Expanding the KBG syndrome phenotype through 2D facial morphometry, clinical and molecular characterization

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Abstract. KBG syndrome (KBGS) is a neurodevelopmental disorder caused by *ANKRD11* (ankyrin repeat domain-containing protein 11) haploinsufficiency. Its broad phenotypic variability and overlap with other types of chromatinopathies frequently hinder clinical recognition, and genotype-phenotype associations remain limited. The present study aimed to characterize the clinical and molecular features of individuals with KBGS and expand the craniofacial phenotype using two-dimensional (2D) facial morphometry. The present retrospective study involved patients with molecularly confirmed KBGS evaluated between January 2017 and February 2025 at Fundación Valle del Lili (Cali, Colombia). Detailed developmental, craniofacial, skeletal, neurological and behavioral features were documented. Molecular diagnoses were established using clinical exome sequencing. Craniofacial differences were quantified using 2D morphometric analysis. A systematic review of the literature was performed to compare the prevalence of clinical manifestations observed in the present cohort with previously reported cohorts. All 10 individuals carried pathogenic or likely pathogenic *ANKRD11* variants, including multiple novel frameshift mutations. Developmental delay and intellectual disability were universal. Recurrent clinical findings included facial asymmetry, low hair implantation, bulbous nasal tip, synophrys, scoliosis, seizures, behavioral disturbance and hearing impairment. Morphometric analysis identified distinctive craniofacial patterns differentiating patients from controls, mainly involving facial asymmetry, increased forehead height, nasal prominence, increased lower lip thickness and reduced chin prominence. The literature review confirmed shared chromatinopathy-related features, including developmental delay, intellectual disability, craniofacial dysmorphism, skeletal anomalies and behavioral disturbances, as well as under-recognized findings such as facial asymmetry, low anterior hairline, hypotonia and hearing impairment. The present study broadens the phenotypic and genotypic landscape of KBGS, providing quantitative craniofacial characterization, and refines genotype-phenotype associations to support improved diagnostic accuracy.

Introduction

KBG syndrome (KBGS, Online Mendelian Inheritance in Man no.148050) is a rare autosomal dominant disorder caused by heterozygous disease-causing variants in the ankyrin repeat domain 11 (*ANKRD11*) gene or by microdeletions of the 16q24.3 region encompassing this gene (1,2-6). ANKRD11-related KBG syndrome is increasingly recognized, with >375 individuals reported in the literature (7,8). ANKRD11 encodes a transcriptional coregulator involved in chromatin remodeling and regulation of gene expression through interactions with histone-modifying enzymes, transcriptional cofactors and the cohesin complex (5,6,8,9,10). *ANKRD11* expression is key for nervous system development and function, influencing neural progenitor proliferation, neuronal generation, positioning and plasticity and dendritic differentiation (6,8). Structurally, the protein contains five N-terminal ankyrin repeats, two repression domains, one activation domain and C-terminal D-box motifs that regulate proteasomal degradation during the cell cycle (5,6). KBGS is primarily caused by heterozygous loss-of-function *ANKRD11* variants, including truncating frameshift and nonsense variants, or 16q24.3 microdeletions involving *ANKRD11*, resulting

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in haploinsufficiency (2-6). Pathogenic mechanisms include impaired chromatin regulation, and altered transcriptional control of developmental genes, supporting the classification of KBGS as a chromatinopathy (8-10). These molecular alterations are consistent with the neurodevelopmental, skeletal and craniofacial manifestations observed in affected individuals, including developmental delay, intellectual disability, short stature, facial dysmorphism and dental anomalies such as macrodontia (1,2,5,9,10).

Currently, the prevalence of KBGS is hypothesized to be underestimated due to its wide phenotypic variability, variable severity and mild presentations in some individuals. Numerous pathogenic *ANKRD11* variants and 16q24.3 deletions have been described (2-4,8,11,12). Although no consensus clinical diagnostic criteria has been published, KBGS should be suspected in individuals with developmental delay and/or intellectual disability, attention-deficit/hyperactivity disorder or autism spectrum disorder, together with characteristic phenotypic features or associated comorbidities. The primary clinical features include postnatal short stature, hand and costovertebral anomalies, macrodontia of the upper central incisors as a key feature and a triangular facial shape (1-4,8,13,14).

Considering the substantial clinical heterogeneity, other disorders with overlapping clinical features with KBGS have been considered in the differential diagnosis, such as Cornelia de Lange syndrome (OMIM No. 122470), Silver-Russell syndrome (OMIM No. 180860), Aarskog-Scott syndrome (OMIM No. 305400) and Coffin-Siris syndrome (OMIM No. 135900) (4, 9,10,15,16). For this reason, KBGS has recently been classified as part of a new class of disorder, known as chromatinopathies. These disorders result from variants in proteins involved in chromatin remodeling and transcriptional regulation (6,8-10,16).

The present study aimed to describe the clinical and molecular findings of 10 individuals with *ANKRD11* variants, highlighting the broad spectrum of associated phenotypes, and to establish genotype-phenotype associations to refine the characterization of this syndrome and compare its phenotypic features with those of classical chromatinopathy (2-4,13,17-19).

The present study conducted a systematic review of the literature addressing the clinical and molecular aspects, providing a broader framework for interpreting our findings (2-4,11,13,17,19,20).

Materials and methods

Study design and participants. The present retrospective observational case series included 10 individuals with molecularly confirmed KBGS evaluated at the Clinical Genetics Service of Fundación Valle del Lili (Cali, Colombia) between January 2017 and February 2025. Inclusion criteria comprised a compatible clinical phenotype and the identification of a pathogenic or likely pathogenic *ANKRD11* variant or a chromosomal rearrangement involving the 16q24.3 region. Patients without molecular confirmation of KBGS or with insufficient clinical or photographic data for analysis were excluded. Clinical, demographic and molecular data were obtained from medical records and standardized clinical genetic evaluations. The patient group comprised six males and four females, with an age range of 6-37 years at the time of evaluation.

To assess facial dysmorphology in KBGS, the present study included a comparative sample of 10 sex- and age-matched controls recruited during data collection sessions at Universidad Icesi and the Clinical Research Center of Fundación Valle del Lili, Cali, Colombia, between January and March 2021. The control group comprised six males and four females, with an age range of 6-37 years. Control individuals were included only for the 2D facial morphometric analysis if they were from the same geographic region, had no known history of neurodevelopmental disorder, craniofacial anomaly or genetic syndrome, and had standardized frontal facial photographs of sufficient quality for landmark annotation. No genetic testing or screening was performed in the control group.

The present study was approved by the Ethics Committee of Hospital Universitario Fundación Valle del Lili (approval no. 2025.140). Written informed consent was obtained from all patients or their legal guardians for the publication of clinical data and photographic images. The present study was conducted in accordance with the ethical principles of the Declaration of Helsinki, ensuring confidentiality and appropriate use of identifiable information for research and publication.

