European Journal of Pediatrics (2025) 184:60
https://doi.org/10.1007/s00431-024-05828-5

RESEARCH

From phenotype to phonotype: a comprehensive description of voice features of Cri du chat syndrome

Elisabetta Sforza[1,2] · Federico Calà[3] · Claudia Manfredi[3] · Antonio Lanatà[3] · Andrea Guala[2,4] · Cesare Danesino[2,5] · Angelina Cistaro[2,6] · Matelda Mazzocca[2] · Lucia D'Alatri[7] · Roberta Onesimo[8] · Lorenzo Frassineti[3] · Giuseppe Zampino[1,8]

Received: 20 July 2024 / Revised: 23 July 2024 / Accepted: 1 November 2024
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2024

Abstract

Genetic syndromes have been studied by extensive research allowing a better definition of their clinical manifestations, natural history, and etiopathogenetic mechanisms. Nevertheless, some relevant, but still unexplored aspects of these multisystemic conditions need to be clarified. One of these aspects is the characterization of the vocal production, especially in some genetic syndromes in which the distinctive voice is the hallmark of the syndrome (e.g., Cri du chat syndrome, CdCS). The aim of this study is to provide a detailed description of phonotype of patients affected by CdCS. We prospectively recorded and analysed acoustical features of three corner vowels [a], [i], and [u] and number listing from 1 to 10 of 29 patients with molecularly confirmed CdCS (age range 4–21 years; mean 11 ± 6; median 10 years). For perceptual analysis, the GIRBAS scale was completed. The acoustical analysis was performed through BioVoice software. When stratified by age and gender, in the older men subgroup the grade, roughness, and asthenia mean values are the highest for each vowel, when compared with values of the same parameters obtained in the other subgroups. Statistical analysis highlighted 26 significant differences: 38% (10) concern the sustained phonation of /a/, 27% (7) are related to /i/ whereas 19% (5) to /u/. Ratio1, Ratio2, VSA, and FCR were also significant.

Conclusion: The voice production not only conveys linguistic and paralinguistic information but also can give information regarding the speaker's biological and clinical characteristics.

Keywords Acoustical analysis · Artificial intelligence · Cri du chat syndrome · Dysphonia · 5p-Syndrome

Abbreviations

aTBN	Average time between each number
CdCS	Cri du chat syndrome
FCR	Formant centralization ratio
NNE	Normalized noise energy
PUVS	Percentage of unvoiced segments
sTBN	Standard deviation time between each number
VSA	Vowel space area
VSL	Voice segment length

Introduction

Cri du chat syndrome (CdCS; OMIM #123450; ORPHA #281), also known as 5p-syndrome, is a neurodevelopmental disorder caused by deletions of variable size in the short arm of chromosome 5 with an incidence ranging from 1:15,000 to 1:50,000 live births [1, 2]. A clinical diagnosis is possible but karyotype analysis, both with conventional techniques and array CGH are mandatory to define the size of the deletion, which is clinically relevant, and to identify the 10% of cases in whom the type of chromosomal anomaly may affect family planning. Approximately, 90% of cases are de novo, mostly of paternal origin, and 10% are inherited [3]. No differences in prevalence between races or geographical areas have been found or related to prenatal events or age of the parents [4]. Most cases (80 to 90%) result from terminal deletions while the remaining are due to an interstitial deletion of 5p15.3 [5]. The regions involved and the size of the deletion are determinants of the phenotypic heterogeneity

Communicated by Peter de Winter

Sforza E and Calà F contributed as cofirst authors.

Frassineti L and Zampino G contributed as the last authors.

Extended author information available on the last page of the article

Published online: 03 December 2024

and severity [6]. The name of the syndrome means a cat's meow as the CdCS cry is monochromatic and with high-pitched tone [7]. In addition, affected patients present low birth weight and growth delay, head circumference below the 3rd percentile (microcephaly), facial asymmetry, tendency to keep head bent forward, epicanthal folds, hypotonia, ocular hypertelorism, low-set ears, prominent nasal bridge, micrognathia, and severe developmental delay (average IQ of 47.81) [8–10], including difficulties in mobility, dexterity, and verbal communication [11, 12]. Cardiac and renal malformations have also been reported [9]. Isolated pontine hypoplasia is the most common neuroradiological finding [13], and an abnormal hypermetabolism in the brain is observable in CdCS patients with severe deficits in intellectual and adaptive functioning [14].

Cat-like cry and peculiar timbre of voice are the hallmark signs of the syndrome, not only at birth but also later, and these are the only signs which might suggest the diagnosis in patients with small deletions and mild clinical picture [9].

Perceptual assessment and digital acoustic analysis of voice are fundamental for the evaluation of specific voice characteristics [15]. The growing knowledge in the field of acoustics, together with the diffusion and accessibility of software to perform acoustical analysis, has fostered the study of human voice. However, except for few genetic conditions, no scientific trial focusing on the voice analysis has been systematically conducted on patients affected by genetic syndromes [16, 17].

Given the extremely fragmented knowledge of voice phenotype and paucity of vocal data available on genetic syndromes, we herein provide a detailed description of patients affected by CdCS focusing on their voice characteristics.

Participants and procedure

Participants

Patients with a confirmed molecular diagnosis of CdCS were prospectively recruited from Rare Disease and Transition Unit of the Paediatrics Department, Fondazione Policlinico Agostino Gemelli IRCCS/Medical Genetics Unit, Rome, and from the Italian Cri du chat Association (ABC Associazione Bambini Cri du chat Onlus, Italy) over a 6-month period.

Inclusion criteria were the laboratory confirmation of clinical diagnosis and the acquisition of the informed consent of parents, legal representatives, or the patients themselves. No age limits were set. Patients were excluded if a concomitant acute inflammatory pathology of the upper respiratory tract was in place.

The normative group, instead, comprised healthy siblings (no age restriction) of enrolled patients whose parents agreed to participate in the study.

Two subgroups on the basis of the following age brackets were made: 3–12 years (paediatric subjects, hereinafter denoted with the acronym PS), 13 years and older (adults, distinguished in females and males and denoted with the acronym AF and AM, respectively) [18]. The Local Ethical Committee approved the study (ID 5802), and all research procedures were in line with the Declaration of Helsinki.

Procedure

Voice recording

Before starting the voice recordings, precise instructions were given. Specifically, each participant was asked to produce a message containing the three corner vowels [a], [i], and [u], prolonged for at least 3 s, and the list of the Italian numbers from one to ten, in ascending order [18–21]. The recording was performed at the normal 'speaking voice', with a constant pitch and intensity. The recordings were made using a smartphone, in a silent environment (<40 dB of background noise) [22], with the device's microphone placed at a constant distance of about 15 cm from the lips (to avoid interference from ambient noise), angled at 45° (to avoid disruption of airflow) [23].

