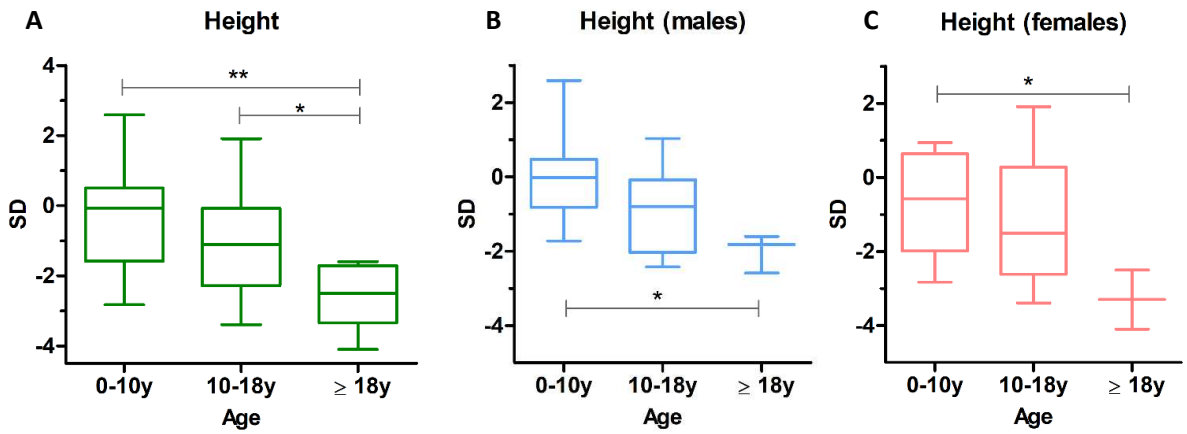
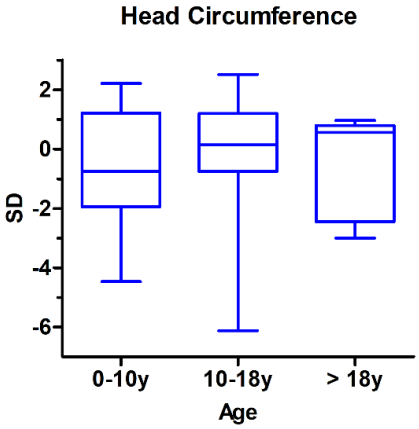
Supplementary File S1 - Clinical Information from our Cohort of 53 Individuals with KBG Syndrome

Some of the clinical information we collected were particularly relevant for complementing the radiological description of dysmorphic skeletal features and altered skeletal development in KBG syndrome.
Abnormal curvature of the vertebral column has already been discussed together with other vertebral anomalies (see "Results: Radiological Features") because of the importance of diagnostic imaging in providing a complete overview of these characteristics (Table 2, Supplementary Table S2, Figure 2G-I).
Another relevant feature is macrodontia of the permanent upper incisors, ostensibly the most distinctive sign of KBG syndrome. Although radioimaging can aid its evaluation, macrodontia is usually detected through physical examination. It was reported in 85-95% cases in the literature[8] and in 85.7% of the individuals with permanent dentition in our cohort (30 of 35 evaluated; Figure 2A-B, Table 2, Supplementary Table S2). Macrodontia could also be detected in the deciduous dentition, but with a lower incidence (56.3%), while other anomalies of dentition, most notably tooth malposition with crowding (41.2%) and oligodontia (13.7%), can be observed at all ages (Table 2, Supplementary Table S2). Physical examination is usually sufficient to detect macrodontia, but given the high frequency of other abnormalities of dentition, specific imaging and an accurate evaluation by an orthodontist are recommended for the prevention and treatment of associated dental diseases.
Short stature was observed in 13/47 individuals in our cohort (27.7%), with 10/27 females (37.0%) and 3/22 males (13.6%) presenting with height > 2 SD below the mean according to the age-appropriate WHO/CDC growth charts[47] (Supplementary Table S4). By dividing the participants into three developmental groups, pre-pubertal (≤ 10 years, n=21), pubertal (10-18 years, n=21), and fully developed (≥ 18 years, n=5), we observed that short stature displayed a significant progression with age (p = 0.006; Supplementary Figure S3A), corroborating a recent report on the natural history of the disease.[48] The fully developed group had a mean final height of -2.50 (SD ± 0.44), which was significantly different from the mean of both the pre-pubertal (p = 0.002) and the pubertal (p = 0.04) participants. The same trend was detected by considering males and females independently, although the significance was affected by the smaller sample size (Supplementary Figure S3B-C). Notably, we observed only one participant (Pt. 12, a boy) with radiological confirmation of short long bones of all limbs, who had a corresponding height at the lower limits of normal (-1.48 SD), but since he was last evaluated at 4 years of age, his final height is unknown (Supplementary Table S2).



Supplementary Figure S3. Box plots representing the distribution of stature in our cohort, expressed as standard deviations (SD) from the sex- and age-matched average: (**A**) across all evaluated individuals, n=47; (**B**) in males only, n=20; (**C**) in females only, n=27. Two male patients had been in treatment with growth hormone and were excluded. y, years; *, significant difference at $p < .05$; **, significant difference at $p < .01$.

Alterations of head circumference were less consistent, with 5/36 evaluated participants (13.9%) showing microcephaly and three (8.9%) macrocephaly (Supplementary Table S4). The overall mean was -0.33 (SD ± 1.85) with a median of -0.04, and did not vary significantly across age groups (Supplementary Figure S4).



Supplementary Figure S4. Box plot representing the distribution of head circumference in our cohort, measured as occipital-frontal circumference and expressed as standard deviations (SD) from the sex- and age-matched average.

Further clinical information obtained from our cohort essentially confirmed the prevalence reported in recent reviews.[16,30] In particular, out of 38 participants who underwent a cardiological evaluation, 13 (31.5%) had cardiac anomalies, generally limited to septal defects (Supplementary Table S4). This reinforces the observation by Digilio et al.[49] that congenital heart defects are more common than previously reported, and the recommendation to include echocardiography in the management of individuals with KBG syndrome.

Additional References:

47 WHO/CDC growth charts. Available online: https://www.cdc.gov/growthcharts/index.htm (accession: August 2022).

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