Clinical evaluation. Phenotypic assessment included growth parameters, neurodevelopmental profile, behavioral manifestations, craniofacial dysmorphism, skeletal anomaly and involvement of other organ systems. Clinical features were described using standardized dysmorphology terminology. Developmental delay, intellectual disability and neuropsychiatric features were recorded based on multidisciplinary clinical and neuropsychological evaluation.

Molecular analysis. Molecular diagnosis and evaluation of clinically relevant differential diagnoses were performed using clinical exome sequencing. In total, four exome analyses were performed institutionally, whereas the remaining studies were performed by external diagnostic laboratories as part of the patient clinical diagnostic workflow. For externally performed tests, sequencing and bioinformatic procedures were performed out according to validated protocols, and the results were reviewed based on the clinical reports available.

For institutionally performed exome analyses, genomic DNA was extracted and purified from peripheral blood samples, followed by preparation of genomic fragment libraries using the KeyExome-GeneSGKit X. 48 Reactions kit, reference LV4283 (Genomic Systems). DNA quantity and purity were assessed using NanoDrop spectrophotometry, including the 260/280 nm ratio, and DNA quantification was performed using Qubit and Quantus fluorometers. Library quality was evaluated using TapeStation capillary electrophoresis, with library fragments showing a Gaussian distribution and a peak of approximately 320 bp. Clonal amplification and sequencing of the selected regions were performed on an Illumina NextSeq 500 platform using Illumina bridge sequencing technology and a paired-end sequencing strategy. Sequencing was performed using the NextSeq 500/550 High Output kit v2.5, 300 cycles, supporting 2x150 bp reads (cat. no. 20024908; Illumina Inc.). Mean sequencing coverage

was recorded according to the clinical laboratory report. Bioinformatic analysis of the DNA sequences was performed by comparison with the reference genome sequence GRCh38 using the GeneSystems® platform v4.0.1 (IVD-CE; https://platform.genesystm.com/services) (21). Variants were considered for analysis when they showed a read depth ≥20X and a variant allele fraction/read ratio ≥0.2.

ANKRD11 variants were described according to the Human Genome Variation Society (HGVS) nomenclature using the NM_013275.6 reference transcript and classified following the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines (22,23). Variant interpretation was supported by variant interpretation platforms, including VarSome (varsome.com/) and Franklin (Genoox/QIAGEN; franklin.genoox.com/clinical-db/home), together with genotype-phenotype association and available clinical evidence. *In silico* predictive analyses were performed for variants of uncertain significance using VarSome (24,25).

Variants classified as pathogenic or likely pathogenic were confirmed by Sanger sequencing in four patients for whom confirmation was available as part of the clinical diagnostic workflow. For the remaining six patients, Sanger sequencing chromatograms were generated by external diagnostic laboratories as part of the clinical diagnostic workflow (data not available).

Parental segregation studies were performed when parental samples were available. Novelty was assessed based on the absence of previous reports in VarSome, Franklin and the available literature. Novel variants are currently in the process of being submitted to ClinVar (26).

Two-dimensional facial morphometry. Two-dimensional facial morphometric analysis was performed in patients and controls using standardized 2D frontal photographs. Images were acquired with participants in an upright head position and neutral expression, with open eyes and closed mouth.

A set of 21 anatomical facial landmarks were manually annotated using the tpsDig2 software version 2.32, 64-bit executable (27) and quantitative shape analyses were conducted to identify craniofacial patterns associated with KBGS. Facial shape variation was assessed using geometric morphometrics, a robust set of statistical tools designed for measuring and comparing 2D/3D shapes with high precision and efficiency (27,28-31). Facial landmark configurations were aligned in a common morphospace using generalized Procrustes analysis, removing non-shape variance due to translation, rotation and scale. Multivariate linear regression was performed to correct for age-associated facial shape differences. The regression residuals were analyzed using principal component analysis (PCA) to explore facial differences between patients with KBGS and matched controls. Morphological variation was visualized in the morphospace defined by the first two principal components. Group differentiation was assessed using Procrustes distances between mean shapes, calculated as the square root of the sum of squared differences between homologous landmarks. All statistical analyses were performed in MorphoJ 1.08.01 (32) and R 4.4.2 using the geomorph package v4.0.10 (33). Statistical significance was determined using 1,000-permutation tests, with $P<0.05$ considered statistically significant.

Results

Cohort characteristics. A total of 10 individuals with molecularly confirmed KBGS were included, comprising six males and four females. Age at molecular diagnosis ranged from 4 to 36 years, with a mean age of 16.4 years. All individuals were followed at Fundación Valle del Lili (Cali, Colombia) and underwent comprehensive clinical genetic evaluation.

Developmental delay was present in all patients (10/10, 100%) and all met criteria for intellectual disability, with severity ranging from mild to severe. Growth parameters were variable. Current height ranged from 99 to 171 cm, and birth length data were available for 4/10 individuals, ranging from 47 to 52 cm.

All phenotypic and molecular characteristics are described in Tables I and II.

Clinical features. Semiological findings and phenotypic abnormalities were defined using terms from Human Phenotype Ontology (34).

Craniofacial findings. Craniofacial dysmorphism was identified in all individuals, although the specific combination and severity of features varied (Fig. 1). The most frequent findings included low anterior hairline (8/10, 80%), bulbous nasal tip (8/10, 80%), synophrys (6/10, 60%), facial asymmetry (7/10, 70%) and prominent ears (6/10, 60%). Additional recurrent features included full or arched eyebrows (7/10, 70%), triangular face, brachycephaly, coarse facial features, hypertelorism, long philtrum and macrodontia of the permanent upper central incisors (all 5/10, 50%) (Fig. 2). Less frequent findings included microcephaly (3/10, 30%), downslanting palpebral fissures (2/10, 20%), upslanting palpebral fissures (3/10, 30%), macrostomy (2/10, 20%), cleft lip and/or palate (1/10, 10%), prognathism (1/10, 10%) and micrognathia (4/10, 40%).

Skeletal manifestation. Skeletal anomalies were commonly observed. Scoliosis was the most frequent finding (6/10, 60%). Digital anomalies were prominent, including clinodactyly and/or campodactyly (7/10, 70%), short fourth and fifth fingers (5/10, 50%) and persistent fetal fingertip pads (4/10, 40%). Less frequent skeletal features included cubitus valgus (2/10, 20%), short neck (2/10, 20%), single transverse palmar crease (1/10, 10%), broad thumbs (1/10, 10%), and broad hallux (1/10, 10%).

Neurological and behavioral features. All individuals exhibited developmental delay and intellectual disability. Hypotonia was observed in half of the cohort (5/10, 50%). Behavioral and neuropsychiatric manifestations were frequent, including behavioral disorder (5/10, 50%), attention-deficit hyperactivity disorder (4/10, 40%) and autistic features (4/10, 40%). Seizures were reported in four individuals (40%). Brain magnetic resonance imaging, when available, demonstrated variable findings, including periventricular white matter signal abnormalities compatible with mild leukoencephalomalacia in one patient.