Signal selection

The vocal signal was acquired by smartphone as a .wav. file, imported into a laptop, and then converted to .mp3format [24]. The vocal signal was checked to verify the absence of background noises [22]. Through Audacity software (Audacity Team 2011) a 3-s central stationary segment was selected from each prolonged vowel in line with Frassineti et al. procedure [25]. Vocal attack and extinction were excluded from the analysis as they represent the most unstable portions of the vocalisation due to aerodynamic and muscular factors.

To perform the selection of a stationary segment, the signal waveform, the signal itself amplified, the fundamental frequency curve, the intensity curve, the wide-band spectrogram, and the formant traces were displayed. Stationarity was assessed as the existence of a relative constancy or uniformity of trends of all these parameters simultaneously.

In cases where the acquired vocalisations had a duration of 3 s or less, it was still possible to analyse the signal, considering only the central stationary segment and excluding the initial and final 100ms from the analysis.

Perceptual and acoustical voice analysis

For perceptual analysis, two otolaryngologists (ENT) with more than 20-year experience in voice assessment (MM and LD) and a speech language pathologist (ES), screened patients' voices for presence of high-pitched tone, roughness,

and marked open nasality (open rhinophonia), and possible discrepancies were solved in a consensus meeting. Subsequently, the GIRBAS (grade, instability, roughness, breathiness, asthenia, and strain) scale was completed by one ENT (MM) for each vowel production of every patient. Each dimension was rated on a four-point scale where 0 = no perceived abnormality, 1 = mild, 2 = moderate, and 3 = severe abnormality and finally total GIRBAS score calculated by averaging all scores [20, 21, 26].

Acoustical analysis was performed through the BioVoice software tool [27]. This tool automatically selects the proper frequency ranges to compute 37 acoustic parameters based on the type of emission (voice, cry, or singing voice), age (child or adult), and gender (male or female) in both frequency and time domains.

The acoustic parameters used to characterise the three sustained vowel emissions of each participant for phonotyping purposes were the fundamental frequency F0 (Hz), jitter (local) (%), normalized noise energy (NNE), and the first, second, and third formant (F1, F2, and F3, respectively) (Hz), indicative of the action of the supraglottic filter rather than the laryngeal oscillator, were also calculated. For each parameter, the mean, median, minimum (min), maximum (max), and standard deviation were also computed. Moreover, five parameters were calculated: the vowel space area (VSA), the formant centralization ratio (FCR), and three formant ratios. The VSA represents a metric sensitive to vowel dispersion, related to articulatory capabilities [28]. The FCR was introduced by Sapir et al. [29] as a metric to assess the degree of dysarthria. The formant ratios are used to monitor formant trajectories and articulatory skills. The first two formant ratios are sensitive to tongue vertical movements, whereas the third to horizontal ones [29] (Supplementary table 1). Therefore, a total of 116 (37 features for each corner vowel + five additional formant metrics) parameters were obtained.

The acoustic parameters used to characterise the emission of number listing task were the following:

- Average time between each number (aTBN), defined as the average time difference in seconds between the offset and onset of two consecutive numbers.
- Standard deviation time between each number (sTBN).
- Voice segment length (VSL), representing the temporal length in seconds of each number.
- Percentage of unvoiced segments (PUVS), which is the percentage of unvoiced segments in the whole recording.
- Task length, i.e., the length of the whole number listing sequence.

These features proved to distinguish dysarthric and dysprosodic from healthy speech in neurodegenerative diseases such as Parkinson's [19] and in patients diagnosed with genetic syndromes [25]. The acoustic parameters were calculated with a custom code written in MATLAB 2022b (The MathWorks, Inc., Natick, MS, USA).

Statistical analysis

Descriptive statistics were performed on demographic and clinical characteristics in the data set. Results are presented as mean ± standard deviation. Due to the small sample size, statistical analysis was performed by comparing pathological and healthy groups, without considering age or gender, with a Mann–Whitney *U* test with level of significance α set to 0.05 (after checking for the normality assumption with a Shapiro–Wilk test). Moreover, a feature reduction strategy was adopted by implementing Spearman correlation analysis (with a threshold $\rho = 0.8$) to remove highly related features and identify more relevant acoustic parameter to characterise the CdCS population. The strength of agreement among perceptual analysis assessors (inter-rater reliability) was calculated by Krippendorff's α [30].

Results

Participants

Forty-one patients with CdCS were prospectively recruited. Of them, *n*=29 unrelated participants were included in the study. The remaining *n*=12 patients were excluded because they were not able to complete the task owing to a severe language delay. The rearrangements observed in our cohort were terminal deletion (*n*= 24/29, 83%), interstitial deletion (*n*=4/29, 14%), and ring deletion (*n*=1/29, 3%) (Table 1).

In the 3–12 years subgroup, a total of *n*=5 children were included (2M; mean age 8.8 years ± 2.4; median age 10 years; age range 5–11 years) (group *a*); in the 13 years and older subgroup a total *n*=24 of adults were included, of whom *n*=12 adult females (mean age 24.4 years ± 8.6; median age 23.5 years; age range 14–40 years) (group *b*); and *n*=12 adult males (mean age 31 years ± 9.3; median age 31; age range 14–49 years) (group *c*). All the CdCS patients presented a mild-to-severe cognitive impairment and were affected by microcephaly (*n*=29/29, 100%).

Normative group was composed by *n*=45 healthy subjects. In the 3–12 years subgroup, a total of *n*=20 children were included (mean age 8.5 years ± 2.3; median age 9 years; age range 5–13 years); in the 13 years and older subgroup, a total of *n*=25 adults was included, of whom *n*=10 adult females (mean age 28.2 years ± 5.7; median age 29.5; age range 16–38 years) and *n*=15 adult males (mean age 28 years ± 5.9; median age 30 years; age range 15–35 years). The normative adult subgroups were composed by only non-smoking participants [31].

