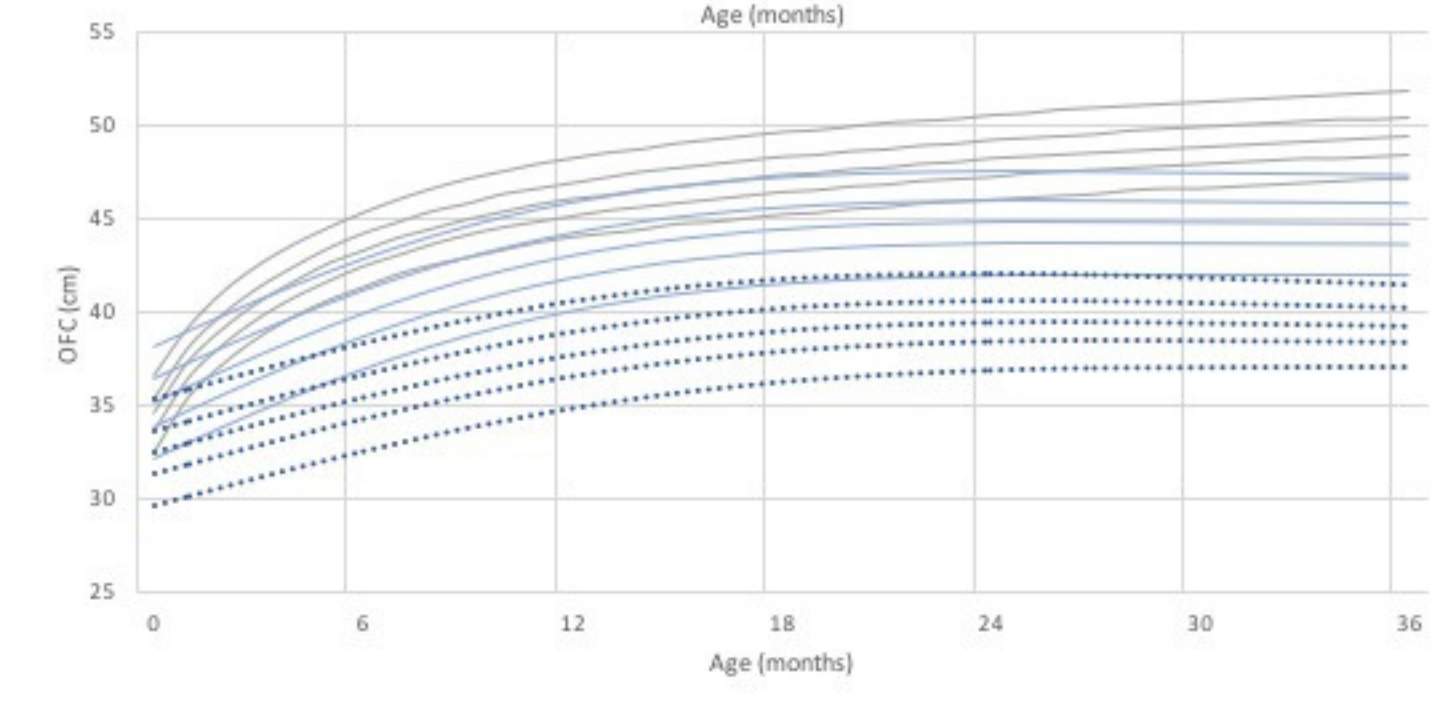

Height (cm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
180
192
Age (months)
P5
CS1-P5
CS2-P5
P25
CS1-P25
CS2-P25
P50
CS1-P50
CS2-P50
P75
CS1-P75
CS2-P75
CS1-P95


Weight (kg)
80
70
60
50
40
30
20
10
0
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
180
192
Age (months)


OFC (cm)
55
50
45
40
35
30
0
6
12
18
24
30
36
42
48
54
60
Age (months)


Height (cm)
110
100
90
80
70
60
50
40
0
6
12
18
24
30
36
Age (months)
P5
CS1-P5
CS2-P5
P25
CS1-P25
CS2-P25
P50
CS1-P50
CS2-P50
P75
CS1-P75
CS2-P75
P95
CS1-P95


Weight (kg)
18
16
14
12
10
8
6
4
2
0
0
6
12
18
24
30
36
Age (months)


OFC (cm)
55
50
45
40
35
30
25
0
6
12
18
24
30
36
Age (months)