Additional systemic findings. Sensorineural or conductive hearing loss was identified in eight individuals (80%), making it one of the most prevalent non-neurological manifestations in the cohort. Gastrointestinal involvement was frequent, including feeding difficulties (6/10, 60%), gastroesophageal

Table I. Clinical and molecular features of patients with KBG Syndrome.

Patient no.	1	2	3	4	5	6	7	8	9	10
Sex	M	F	M	M	M	M	M	F	F	F
Age at diagnosis years	36	27	15	17	15	10	7	4	16	17
Age at last evaluation, years (March 2025)	37	29	19	19	21	16	11	6	18	20
Exon	9	12	7	9	12	9	9	9	9	9
Heterozygous variant	c.3600dup (p. Val1201 SerfsTer3)	c.7753C>T (p. Arg2585 Cys)	c.741C>A (p.Tyr247Ter)	c.4218C>A (p. Tyr1406 Ter)	c.7744_7745 dup (p. Asn2583 Serfs*20)	c.6517delG (p. Val2173 Serfs*2)	c.1903_1907del (p. Lys635 Glnfs*26)	c.5397dup (p. Glu1800 ArgfsTer150)	c.3499dup (p.Ser1167 PhefsTer)	c.3055_ 3059del (p.Arg1019 GlyfsTer14)
Type of mutation	Frameshift	Missense	Nonsense	Nonsense	Frameshift	Frameshift	Frameshift	Frameshift	Frameshift	Frameshift
Novel variant	+	+	+	-	+	+	-	+	+	+
Inheritance	NI	NI	*De novo*	*De novo*	NI	*De novo*	*De novo*	*De novo*	NI	NI
ACMG/AMP classification	LP	LP	LP	P	LP	LP	P	LP	LP	P
Height at birth, cm	NI	NI	NI	50	52	NI	47	NI	50	NI
Height at at last evaluatio, cm (March 2025)	147	141	162	149	171	154	153	99	149	150
Craniofacial features										
Brachycephaly HP:0000248	+	-	-	-	+	+	-	-	+	-
Microcephaly HP:0000252	-	+	+	-	-	-	-	+	-	-
Low hair implantation HP:0002162	+	+	+	+	+	+	+	-	+	-
Coarse facies HP:0000280	+	+	-	+	-	+	+	-	-	-
Facial asymmetry HP:0000324	+	+	-	+	+	+	+	-	-	+

Table I. Continued.

Patient no.	1	2	3	4	5	6	7	8	9	10
Triangular face HP:0000325	-	-	+	-	-	+	+	-	+	+
Prominent forehead HP:0011220	-	-	+	-	-	+	-	-	-	-
Synophrys HP:0000664	+	+	-	+	-	-	+	-	+	+
Full, arched eyebrows HP:0002553	-	+	+	+	+	-	+	-	+	+
Hypertrichosis HP:0000998	-	-	+	+	-	-	-	-	+	-
Hypertelorism HP:0000316	-	-	+	-	+	+	-	-	+	-
Downslanting palpebral fissures HP:0000494	-	-	-	-	+; left	+	+	-	-	-
Upslanting palpebral fissures HP:0000582	+	-	-	-	-	-	-	+	-	+
Prominent nasal bridge HP:0000426	-	+	+	+	-	+	+	-	+	+
Bulbous nose HP:0000414	+	+	+	+	+	+	+	-	+	+
Long philtrum HP:0000343	-	+	+	+	-	-	-	-	+	-
Tented upper lip HP:0010804	-	-	-	-	-	-	-	-	+	-
Thin upper lip HP:0000219	-	+	-	-	-	-	-	-	-	-
Thick lips HP:0012471	-	-	-	+	-	-	+	-	-	-
Macrostomy HP:0000154	+	-	-	-	-	+	+	-	-	-

Table I. Continued.

Patient no.	1	2	3	4	5	6	7	8	9	10
Macrodontia HP:0001572	-	-	+	+	+	-	+	-	+	-
Wide-spaced teeth HP:0000687	-	-	-	+	-	+	+	-	-	-
Prominent ears HP:0000411	+	-	+	+	+	+	-	-	-	+
Cleft palate/lip HP:0000175, HP:0410030	-	+	-	-	-	-	-	-	-	-
Prognathism HP:0000303	-	+	-	-	-	-	-	-	-	-
Micrognathia HP:0000347	-	-	+	+	+	-	+	-	+	-
Low-set posteriorly rotated ears HP:0000358	-	-	-	+	+	+	+	-	-	-
Cupped ears HP:0000378	-	-	-	-	+	+	-	-	-	-
Preauricular skin tags HP:0000384	-	-	-	-	-	-	-	-	-	+
Skeletal features										
Scoliosis HP:00026 50	-	+	-	-	+	+	+	-	+	+
Short neck HP:0000470	-	-	-	-	-	-	-	-	+	+
Cubitus valgus HP:0002967	+	-	-	+	-	-	-	-	-	-
Single transverse line HP:0000954	-	-	+	-	-	-	+	-	-	-
Clinodactyly and camptodactyly HP:0030084 and HP:0012385	-	+	+	+	-	+	+	-	+	+
Broad thumbs HP:0011304	-	-	-	+	-	-	+	-	-	-

Table I. Continued.

Patient no.	1	2	3	4	5	6	7	8	9	10
Broad hallux HP:0010055	-	-	-	+	-	-	-	-	-	-
Short 4th and 5th fingers HP:0008093, HP:0009237	+	-	-	+	+	-	+	-	+	+
Persistence of the fingerpads HP:0001212	-	-	-	+	+	+	+	-	+	-
Neurological findings										
Developmental delay HP:0001263	+	+	+	+	+	+	+	+	+	+
Intellectual disability HP:0001249	+	+; mild	+;moderate to severe	+; severe	+; mild	+; mild	+; moderate	+	+; moderate	+; moderate
Hypotonia HP:0001252	+	-	-	+	+	+	-	+	-	-
Attention-deficit hyperactivity disorder HP:0007018	-	-	-	+	-	+	+	+	-	-
Autistic features HP:0000729	-	-	+	+	-	-	+	+	-	-
Behavioral disorder HP:0000708	-	+	-	+	-	+	+	+	-	-
Seizures HP:0001250	+	+	-	+	-	-	+	-	+	-
Abnormal brain MRI HP:0410263	-	-	-	NI	-	-	-	Periventricular hyperintensity compatible with mild leukoencephalomalacia	-	-

Table I. Continued.