Table 1 Main genetic findings in our cohort of 19 patients

	Deletion		Duplication	Voice	
	p5-	extension		Hoarse (severe)	High pitched with rhinophonia (severe)
1	(15.33p14.1)	25.5 Mb			+
2	(15.3p15.2)	11.8Mb			
3	(pter 14.1)	28 Mb		+	
4	(pter14.3q35.3)				+
5	(15.33p15.2)	14.3 Mb			
6	(pterp15.33)			+	
7	(14.3)				+
8	(pter p15.2)	11.14 Mb			+
9	(15.33–15.1)				+
10	(pter p15.1)				+
11	(15.33p.15.31)	8 Mb	(19)(p13.3)		+
12	(pter p14.3)		(6)(q25)	+	
13	(pter p14.1)				
14	(p15.31p13.2)				
15	(pter p14.1)				+
16	(pter p14)				
17	(pter p14)*				+
18	(15.33–15.2)		(3)(q13.13)		
19	(pter p15.1)			+	
20	(pter p14)			+	
21	(15.33–15.2)	13.2 Mb			
22	(15.33–15.2)		(X)(p22.3)		
23	(pter p14)				
24	(15.33–13.3)		(5)(5p13.3)		+
25	(pter p14.1)				
26	(p15.2p14.1)				
27	(pter p14.1)				+
28	(pter p14.2)				
29	(pter15.1)				

*Mosaicism 50–50% from birth

Procedure

The vocal signal was acquired by smartphone devices. During voice registration, background noises never exceeded 40 dB. Based on the experts' assessment, the perceptual analysis showed that high-pitched tone (n=19/29), roughness (n=13/29), and open rhinophonia (n=25/29) were commonly present, in 65%, 45%, and 86% of patients respectively. The level of agreement between the evaluators was high (α=0.8).

Table 2 shows the perceptual analysis results measured by GIRBAS scale. When stratified by age and gender, in the older men subgroup (group c), the grade, roughness, and asthenia mean values are the highest for each vowel, if compared with values of the same parameters obtained in the other subgroups (a and b).

Table 3 report the statistical description of both healthy and pathological population, highlighting the mean and standard deviation for F0 mean, F0 min, F0 max, jitter, NNE, F1 mean, F2 mean, F3 mean, and vowel length for each corner vowel /a/, /i/, and /u/. Moreover, these parameters were grouped by age and gender. Similarly, Supplementary table 2 concerns the articulatory parameters.

Correlation analysis was applied to the pathological group only. A set of 45 acoustic parameters was retained, which were used as comparison metrics with the healthy population. Statistical analysis highlighted 26 significant differences: 38% (10) concerns the sustained phonation of /a/, 27% (7) are related to /i/ whereas 19% (5) to /u/. Ratio1, Ratio2, VSA, and FCR were also significant. Specifically, with respect to the control group:

Table 2 GIRBAS evaluation of CdCS cohort expressed as mean and ±standard deviation

CdCS subgroups	G	I	R	B	A	S
/A/						
Group PS	0.50, 0.50	2.00, 0.71	0.75, 0.83	1.00, 1.22	1.00, 0.71	0.50, 0.50
Group AF	0.67, 0.85	1.50, 0.96	1.17, 0.80	0.58, 0.64	1.00, 0.91	0.83, 0.99
Group AM	1.64, 1.07	2.25, 0.92	1.92, 0.86	1.00, 0.95	1.58, 1.04	0.42, 0.49
/I/						
Group PS	1.00, 1.41	1.75, 0.83	1.25, 1.30	1.50, 1.50	1.50, 1.12	1.00, 1.22
Group AF	0.50, 0.76	1.50, 1.04	1.00, 1.00	0.50, 0.50	1.25, 1.09	1.17, 0.99
Group AM	1.50, 1.12	2.00, 1.00	2.09, 1.08	1.00, 1.04	1.75, 1.09	0.45, 0.66
/U/						
Group PS	0.00, 0.00	1.80, 1.17	0.60, 0.80	0.25, 0.43	1.40, 1.02	0.60, 0.80
Group AF	0.38, 0.70	1.17, 0.80	0.73, 0.75	0.33, 0.47	1.42, 0.95	0.58, 0.86
Group AM	1.50, 0.92	1.67, 1.25	1.83, 0.80	0.73, 0.96	2.08, 0.95	0.09, 0.29

Group PS, tot n= 5; group AF, tot n=12; group AM, tot n=12

- F0 mean /a/ is higher
- Formant F2 and F3 for /a/, /i/, and /u/ are lower
- Sustained vowel phonation time for /a/ and /u/ are shorter
- Jitter /u/ is higher
- VSA is lower
- FCR is higher
- Formant ratios Ratio1 and Ratio2 are lower

Figure 1 and Supplementary fig. 1–4 show the boxplots for the significant metrics.

As far as the number listing task is concerned, Supplementary table 3 summarises the statistical description of CdCS and HS population, divided by age and gender. Moreover, a Mann–Whitney test highlighted that aTBN, sTBN, PUVS, and task length are significantly different between CdCS and control groups. Particularly, the average time between numbers and its variation (aTBN and sTBN), the percentage of unvoiced parts in the number sequence (PUVS), and the overall task length are higher for the CdCS with respect to the control group.

Discussion

Genetic factors play an important role not only in the determination of distinct phenotypes and neurobehavioral profiles, but also in establishing voice patterns with constant and recognizable sound characteristics. Vocal production is the result of several interacting components. Mechanically, voice sound production involves vocal fold vibration and the subsequent selective amplification of the airflow through the vocal tract [32]. Formants are prominent resonances resulting from the specific configuration of the vocal tract at a given moment; specifically, F1 and F2 relate to the movement of the jaw and tongue, whereas F3 depends on lips rounding. In general, the first formant has an inverse relationship to the opening of the mouth: F1 is higher the lower the jaw and vice versa. The second formant has a direct relationship with the tongue: F2 is higher the further forward the tongue is in the oral tract and vice versa [28]. The examination of the first two formants involves knowing the activity of some essential organs in the articulation of speech, and it is important for measuring speech intelligibility [33, 34]. A classic measure used in this type of studies is the VSA, related to the dimensions of the acoustic vowel chart formed the first two formants of a vowel. The VSA space reflects the degree of separation between the vowels of a speaker, that is, the articulatory distinction between them in the same speaker. Previous studies on CdCS reported that the majority of patients (88.25%) have a high-pitched, monochromatic cat-like cry and acute voice [5, 9, 35–38]. The pathogenesis is attributable to the anatomical alteration of the laryngeal morphology, which may be a result of a small, floppy epiglottis, hypoplasia of the larynx, narrow or diamond-shaped larynx, and abnormal airspace in the posterior area during phonation [39]. Recently, Mazzocca et al. described CdCS voice using a spectrographic analysis as mostly monotonous, with poor intelligibility and a stiff vocal attachment [10].