Patient no.	1	2	3	4	5	6	7	8	9	10
Other										
Cardiovascular congenital disease HP:0030680	-	-	-	+; ASD and VSD	-	-	-	-	-	+; persistent vena cava and dilated pulmonary trunk
Renal defects HP:0000077	-	-	-	+; left hydrone-phrosis	-	-	-	-	-	-
Sensorineural hearing loss HP:0000407	+	+	-	+; bilateral conductive deafness	-	+; bilateral sensorineu-ral hearing loss	+; mild to moderate bilateral conductive hearing loss	+; right mild conductive hearing loss	+; mild conductive hearing loss	+; severe mixed conductive hearing impairment
Cryptorchidism HP:0000028	-	-	-	-	-	-	+	-	-	-
Gastrointestinal disorder										
Feeding difficulties HP:0011968	+	+	-	+	-	+	-	+	-	+
Low weight HP:0004325	-	+	-	-	-	+	-	+	-	-
Gastric reflux HP:0002020	+	-	-	+	-	-	-	+	-	-
Anal anomalies HP:0002023	-	-	-	-	-	-	-	-	-	+; imperforate anus
Intestinal abnormalities HP:0002242	-	-	-	+; intestinal malrotation	-	-	-	-	-	-

NI, no information; LP, likely pathogenic; P, pathogenic; ASD, atrial septal defect; VSD, ventricular septal defect; M, male; F, female; HPO, Human Phenotype Ontology.

Table II. Frequency of the main clinical features observed in the KBG syndrome cohort (n=10).

Clinical feature	n (%)
Craniofacial features	
Brachycephaly	4 (40)
Microcephaly	3 (30)
Low hair implantation	8 (80)
Coarse facies	4 (40)
Facial asymmetry	7 (70)
Triangular face	4 (40)
Prominent forehead	2 (20)
Synophrys	6 (60)
Full, arched eyebrows	7 (70)
Hypertrichosis	3 (30)
Hypertelorism	4 (40)
Downslanting palpebral fissures	2 (20)
Upslanting palpebral fissures	3 (30)
Prominent nasal bridge	6 (60)
Bulbous nose	9 (90)
Long philtrum	4 (40)
Tented upper lip	1 (10)
Thin upper lip	1 (10)
Thick lips	1 (10)
Macrostomy	2 (20)
Macrodontia	5 (50)
Wide-spaced teeth	2 (20)
Prominent ears	6 (60)
Cleft palate/lip	1 (10)
Prognathism	1 (10)
Micrognathia	4 (40)
Low-set posteriorly rotated ears	3 (30)
Cupped ears	2 (20)
Preauricular skin tags	2 (20)
Skeletal features	
Scoliosis	6 (60)
Short neck	2 (20)
Cubitus valgus	2 (20)
Single transverse line	1 (10)
Clinodactyly and campodactyly	7 (70)
Broad thumbs	1 (10)
Broad hallux	1 (10)
Short 4th and 5th fingers	5 (50)
Persistence of the fingerpads	4 (40)
Neurological features	
Developmental delay	10 (100)
Intellectual disability	10 (100)
Hypotonia	5 (50)
Attention-deficit hyperactivity disorder	4 (40)
Autistic features	4 (40)
Behavioral disorder	5 (50)
Seizures	4 (40)
Gastrointestinal features	
Feeding difficulties	6 (60)
Low weight	3 (30)
Gastric reflux	3 (30)
Anal anomalies	1 (10)
Intestinal abnormality	1 (10)
Other features	
Cardiovascular congenital disease	2 (20)
Renal defects	1 (10)
Sensorineural hearing loss	8 (80)

reflux (3/10, 30%), low weight (3/10, 30%) and isolated cases of anal anomaly (1/10, 10%) and intestinal abnormality (1/10, 10%). Congenital cardiovascular defects were observed in two individuals (20%) and renal anomalies were identified in one patient. Cryptorchidism was documented in one male individual.

Molecular findings. All 10 individuals carried heterozygous *ANKRD11* variants, consistent with autosomal dominant KBGS. The molecular spectrum was predominantly composed of loss-of-function variants, primarily frameshift and nonsense mutations, supporting *ANKRD11* haploinsufficiency as the underlying pathogenic mechanism (Table I; Fig. 3). In addition to the *ANKRD11* variants reported, no other variants were identified during exome analysis that were considered likely to contribute to the clinical conditions.

Most variants were located in exon 9, a known mutational hotspot, and a single missense variant was identified in one patient (2,6). There were no recurrent variants or 16q24.3 chromosomal rearrangements. Eight variants were considered novel based on the absence of previous reports in variant interpretation platforms, including VarSome and Franklin (24,25), and available literature: c.3600dup (p.Val1201SerfsTer3), c.7753C>T (p.Arg2585Cys), c.741C>A (p.Tyr247Ter), c.7744_7745dup (p.Asn2583Serfs*20), c.6517delG (p.Val2173Serfs*2), c.5397dup (p.Glu1800ArgfsTer150), c.3499dup (p.Ser1167PhefsTer) and c.3055_3059del (p.Arg1019GlyfsTer14) (Table I; Fig. 3). These variants are currently in the process of being submitted to ClinVar (26).

According to ACMG/AMP guidelines, three variants were classified as pathogenic and seven as likely pathogenic, with strong phenotypic concordance (23). Pathogenic or likely pathogenic were confirmed by Sanger sequencing in four patients for whom confirmation was available as part of the clinical diagnostic workflow (Figs. S1-S4). Parental studies, when available, confirmed multiple *de novo* occurrences. Detailed molecular data are summarized in Table I and Fig. 3.

2D facial morphometric analysis. The PCA of 2D facial landmarks revealed partial overlap among diagnostic groups. In total, two patients fell within the range of variation of control

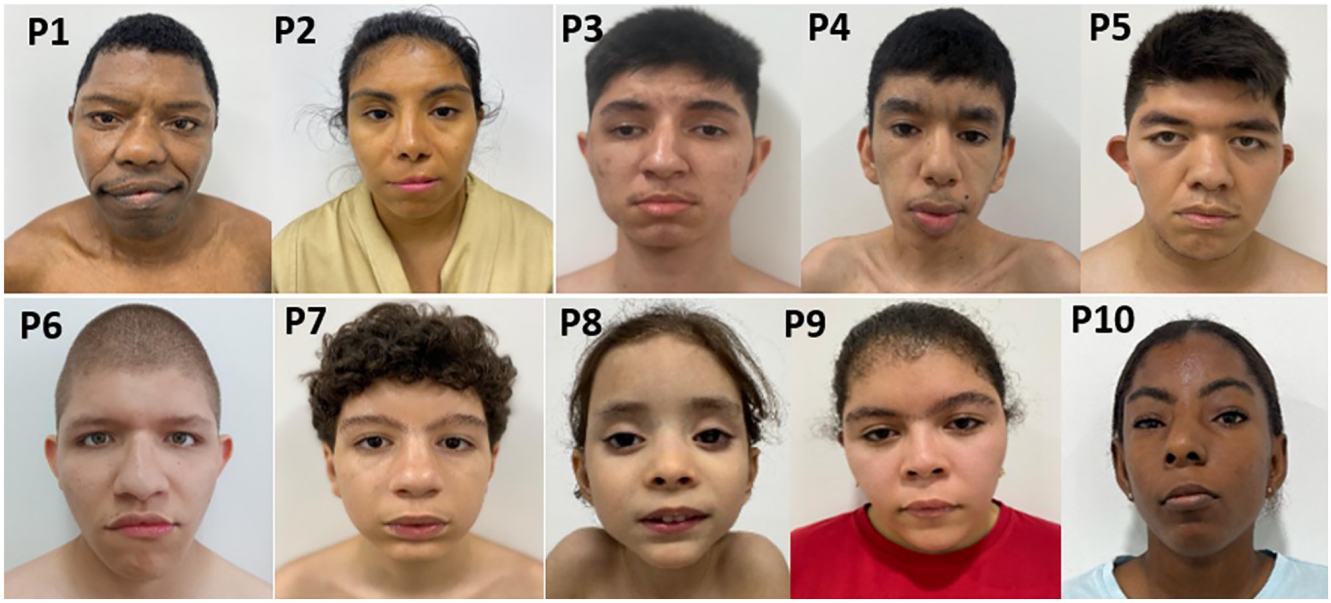

Figure 1. Frontal facial photographs of patients, illustrating the spectrum of facial features associated with *ANKRD11*-related disorder. Images highlight shared and variable dysmorphic traits across the cohort including low anterior hairline, synophrys or full arched eyebrows, bulbous nasal tip, facial asymmetry, prominent ears and variable facial shape. *ANKRD11*, ankyrin repeat domain-containing protein 11.

Figure 2. Representative buccal and dental features in patients with ankyrin repeat domain-containing protein 11 mutations, including macrodontia, dental crowding, and malocclusion. Relevant findings in the extremities observed in P9, including clinodactyly/camptodactyly, short fourth and fifth fingers and persistent fingerpads, are also shown. P, patient.

individuals, whereas the remaining eight exhibited broad dispersion along PC1, which accounted for 34.7% of the total variance. PC2 accounted for 16.1% of variance and revealed a distinct separation between patients and controls (Fig. 4). Permutation tests based on Procrustes distances confirmed that facial shape differences between controls and patients with KBGS were statistically significant (Procrustes distance=0.045; P=0.0288).

At the extremes of PC1, individuals with the most severe dysmorphic features exhibited pronounced facial asymmetries, affecting either the left or the right side of the face (Fig. 4). At the positive extreme, patients had narrower faces, upward displacement of the right orbit, downward nasal tip displacement, increased lower lip thickness and lateral chin deviation to the right. At the negative extreme, patients exhibited wider faces, downward displacement of the right orbit, upward nasal tip displacement, increased upper lip thickness and lateral chin deviation to the left (Fig. 4).

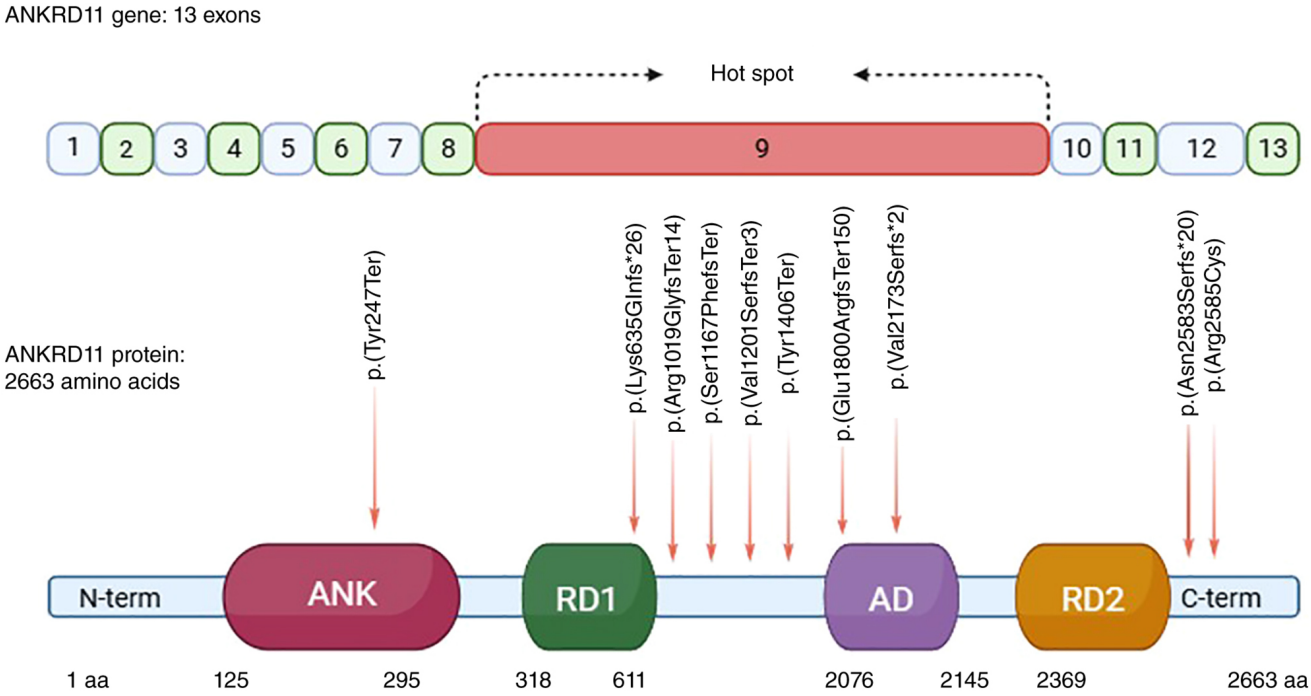

Figure 3. Schematic overview of the *ANKRD11* gene (13 exons) and its protein product (2,663 amino acids), showing the distribution of reported pathogenic variants. Exon 9 is highlighted as a mutational hotspot. Variants identified in the present cohort (n=10) are mapped alongside previously reported variants across key functional domains of the protein (ANK, RD1, AD, and RD2). *ANKRD11*, ankyrin repeat domain-containing protein 11; RD1, repression domain 1; AD, activation domain; N-term, N-terminal region; C-term, C-terminal region; aa, amino acids.