In our study we found that for CdCS children the /a/ F0 mean (356±85 Hz) was on average more than 100 Hz higher than the healthy controls (250±29). This confirms that CdCs children have higher voice pitches, as for perceptual evaluation. This also applies to adult female and male CdCS populations. Indeed, a statistical comparison performed with a Mann–Whitney test highlighted that, overall, the vocal fold frequency of the pathological population is significantly higher with respect to the control group. Jitter represents a widely used perturbation measure that is mainly affected by the lack of control of vibration of the vocal cords due to both mechanical (i.e., the presence of benign masses) and central or peripheral nervous system

Table 3 Key acoustic parameters (mean ± standard deviation) of **/a/**, **/i/**, and **/u/** in the CdCS and normative groups

	F0 mean [Hz]	F0 min [Hz]	F0 max [Hz]	Jitter	NNE	F1 mean [Hz]	F2 mean [Hz]	F3 mean [Hz]	Length
/A/									
Group PS—CdCS	356±85	252±69	404±118	4.7±9.8	−26.8±5.9	1062±163	1399±110	3989±295	2.4±1.3
Group PS—healthy	250±29	209±60	270±30	1.2±1.3	−21.7±3.5	1086±151	1440±108	3535±784	1.9±1.2
Group AF—CdCS	304±36	203±65	337±37	3.6±3.9	−17.7±8.6	850±209	1337±202	2535±295	1.2±1.0
Group AF—healthy	205±22	174±45	226±31	1.6±2.2	−21.1±4.0	717±167	1249±212	2693±360	2.9±1.3
Group AM–CdCS	208±30	177±45	223±35	1.3±1.5	−24.0±5.6	562±151	1204±107	2470±406	1.8±1.2
Group AM—healthy	119±29	115±26	124±30	0.5±1.2	−19.0±4.5	660±73	1089±67	2752±316	3.1±1.2
/I/									
Group PS—CdCS	349±81	261±106	400±129	4.2±9.0	−30.0±6.2	582±61	2518±548	3795±363	2.0±1.1
Group PS—healthy	263±31	195±51	286±40	0.9±0.5	−27.2±4.9	563±62	2877±671	3748±233	1.6±1.1
Group AF—CdCS	320±35	263±68	337±37	1.7±1.9	−23.7±8.5	493±201	1801±396	3287±422	1.0±0.6
Group AF—healthy	210±23	195±40	223±26	0.7±0.6	−26.3±4.2	343±39	2039±413	3361±317	3.0±1.2
Group AM—CdCS	210±28	183±37	230±29	1.4±1.2	−30.0±5.0	346±43	1565±188	2800±272	1.4±0.9
Group AM—healthy	119±30	104±27	127±32	1.2±1.8	−25.6±2.7	318±21	1834±316	3085±379	3.1±1.1
/U/									
Group PS—CdCS	365±102	243±40	415±109	1.8±2.1	−31.5±2.5	698±91	1408±214	4120±290	2.4±1.0
Group PS—healthy	262±30	234±43	224±32	1.0±1.0	−27.9±4.2	602±61	1374±198	3961±244	1.4±1.0
Group AF—CdCS	315±36	234±61	337±34	3.0±3.9	−20.4±10.5	534±124	1205±171	2964±367	1.2±1.0
Group AF—healthy	210±25	193±36	224±32	1.1±2.0	−27.5±5.3	389±38	1165±223	3080±581	2.6±1.0
Group AM—CdCS	205±31	170±47	227±37	2.0±2.4	−29.2±4.9	414±126	1221±186	2528±361	1.6±1.0
Group AM—healthy	121±33	117±32	128±35	0.6±0.3	−26.6±2.9	367±51	991±97	2889±318	2.8±1.0

neurological damages [40, 41]. Several studies showed that dysphonic voices are typically characterised by higher jitter values [42, 43] and our study supports this result, especially for paediatric and adult female patients, whose jitter is up to 2 percentage points higher with respect to the control group. Moreover, jitter /u/ showed a significant difference between the two population, with jitter of CdCS patients being higher and with larger variability than control group. Interestingly, NNE values from the three corner vowels were retained after correlation analysis, but none of them showed statistically significant differences between the groups. This could mean that the perceived hoarseness of CdCS voices, which was also detected in our sample, does not depend on abnormal noise level. On the other hand, it could be due to a more prominent roughness, which jitter is known to be sensitive to [44] and that could be determined by neurological causes rather than mechanical or morphological ones [45]. Our study also shows relevant differences for F2 mean /i/ and /u/. Specifically, F2 mean /i/ is lower (which was also discovered to be statistically significant), and F2 mean /u/ is higher in the CdCS with respect to the control group. Moreover, all corner vowels F3 mean are significantly lower in the pathological condition. These results suggest that neurological and possibly morphological alterations concerning tongue and lips motility are present in CdCS that contribute to produce abnormal voice.

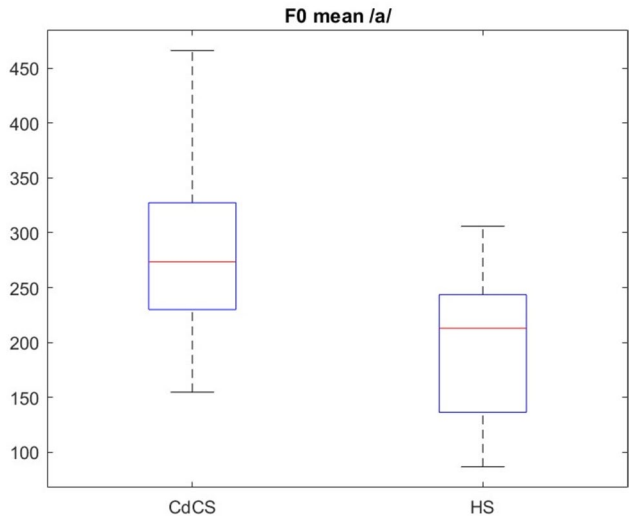

Fig. 1 Boxplot for F0 mean /a/

A reduced VSA area implies less articulatory capacity and, as a consequence, less intelligibility [46]. A smaller area of this inter-vocalic space has also been observed in speakers with cerebral palsy [46–48]. Similar results have been obtained with adult populations with Down syndrome [49], and a high degree of intrasubject variability was observed in the first two formants of the vowel /a/, but not a reduced VSA, in the X-fragile syndrome [50]. Our study highlights that CdCS presents a significantly smaller VSA, thus aligning with a perceived difficult intelligibility for patients diagnosed with this syndrome. This is also supported by a significantly larger FCR that indeed indicate reduced articulatory capabilities [51]. Moreover, it matches the perceptual judgements of this samples; as in some cases, it was noted that phonation of /i/ and /u/ were practically identical. Finally, Ratio1 and Ratio2 (ratio 3 was indeed removed after correlation analysis) showed significant differences between CdCS and healthy controls. Mean values may suggest that the main contribution for such an alteration was brought by adult patients. Indeed, it seems that they experience greater difficulties in controlling and positioning the tongue in the oral cavity to articulate more complex sound such as /i/ and /u/ with respect to /a/.