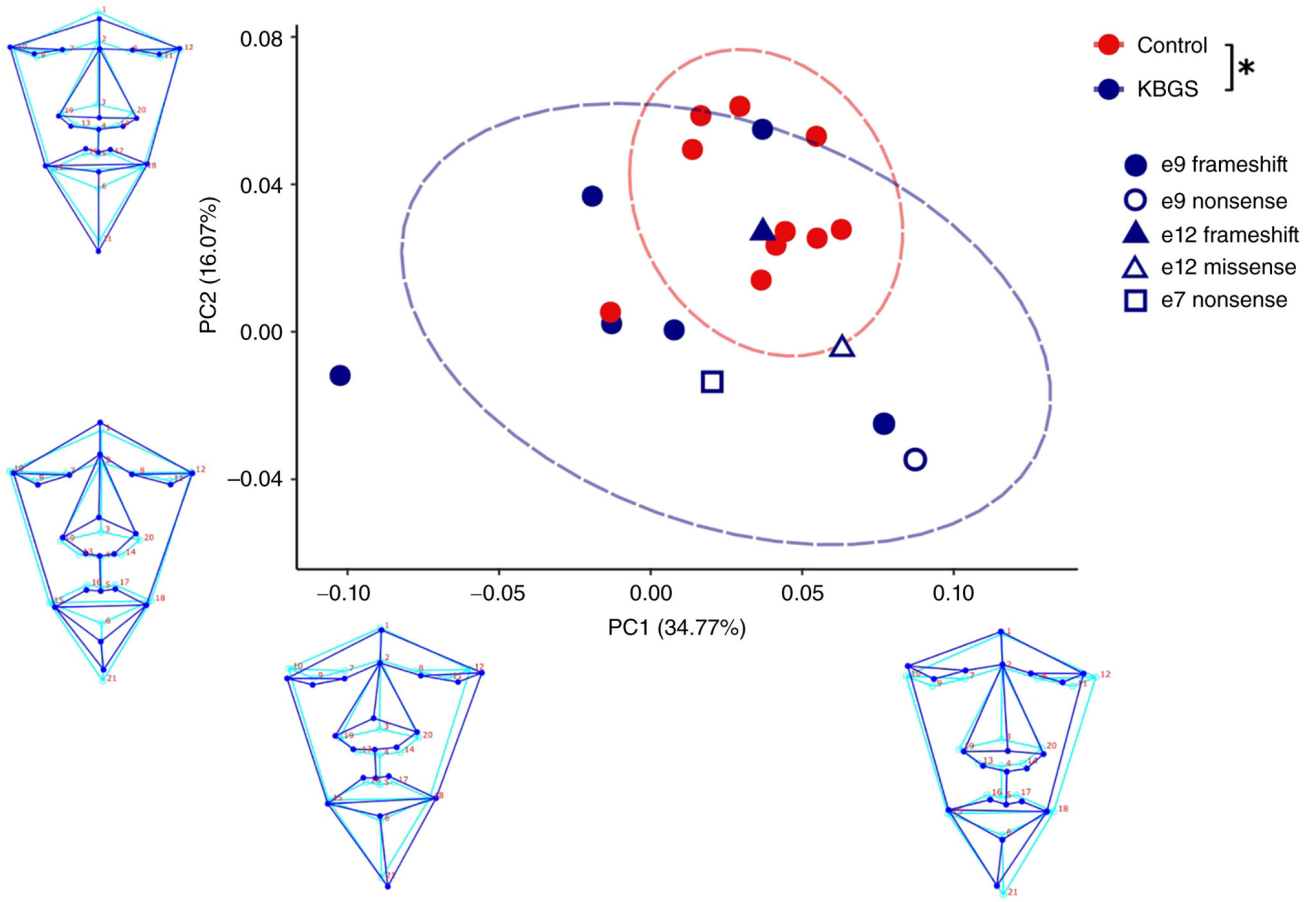

Figure 4. PCA based on facial shape according to diagnosis. Females are indicated with empty symbols. Wireframes represent facial morphology, where the light blue lines represent the average shape and the dark blue lines represent shapes associated with the positive (right side of the morphospace) and negative (left side of the morphospace) extremes of PC1 and PC2. *P<0.05. PCA, principal components analysis; KBGS, KBG syndrome.

Table III. Comparative summary of the primary clinical features reported in six previously published large cohorts of individuals with KBG syndrome (2,3,6,11,19,20) and the present study.

	Study							
Feature	Serra *et al*, 2025	Choi *et al*, 2022	Parenti *et al*, 2021	Low *et al*, 2016	Goldenberg *et al*, 2016	Ockeloen *et al*, 2016	Present study	Overall
Number of patients	3	8	23	32	39	19	10	134
Country	Italy	South Korea	Multiple, including: Ger, Ita, Can, Ire, USA and Col	United Kingdom	France	Netherlands	Colombia	Multiple countries
Sex (female/male)	2/1	5/3	11/12	20/12	23/16	9/10	4/6	74/60
Age at diagnosis, years	0.25-18.00 (mean, 6.44)	0.25-37.00 (mean, 8.95)	4.00-23.00 (mean, 6.40)	2.00-47.00 (mean, 13.30)	1.00-66.00 (mean, 14.26)	6.00-47.00 (mean, 20.74)	4.00-36.00 (mean, 16.40)	0.25-66.00 (mean, 12.36)
Intellectual disability/ developmental delay	3/3 (100.00%)	8/8 (100.00%)	16/23 (69.57%)	31/32 (96.88%)	28/39 (71.79%)	18/19 (94.74%)	10/10 (100.00%)	114/134 (85.07%)
Low hair implantation	ND	ND	15/23 (65.22%)	ND	ND	ND	8/10 (80.00%)	23/33 (69.7%)
Facial asymmetry	ND	ND	ND	ND	ND	ND	7/10 (70.00%)	7/10 (70%)
Clinodactyly and camptodactyly	3/3 (100.00%)	ND	15/23 (65.22%)	15/32 (46.88%)	23/39 (58.97%)	18/19 (94.74%)	7/10 (70.00%)	81/126 (64.28%)
Bulbous nose	2/3 (66.67%)	1/8 (12.50%)	16/23 (69.57%)	ND	ND	ND	9/10 (90.00%)	28/44 (63.64%)
Macrodontia	1/3 (33.33%)	6/8 (75.00%)	15/23 (65.22%)	23/32 (71.88%)	18/39 (46.15%)	17/19 (89.47%)	5/10 (50.00%)	85/134 (63.43%)
Synophrys	1/3 (33.33%)	4/8 (50.00%)	15/23 (65.22%)	ND	ND	ND	6/10 (60.00%)	26/44 (59.1%)
Prominent ears	1/3 (33.33%)	5/8 (62.50%)	ND	ND	ND	ND	6/10 (60.00%)	12/21 (57.14%)
Full, arched eyebrows	1/3 (33.33%)	ND	11/23 (47.83%)	ND	ND	ND	7/10 (70.00%)	19/36 (52,78%)
Psychiatric features	1/3 (33.33%)	ND	15/23 (65.22%)	12/32 (37.50%)	17/39 (43.59%)	17/19 (89.47%)	4/10 (40.00%)	66/126 (52.38%)
Hypotonia	1/3 (33.33%)	ND	ND	ND	ND	ND	5/10 (50.00%)	6/13 (46,14%)
Prominent nasal bridge	1/3 (33.33%)	1/8 (12.50%)	ND	ND	ND	ND	7/10 (70.00%)	9/21 (42.85%)
Scoliosis	0/3 (0.00%)	1/8 (12.50%)	ND	ND	ND	9/19	6/10 (60.00%)	16/40 (40%)
Feeding difficulties	ND	ND	7/23 (30.43%)	10/32 (31.25%)	ND	ND	6/10 (60.00%)	23/65 (35.38%)
Seizures	1/3 (33.33%)	3/8 (37.50%)	6/23 (26.09%)	13/32 (40.62%)	12/39 (30.77%)	5/19 (26.32%)	5/10 (50.00%)	45/134 (33.58%)
Sensorineural hearing loss	1/3 (33.33%)	ND	6/23 (26.09%)	8/32 (25.00%)	11/39 (28.21%)	6/19 (31.58%)	8/10 (80.00%)	40/126 (31.74%)
Hypertrichosis	0/3 (0.00%)	ND	5/23 (21.74%)	ND	ND	ND	3/10 (30.00%)	8/36 (22.22%)
Coarse facies	ND	ND	2/23 (8.70%)	ND	ND	ND	5/10 (50.00%)	7/33 (21.21%)

Ger, Germany; Ita, Italy; Can, Canada; Ire, Ireland; Col, Colombia; ND, no data available.

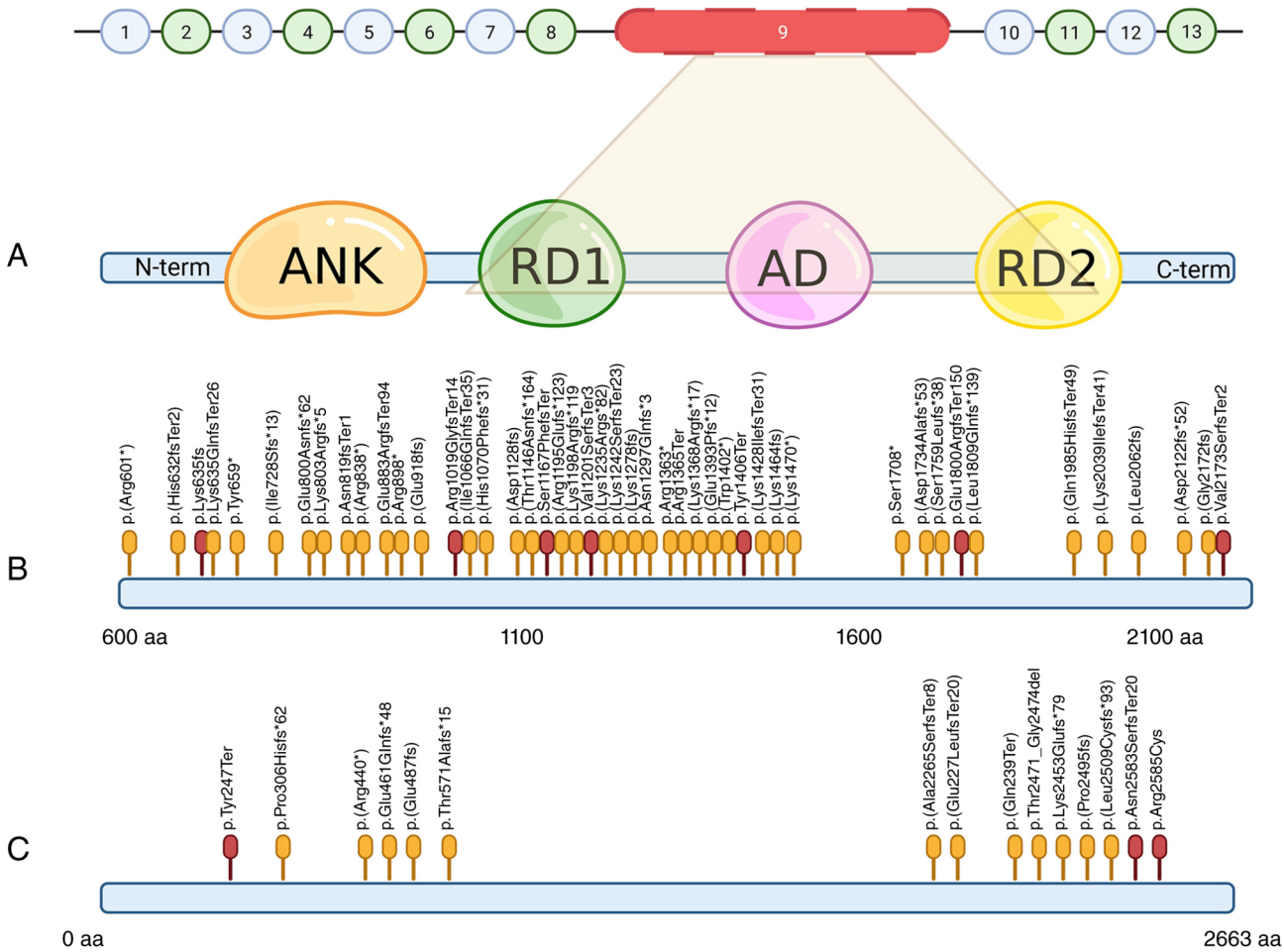

Figure 5. Schematic representation of *ANKRD11*, its functional domains and the distribution of pathogenic variants associated with KBG syndrome. (A) Exonic structure of *ANKRD11* and major protein functional domains, including ANK, RD1 and RD2 and AD. Exon 9 is highlighted as a mutational hotspot. Distribution of pathogenic variants located (B) within and (C) outside exon 9. Variants identified in the present study are highlighted in red, whereas previously reported variants are shown in yellow. *ANKRD11*, ankyrin repeat domain-containing protein 11; RD1, repression domain 1; AD, activation domain; N-term, N-terminal region; C-term, C-terminal region; aa, amino acids.

PC2 highlighted characteristic KBGS facial features, including increased forehead height, nasal prominence, ticker lower lip and reduced chins (Fig. 4).

Patients displayed heterogeneous craniofacial phenotypes (Fig. 4), but no significant associations were detected between facial variation and mutation type (frameshift, nonsense, missense) or exon location (11,14,20).

Discussion

KBGS is a rare autosomal dominant neurodevelopmental disorder caused by haploinsufficiency of *ANKRD11*, a gene encoding a chromatin regulator involved in transcriptional control, neuronal development and skeletal formation (2,5,9,10). Since its initial description, the phenotypic spectrum of KBGS has expanded to include a wide range of neurodevelopmental, craniofacial, skeletal, behavioral and systemic manifestations (1-4,11,13,17,20). To date, >300 molecularly confirmed cases have been reported worldwide, with >1,000 distinct *ANKRD11* variants described, the majority of which are truncating and cluster within exon 9, a well-established mutational hotspot (2-4,11,12,19).