The co-articulation task, which was administered in the form of a number listing task, underlined relevant results to help outlining the phonotype of the CdCS as well. Specifically, we found that for each subgroup, unvoiced segments in recordings are up to three times longer in the CdCS with respect to the healthy controls, e.g., the average time between each number (aTBN) in the AM group is 0.63±0.34 for the pathological condition and 0.20±0.34 for healthy controls. This could be due to reduced coarticulation capabilities: indeed, numbers as \'kwattro\ (English translation: four), \’sɛtte\ (English translation: seven), and \’ɔtto\ (English translation: eight) contain complex utterance patterns such as the double \tt\ sound which may require longer times to re-arrange the articulators in the vocal tract in order to utter the subsequent number. This result seems to be supported by a larger sTBN (e.g., 0.25±0.29 and 0.08±0.07 in the PS group, for CdCS and healthy controls, respectively): some vocalic number as \’uno\ or \’due\ (English translations: one and two) might be easier to co-articulate rather than pronouncing numbers richer in consonants as \’tre\ (English translation: three) and \kwattro\. Moreover, the larger PUVS and longer task length could confirm this hypothesis. The overall statistical analysis showed that aTBN, sTBN, PUVS, and task length are all significantly larger in the CdCS population. However, longer unvoiced segments and task length in the pathological group could also be caused by cognitive impairments [18]. In severe cases, learning numbers and uttering them in the correct sequence may be just impossible. Indeed, qualitatively, two subjects skipped a number, and another one uttered the numbers in random order. In mild cases, instead, longer times could be caused by a delayed memory recalling, e.g., three subjects were helped by assistants or parents in cases of longer pauses.

Interestingly, voiced segment lengths are similar in the PS, AF, and AM groups between CdCS and HS and statistical analysis did not find a significant difference for VSL. However, this aspect will need further analysis since this parameter was obtained by averaging the length of all numbers for each subject. This approach was applied according to Bandini et al. [19]; nonetheless, it does not consider the inherent variability of individual numbers length and articulation properties. Therefore, in the future, it could be helpful to compute a VSL for each single number to understand whether this metric for more complex numbers (as \’kwattro\) could be more sensitive, more efficient to detect the pathological condition with respect to simpler, vocalic ones (as \’due\). This could also be applied to study the aTBN before specific, indicative numbers to further corroborate the hypothesis of more difficult coarticulation skills in the CdCS population.

Data from our healthy group are in line with those previously reported in the literature. For instance, for /a/ jitter local of normal Italian (age range 26–69 years) have been reported to be 0.30 ±0.12 (F) and 0.38±0.26 (M); mean F0 213.34 ±41.40 (F) and 131.80 ±24.40 (M) [52].

To note, the vocal phonotype of patients with CdCS differs not only from the healthy population, but also from the voice characteristics of other genetic conditions.

In terms of voice analysis methodology, the present study follows the procedure used to evaluate the phonotype of SMS, Costello, Noonan, and Down syndromes [23]. Moreover, the novelty of this method also relies on the use of smartphone microphone that can provide reliable recordings for acoustic signal analysis [24]. It has been previously

demonstrated that period-to-period perturbation parameters obtained from audio recordings made with smartphones show similar levels of diagnostic accuracy to external microphones used in clinical conditions [53].

To substantiate the objective assessment, the subjective assessment was based on GIRBAS scale that is probably the most widely used scale for voice assessment, partly due to its relative simplicity [54].

Although multiple critical regions have been reported for striking clinical features, genotype–phenotype relationships have not been established yet for vocal phenotype. For example, Elmakky et al. suggested that a terminal region of 5.5 Mb found between 5p15.32 and 33 would regulate the growth of the head throughout life and is also related to other dysmorphic features [55]. According to Chehimi et al., the genomic region associated with the presence of microcephaly and the cat-like cry would be narrowed to 4.7 Mb between 25,328 and 4,788,892 breakpoint [56]. Moreover, multiple critical regions have been reported also for the characteristic cry, including a 640-kb region between 6,365,349 and 7,003,686 and a 1.7-Mb region between 5,791,886 and 7,539,901 [56–58].

Chehimi et al. recently found that the 5p15.2 region is related to the striking high-pitched voice pattern of CDCS patients [37]. Although chromosome 5 is one of the chromosomes with the lowest gene density, the haploinsufficiency of the genes is responsible for the wide phenotypic spectrum of these patients [59]. Similarly, voice variability seen among individuals may be attributed to the differences in their genotypes.

Conclusion

The voice production not only conveys linguistic and paralinguistic information, but also can give information regarding the speaker's biological and clinical characteristics. Vocal patterns, including infant cry, can represent one of the earliest indicators for detecting specific conditions, such as Cri du chat syndrome. The analysis of voice can be a diagnostic sign of a malformative syndrome and could be used to detect any suspicion especially in patients with mild phenotypes. Voice is a promising research field which may contribute to a better definition of many rare diseases and also have a significant impact on our knowledge of more frequent medical conditions.

Limits and future research

The age range of our cohort is limited, which provides opportunity for future research to better characterize the clinical history of the syndrome also in older patients. Further research and collaborations are warranted to advance our knowledge on genotype–phenotype correlations of this rare syndrome. Adding magnetic resonance imaging–based brain volumetric data and expanding the group size of CDCS including both array CGH (not available for older cases) and NGS (next generation sequencing) will likely result in identification of well-defined 5p regions and eventually of single genes relevant to different aspects of voice production; this work is in progress and will be topic for a different report. Additionally, studies in languages other than Italian based on this protocol could further confirm the reported results.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-024-05828-5.

Acknowledgements The authors want to thank the European Reference Networks on Rare Bone Diseases (ERN BOND) and Intellectual Disability, TeleHealth, Autism, and Congenital Anomalies (ERN-ITHACA), and the national family support group (A.B.C. Associazione Bambini Cri du chat). We sincerely thank all the patients and their families who participated in this study. Their contributions have been invaluable to our research and the broader medical community and will undoubtedly aid in furthering scientific research.

Authors' contributions Study concept and design: GZ, ES, FC, LF and CM. Drafting the manuscript: ES, FC. Critical version of the manuscript for important intellectual content: AL, AG, CD, AC, MM, LC, RO. All authors contributed to the manuscript and approved the final version for publication.

Funding This work was supported by the PNRR (National Recovery and Resilience Plan), project code: PNRR-MR1-2022-12376346.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki and approved by the Research Ethical Committee of the Catholic University of Sacred Heart, Rome.

Consent to participate Informed consent was obtained from parents of all participants included in the study.

Competing interests The authors declare no competing interests.