Despite increasing recognition, KBGS remains underdiagnosed and typically misclassified due to its marked phenotypic variability and overlap with other genetic conditions (4,9,10,13,15,16,35). The syndrome is referred to as a 'great imitator' because of its clinical resemblance to other chromatinopathies, such as Cornelia de Lange and Coffin-Siris syndromes, as well as multisystem developmental conditions including VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula/esophageal atresia, renal anomalies and limb abnormality (VACTERL) and Turner syndrome (4,9,10,15,16). Genotype-phenotype associations in KBGS are weak or absent, with variant type and location providing little predictive value for clinical severity (2,3,13,18). Consequently, molecular studies are essential to establish a definitive diagnosis, as clinical features alone are not pathognomonic and genotype-phenotype associations in KBGS remain weak or absent (5,12,36,37).

The present study presents a comprehensive characterization of 10 individuals with KBGS, integrating detailed clinical evaluation, molecular findings, 2D facial morphometric analysis and a structured comparison with previously published large cohorts. The present findings reinforce the concept of KBGS as a highly heterogeneous chromatinopathy and demonstrate the diagnostic challenges associated with its broad phenotypic spectrum.

Clinically, all individuals in the present cohort exhibited neurodevelopmental involvement, confirming developmental delay and intellectual disability as key features of KBGS. Craniofacial dysmorphism was universal, although the specific combination and severity of features varied. Notably, the most frequent craniofacial findings included facial asymmetry, coarse facial features, low anterior hairline, bulbous nasal tip and prominent ears. These features appeared at higher frequencies than in previously reported cohorts (2,3,6,11,19,20), suggesting they may be under-recognized or inconsistently documented in previous studies. This underscores the importance of detailed and systematic dysmorphological assessment in individuals with suspected KBGS.

Comparison with six previously published cohorts with detailed phenotypic data showed that the present cohort shares the core clinical features of KBGS, including intellectual disability/developmental delay, craniofacial dysmorphism, skeletal anomaly and neuropsychiatric manifestations (2,3,6,11,19,20). Certain features, such as low anterior hairline, facial asymmetry, hearing loss, and hypotonia, were observed at higher frequencies in the present series, potentially reflecting more systematic phenotypic assessment or cohort-specific differences (Table III) (2,3,6,11,19,20).

Skeletal anomaly and neurological manifestations were also common, including scoliosis, digital anomaly, hypotonia, seizures and behavioral disturbances. Hearing impairment was identified in a high proportion of patients, representing one of the most prevalent extracranial manifestations in the present series and reinforcing the need for routine auditory screening in the clinical evaluation of individuals with KBGS.

At the molecular level, the present findings support *ANKRD11* haploinsufficiency as the primary pathogenic mechanism underlying KBGS. The predominance of truncating variants and their clustering within exon 9 align with previous reports, confirming this region as a global mutational hotspot (2,6). Previously reported *ANKRD11* variants and the 10 variants identified in the present cohort are summarized in Fig. 5. Importantly, several variants in the present cohort were novel, expanding the *ANKRD11* mutational spectrum and contributing data from an under-represented Latin American population. Despite this detailed molecular characterization, no association between variant type, location, or novelty and phenotypic severity was established, reinforcing the lack of robust genotype-phenotype association in KBGS.

A novel aspect of the present study is the incorporation of 2D facial morphometric analysis. Quantitative assessment demonstrated consistent alterations in facial shape, especially asymmetry and dysmorphologies in the upper face, midface and nasal regions, supporting the existence of a craniofacial signature associated with *ANKRD11* haploinsufficiency. However, substantial interindividual variability persisted, reinforcing that genotype-phenotype associations cannot yet be reliably inferred from facial features alone. Future research should include larger cohorts to explore potential genetic associations between facial dysmorphology, the impact of developmental canalization on varying degrees of asymmetry and the influence of genetic ancestry. This is particularly relevant in populations with high ancestral diversity and admixture, where phenotypic expression may be modulated by complex genetic backgrounds that are under-represented in existing reference datasets. Longitudinal studies employing 3D facial modeling may clarify whether KBGS facial phenotype changes over time, as facial dysmorphology may become more pronounced during postnatal development (38). Rather than defining molecular subgroups, facial morphometry serves as a complementary tool that enhances phenotypic recognition and diagnostic confidence.

Comparison with six large published cohorts (2,3,6,11,19,20) revealed substantial overlap in key clinical features but also highlighted differences that may reflect cohort-specific characteristics or improved phenotypic recognition. By contrast with the literature, macrodontia, typically described as a cardinal feature of KBGS, was not prominent in the present cohort. This emphasizes that its absence should not preclude diagnosis and supports the need for comprehensive phenotypic evaluation rather than relying on isolated hallmark features.

Overall, the present findings reinforce KBGS as a complex and heterogeneous disorder that frequently overlaps with other genetic conditions, making clinical diagnosis challenging. Molecular testing remains essential for accurate diagnosis, appropriate classification and the implementation of targeted clinical interventions.

The present study expanded the clinical and molecular spectrum of KBGS through the detailed characterization of a Colombian case series, contributing novel data regarding *ANKRD11*-associated disorders. The present findings confirm the marked phenotypic variability of KBGS and demonstrated that variant type and location are not directly associated with phenotypic severity.

Despite the use of advanced approaches, such as 2D facial morphometric analysis, no robust genotype-phenotype association was identified. Instead, KBGS emerges as a highly heterogeneous condition that frequently mimics other genetic syndromes, particularly chromatinopathy, VACTERL association and Turner syndrome, making clinical diagnosis challenging.

The prominence of facial asymmetry, coarse facial features, low anterior hairline, bulbous nasal tip and prominent ears in the present cohort, together with the limited relevance of macrodontia, underscores the importance of detailed and systematic dysmorphological evaluation. Ultimately, the present study highlights the critical role of molecular testing in confirming the diagnosis, enabling appropriate intervention and improving clinical care of individuals with KBGS.

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Availability of data and materials

The data generated in the present study are not publicly available due to ethical, legal, consent-related and identifiability

restrictions but may be requested from the corresponding author.

Authors' contributions

SBN, JANC and HP conceived and designed the study and analyzed and interpreted data. SBN, LEP and LVCC interpreted data and wrote the manuscript. MAM and NMA performed the two-dimensional facial morphometric analysis and wrote the manuscript. NMA revised the manuscript. All authors have read and approved the final manuscript. JANC and HP confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by the ethics committee of the Hospital Universitario Fundación Valle del Lili, Cali, Colombia; approval no. 2025.140). Written informed consent to participate was obtained from all adult participants, including healthy controls and individuals with KBGS, who were capable of providing consent. For minors and individuals with intellectual disability impairing autonomous consent capacity, written informed consent was obtained from parents or legal guardians.

Patient consent for publication

Written informed consent for publication of clinical data and unredacted photographs was obtained from all adult participants, including healthy controls and individuals with KBGS, who were capable of providing consent, and from parents or legal guardians of minors and individuals with intellectual disability impairing autonomous consent capacity. This consent was obtained specifically for this study.

Competing interests

The authors declare that they have no competing interests.

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