References

1. Niebuhr E (1978) The Cri du Chat syndrome: epidemiology, cytogenetics, and clinical features. Human Gen 44(3):227–275. https://doi.org/10.1007/BF00394291
2. Lejeune J, Lafourcade J, Berger R, Vialatte J, Boeswillwald M, Seringe P, Turpin R (1963) Trois cas de d'el'etion partielle du bras court d'un chromosome 5 [3 cases of partial deletion of the short arm of a 5 chromosome]. Comptes rendus hebdomadaires des seances de l'Academie des sciences 257:3098–3102
3. Cerruti Mainardi P, Perfumo C, Calì A, Coucourde G, Pastore G, Cavani S, Zara F, Overhauser J, Pierluigi M, Bricarelli FD (2001) Clinical and molecular characterisation of 80 patients with 5p deletion: genotype-phenotype correlation. J Med Gen 38(3):151–158. https://doi.org/10.1136/jmg.38.3.151

4. Nevado J, Bel-Fenellós C, Sandoval-Talamantes AK, Hernández A, Biencinto-López C, Martínez-Fernández ML, Barrúz P, Santos-Simarro F, Mori-Álvarez MÁ, Mansilla E, García-Santiago FA, Valcorba I, Sáenz-Rico B, Martínez-Frías ML, Lapunzina P (2021) Deep phenotyping and genetic characterization of a cohort of 70 individuals with 5p minus syndrome. Front Gen 12:645595. https://doi.org/10.3389/fgene.2021.645595
5. Rodríguez-Caballero A, Torres-Lagares D, Rodríguez-Pérez A, Serrera-Figallo MA, Hernández-Guisado JM, Machuca-Portillo G (2010) Cri du chat syndrome: a critical review. Med Oral Patol Oral y Cirugia Bucal 15(3):e473–e478. https://doi.org/10.4317/medoral.15.e473
6. Kodra Y, Cavazza M, de Santis M, Guala A, Liverani ME, Armeni P, Masini M, Taruscio D (2020) Social economic costs, health-related quality of life and disability in patients with Cri du chat syndrome. Int J Environ Res Public Health 17(16):5951. https://doi.org/10.3390/ijerph17165951
7. Bel-Fenellós C, Biencinto-López C, Sáenz-Rico B, Hernández A, Sandoval-Talamantes AK, Tenorio-Castaño J, Lapunzina P, Nevado J (2023) Cognitive-behavioral profile in pediatric patients with syndrome 5p-; genotype-phenotype correlationships. Genes 14(8):1628. https://doi.org/10.3390/genes14081628
8. Cornish KM, Bramble D, Munir F, Pigram J (1999) Cognitive functioning in children with typical cri du chat (5p-) syndrome. Dev Med Child Neurol 41(4):263–266. https://doi.org/10.1017/s0012162299000559
9. Cerruti MP (2006) Cri du chat syndrome. Orphanet J Rare Dis 1:33. https://doi.org/10.1186/1750-1172-1-33
10. Mazzocca M, Cistaro A, Liava A, Danesino C, Guala A (2023) Voice analysis in 63 Italian Cri du chat patients. Fam Med Prim Care Open Access 7:220. https://doi.org/10.29011/2688-7460.100220
11. Almeida VT, Chehimi SN, Gasparini Y, Nascimento AM, Carvalho GFS, Montenegro MM, Zanardo ÉA, Dias AT, Assunção NA, Kim CA, Kulikowski LD (2023) Cri-du-chat syndrome: revealing a familial atypical deletion in 5p. Mol Syndromol 13(6):527–536. https://doi.org/10.1159/000524371
12. Guala A, Spunton M, Tognon F, Pedrinazzi M, Medolago L, Cerutti Mainardi P, Spairani S, Malacarne M, Finale E, Comelli M, Danesino C (2016) Psychomotor development in Cri du chat syndrome: comparison in two Italian cohorts with different rehabilitation methods. Sci World J 2016:3125283. https://doi.org/10.1155/2016/3125283
13. Villa R, Fergnani VGC, Silipigni R, Guerneri S, Cinnante C, Guala A, Danesino C, Scola E, Conte G, Fumagalli M, Gangi S, Colombo L, Picciolini O, Ajmone PF, Accogli A, Madia F, Tassano E, Scala M, Capra V, Srour M, Bedeschi MF (2020) Structural brain anomalies in Cri-du-chat syndrome: MRI findings in 14 patients and possible genotype-phenotype correlations. Eur J Paediatr Neurol EJPN Off J Eur Paediatric Neurol Soc 28:110–119. https://doi.org/10.1016/j.ejpn.2020.07.002
14. Cistaro A, Quartuccio N, Piccardo A, Fania P, Spunton M, Liava A, Danesino C, Albani G, Guala A (2020) 18F-FDG PET identifies altered brain metabolism in patients with Cri du chat syndrome. J Nucl Med Off Public Soc Nuclear Med 61(8):1195–1199. https://doi.org/10.2967/jnumed.119.236893
15. Villafuerte-Gonzalez R, Valadez-Jimenez VM, Hernandez-Lopez X, Ysunza PA (2015) Acoustic analysis of voice in children with cleft palate and velopharyngeal insufficiency. Int J Pediatr Otorhinolaryngol 79(7):1073–1076. https://doi.org/10.1016/j.ijporl.2015.04.030
16. Shriberg LD, Strand EA, Jakielski KJ, Mabie HL (2019) Estimates of the prevalence of speech and motor speech disorders in persons with complex neurodevelopmental disorders. Clin linguistics Phonet 33(8):707–736. https://doi.org/10.1080/02699206.2019.1595732
17. Gorris C, Ricci Maccarini A, Vanoni F, Poggioli M, Vaschetto R, Garzaro M, Aluffi Valletti P (2020) Acoustic analysis of normal voice patterns in Italian adults by using Praat. J Voice Off J Voice Found 34(6):961.e9-961.e18. https://doi.org/10.1016/j.jvoice.2019.04.016
18. Frassineti L, Calà F, Sforza E, Onesimo R, Leoni C, Lanatà A, Zampino G, Manfredi C (2023) Quantitative acoustical analysis of genetic syndromes in the number listing task. Biomed Signal Process Contr 85:104887. https://doi.org/10.1016/j.bspc.2023.104887
19. Bandini A, Giovannelli F, Orlandi S, Barbagallo SD, Cincotta M, Vanni P, Chiaramonti R, Borgheresi A, Zaccara G, Manfredi C (2015) Automatic identification of dysprosody in idiopathic Parkinson's disease, Biomed. Signal Processing. Control 17:47–54. https://doi.org/10.1016/j.bspc.2014.07.006
20. Dejonckere PH, Bradley P, Clemente P, Cornut G, Crevier-Buchman L, Friedrich G, Van De Heyning P, Remacle M, Woisard V, Committee on Phoniatrics of the European Laryngological Society (ELS) (2001) A basic protocol for functional assessment of voice pathology, especially for investigating the efficacy of (phonosurgical) treatments and evaluating new assessment techniques. Guideline elaborated by the Committee on Phoniatrics of the European Laryngological Society (ELS). Eur Arch Oto-rhino-laryngology Off J Eur Federat Oto-Rhino-Laryngological Societies (EUFOS) Affiliated German Soc Oto-Rhino-Laryngology - Head Neck Surge 258(2):77–82. https://doi.org/10.1007/s004050000299
21. Dejonckere PH, Remacle M, Fresnel-Elbaz E, Woisard V, Crevier-Buchman L, Millet B (1996) Differentiated perceptual evaluation of pathological voice quality: reliability and correlations with acoustic measurements. Revue de Laryngologie - otologie - rhinologie 117(3):219–224
22. Marsano-Cornejo MJ, Roco-Videla Á (2023) Variation of the acoustic parameters: f0, jitter, shimmer and alpha ratio in relation with different background noise levels. Acta Otorrinolaringologica Espanola 74(4):219–225. https://doi.org/10.1016/j.otoeng.2022.10.004
23. Calà F, Frassineti L, Sforza E, Onesimo R, D'Alatri L, Manfredi C, Lanata A, Zampino G (2023) Artificial intelligence procedure for the screening of genetic syndromes based on voice characteristics. Bioengineering 10(12):1375. https://doi.org/10.3390/bioengineering10121375
24. van der Woerd B, Wu M, Parsa V, Doyle PC, Fung K (2020) Evaluation of acoustic analyses of voice in nonoptimized conditions. J Speech Language Hear Res JSLHR 63(12):3991–3999. https://doi.org/10.1044/2020_JSLHR-20-00212
25. Frassineti L, Zucconi A, Calà F, Sforza E, Onesimo R, Leoni C, Rigante M, Manfredi C, Zampino G (2021) Analysis of vocal patterns as a diagnostic tool in patients with genetic syndromes, in: 12th International Workshop, Models and Analysis of Vocal Emissions for Biomedical Applications, pp. 83–86. Available from: http://digital.casalini.it/978885518449
26. Hirano M, McCormick KR (1986) Clinical examination of voice. J Acoust Soc Am 80(4):1273
27. Morelli MS, Orlandi S, Manfredi C (2021) BioVoice: a multipurpose tool for voice analysis. Biomed Signal Process Contr 64:102302. https://doi.org/10.1016/j.bspc.2020.102302
28. Kent RD, Kim YJ (2003) Toward an acoustic typology of motor speech disorders. Clin Linguist Phonet 17(6):427–445. https://doi.org/10.1080/0269920031000086248
29. Sapir S, Spielman JL, Ramig LO, Story BH, Fox C (2007) Effects of intensive voice treatment (the Lee Silverman Voice Treatment [LSVT]) on vowel articulation in dysarthric individuals with idiopathic Parkinson disease: acoustic and perceptual findings. J Speech Language Hear Res JSLHR 50(4):899–912. https://doi.org/10.1044/1092-4388(2007/064)
30. Walter SR, Dunsmuir WTM, Westbrook JI (2019) Inter-observer agreement and reliability assessment for observational studies of clinical work. J Biomedical Informat 100:103317. https://doi.org/10.1016/j.jbi.2019.103317

31. Ma Z, Bullen C, Chu JTW, Wang R, Wang Y, Singh S (2023) Towards the objective speech assessment of smoking status based on voice features: a review of the literature. J Voice Off J Voice Found 37(2):300.e11-300.e20. https://doi.org/10.1016/j.jvoice.2020.12.014
32. Van den Berg J (1958) Myoelastic-aerodynamic theory of voice production. J Speech Hear Res 1(3):227–244. https://doi.org/10.1044/jshr.0103.227
33. Kent RD, Vorperian HK (2018) Static measurements of vowel formant frequencies and bandwidths: a review. J Commun Disord 74:74–97. https://doi.org/10.1016/j.jcomdis.2018.05.004
34. Kent RD, Rountrey C (2020) What acoustic studies tell us about vowels in developing and disordered speech. Am J Speech-language Pathol 29(3):1749–1778. https://doi.org/10.1044/2020_AJSLP-19-00178
35. Espirito Santo LD, Moreira LM, Riegel M (2016) Cri-du-chat syndrome: clinical profile and chromosomal microarray analysis in six patients. BioMed Res Int 2016:5467083. https://doi.org/10.1155/2016/5467083
36. Honjo RS, Mello CB, Pimenta LSE, Nuñes-Vaca EC, Benedetto LM, Khoury RBF, Befi-Lopes DM, Kim CA (2018) Cri du chat syndrome: characteristics of 73 Brazilian patients. J Intellect Disab Res JIDR 62(6):467–473. https://doi.org/10.1111/jir.12476
37. Chehimi SN, Zanardo ÉA, Ceroni JRM, Nascimento AM, Madia FAR, Dias AT, Filho GMN, Montenegro MM, Damasceno J, Costa TVMM, Gasparini Y, Kim CA, Kulikowski LD (2019) Breakpoint delineation in 5p- patients leads to new insights about microcephaly and the typical high-pitched cry. Mol Gen Gen Med 8(2):e957. https://doi.org/10.1002/mgg3.957
38. Van Buggenhout GJ, Pijkels E, Holvoet M, Schaap C, Hamel BC, Fryns JP (2000) Cri du chat syndrome: changing phenotype in older patients. Am J Med Gen 90(3):203–215. https://doi.org/10.1002/(sici)1096-8628(20000131)90:3%3c203::aid-ajmg5%3e3.0.co;2-a
39. Ajitkumar A, Jamil RT, Mathai JK (2022) Cri du chat syndrome. StatPearls Publishing, In StatPearls
40. Azadi H, Akbarzadeh-T MR, Shoeibi A, Kobravi HR (2021) Evaluating the effect of Parkinson's disease on jitter and shimmer speech features. Adv Biomed Res 10:54. https://doi.org/10.4103/abr.abr_254_21
41. Hecker P, Steckhan N, Eyben F, Schuller BW, Arnrich B (2022) Voice analysis for neurological disorder recognition-a systematic review and perspective on emerging trends. Front Digit Health 4:842301. https://doi.org/10.3389/fdgth.2022.842301
42. Forero MLA, Kohler M, Vellasco MM, Cataldo E (2016) Analysis and classification of voice pathologies using glottal signal parameters. J Voice Off J Voice Found 30(5):549–556. https://doi.org/10.1016/j.jvoice.2015.06.010
43. Zhang Y, Jiang JJ (2008) Acoustic analyses of sustained and running voices from patients with laryngeal pathologies. J Voice Off J Voice Found 22(1):1–9. https://doi.org/10.1016/j.jvoice.2006.08.003
44. Latoszek BBV, De Bodt M, Gerrits E, Maryn Y (2018) The exploration of an objective model for roughness with several acoustic markers. J Voice Off J Voice Found 32(2):149–161. https://doi.org/10.1016/j.jvoice.2017.04.017
45. Kasuya H, Ogawa S, Mashima K, Ebihara S (1986) Normalized noise energy as an acoustic measure to evaluate pathologic voice. J Acoustic Soc Am 80(5):1329–1334. https://doi.org/10.1121/1.394384
46. Liu HM, Tsao FM, Kuhl PK (2005) The effect of reduced vowel working space on speech intelligibility in Mandarin-speaking young adults with cerebral palsy. J Acoustic Soc Am 117(6):3879–3889. https://doi.org/10.1121/1.1898623
47. Hustad KC, Schueler B, Schultz L, DuHadway C (2012) Intelligibility of 4-year-old children with and without cerebral palsy. J Speech Lang Hear Res JSLHR 55(4):1177–1189. https://doi.org/10.1044/1092-4388(2011/11-0083)
48. Levy ES, Chang YM, Ancelle JA, McAuliffe MJ (2017) Acoustic and perceptual consequences of speech cues for children with dysarthria. J Speech Lang Hear Res JSLHR 60(6S):1766–1779. https://doi.org/10.1044/2017_JSLHR-S-16-0274
49. Bunton K, Leddy M (2011) An evaluation of articulatory working space area in vowel production of adults with Down syndrome. Clin Linguist Phonet 25(4):321–334. https://doi.org/10.3109/02699206.2010.535647
50. Zajac DJ, Roberts JE, Hennon EA, Harris AA, Barnes EF, Misenheimer J (2006) Articulation rate and vowel space characteristics of young males with fragile X syndrome: preliminary acoustic findings. J Speech Lang Hear Res JSLHR 49(5):1147–1155. https://doi.org/10.1044/1092-4388(2006/082)
51. Sapir S, Spielman JL, Ramig LO, Story BH, Fox C (2007) Effects of intensive voice treatment (the Lee Silverman Voice Treatment [LSVT]) on vowel articulation in dysarthric individuals with idiopathic Parkinson disease: acoustic and perceptual findings. J Speech Lang Hear Res JSLHR 50(4):899–912. https://doi.org/10.1044/1092-4388(2007/064)
52. Fiorella ML, Cavallaro G, Di Nicola V, Quaranta N (2023) Voice differences when wearing and not wearing a surgical mask. J Voice Off J Voice Found 37(3):467.e1-467.e7. https://doi.org/10.1016/j.jvoice.2021.01.026
53. Ceylan ME, Cangi ME, Yılmaz G, Peru BS, Yiğit Ö (2023) Are smartphones and low-cost external microphones comparable for measuring time-domain acoustic parameters?. European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery, https://doi.org/10.1007/s00405-023-08179-3. Advance online publication. https://doi.org/10.1007/s00405-023-08179-3
54. Carding PN, Wilson JA, MacKenzie K, Deary IJ (2009) Measuring voice outcomes: state of the science review. J Laryngol Otol 123(8):823–829. https://doi.org/10.1017/S0022215109005398
55. Elmakky A, Carli D, Lugli L, Torelli P, Guidi B, Falcinelli C, Fini S, Ferrari F, Percesepe A (2014) A three-generation family with terminal microdeletion involving 5p1533-32 due to a whole-arm 5;15 chromosomal translocation with a steady phenotype of atypical cri du chat syndrome. Eur J Med Gen 57(4):145–150. https://doi.org/10.1016/j.ejmg.2014.02.005
56. Wu Q, Niebuhr E, Yang H, Hansen L (2005) Determination of the 'critical region' for cat-like cry of Cri-du-chat syndrome and analysis of candidate genes by quantitative PCR. Eur J Human Gen EJHG 13(4):475–485. https://doi.org/10.1038/sj.ejhg.5201345
57. Zhang Z (2016) Mechanics of human voice production and control. J Acoustic Soc Am 140(4):2614. https://doi.org/10.1121/1.4964509
58. Zhang B, Willing M, Grange DK, Shinawi M, Manwaring L, Vineyard M, Cottrell CE (2016) Multigenerational autosomal dominant inheritance of 5p chromosomal deletions. Am J Med Gen Part A 170(3):583–593. https://doi.org/10.1002/ajmg.a.37445
59. Nguyen JM, Qualmann KJ, Okashah R, Reilly A, Alexeyev MF, Campbell DJ (2015) 5p deletions: current knowledge and future directions. Am J Med Gen Part C Semin Med Gen 169(3):224–238. https://doi.org/10.1002/ajmg.c.31444

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

Authors and Affiliations

Elisabetta Sforza[1,2] · Federico Calà[3] · Claudia Manfredi[3] · Antonio Lanatà[3] · Andrea Guala[2,4] · Cesare Danesino[2,5] · Angelina Cistaro[2,6] · Matelda Mazzocca[2] · Lucia D'Alatri[7] · Roberta Onesimo[8] · Lorenzo Frassineti[3] · Giuseppe Zampino[1,8]

✉ Giuseppe Zampino
giuseppe.zampino@unicatt.it

Elisabetta Sforza
elisabetta.sforza@unicatt.it

Federico Calà
federico.cala@unifi.it

Claudia Manfredi
claudia.manfredi@unifi.it

Antonio Lanatà
antonio.lanata@unifi.it

Andrea Guala
gualaandrea0@gmail.com

Cesare Danesino
cesare.danesino@unipv.it

Angelina Cistaro
angelinacistaro06@gmail.com

Matelda Mazzocca
matelda.mazzocca@gmail.com

Lucia D'Alatri
lucia.dalatri@policlinicogemelli.it

Roberta Onesimo
roberta.onesimo@policlinicogemelli.it

Lorenzo Frassineti
lorenzo.frassineti@unifi.it

[1] Università Cattolica del Sacro Cuore, Rome 00168, Italy

[2] A.B.C. Associazione Bambini Cri du chat Scientific Committee, Firenze, Italy

[3] Department of Information Engineering, University of Florence, Florence 50139, Italy

[4] Department of Pediatrics, Castelli Hospital, Verbania, Italy

[5] Department of Molecular Medicine, University of Pavia, Pavia, Italy

[6] Nuclear Medicine Department, Salus Alliance Medical, Genoa, Italy

[7] Unit for Ear, Nose and Throat Medicine, Department of Neuroscience, Sensory Organs and Chest, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome 00168, Italy

[8] Center for Rare Diseases and Birth Defects, Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome 00168, Italy