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Review Article

A CRITICAL REVIEW ON SYMPTOMS, GENETICS AND PHENOTYPIC ANALYSIS OF CRI DU CHAT

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ABSTRACT

This article scrutinizes research based on Cri du chat syndrome (CDCS). CDCS is a rare disorder which accounts around 3rd part of total females as males. It is caused due to random deletion of a part of 5p chromosome in Homo sapiens. Some of the symptoms include low weight, cat like cry, different facial features, developmental delays and other health issues. Another aspect covered by this article is epigenetic changes and sleep patterns associated with syndrome. It also highlights Prenatal and Postnatal diagnostic approaches with specified modern clinical techniques used for detection of this rare genetic disorder. Research made on recent case study has been reviewed along with understanding of Genotype-Phenotype co-relation to get deep and practical insights. Through this observation we will update the scientific news of this rare syndrome, as well as the place of cytogenetic explorations in the precise diagnosis. We will be having a deep acknowledgement about how emerging technologies could be used effectively to either treat or improve the effects of respective rare genetic disorder besides, existing experimented techniques used till date. Thus, providing future scope for upcoming research fellows in this field.

Keywords: *Cri Du Chat Syndrome, Rare Disorder, Cytogenetics, Case Studies*

INTRODUCTION

Understanding Cri du chat:

Cri du chat is a rare genetic disorder first discovered by French geneticist Dr. Lejeune in 1963. In early 1960, he was investigating a group of children undergoing through mental disabilities. Among which he noticed majority of children in their first year of birth had high pitched cry like a cat's meow. Thus, he came to discover a disease named "cri du chat" that actually reflects its literal meaning a "cat's cry" (**Sigafoos *et al*., 2009**). The main cause of this syndrome is the deletion of short arm p of chromosome 5 resulting in the change of it's size. CDCS frequency estimated from research is 1 in 15,000 to 1 in 50,000 live births **(Kristoffersen, K. E., 2008**). The size of the CdCS deletion ranges from approximately 10-45 Mb **(de Jesus Graça *et al*., 2025).** CDCS patients are seen with the signs and symptoms including craniofacial malformations, varying degrees of mental retardation, and language/communication delays. Deletion of δ-catenin, encoded by the *CTNND2* gene at 5p15.2 results in mental retardation. CTNND2 defficiency causes developmental delay and is significanctly linked to autism spectrum disorder (ASD) **(J. Shen, Y *et al*., 2025),** however, Overall, ASD-related characteristics show little change over time during follow-up (**Cochran, L *et al*., 2015**). A case of 8 years old African-American female was reported that resulted in mild cognitive phenotype because of breakout in the middle of CTNND2 gene and it's duplication (**Sardina *et al*., 2014**). Additionally, it causes low birth weight in newborns. Many of these features cannot be diagnosed prenatally on ultrasonography (US), and hence, the majority of such cases have been diagnosed postnatally. However prenatal or early diagnosis is suggested to prevent onset of drastic symptoms in later stages of life **(Teoh, X. H *et al*., 2009)**. A study suggested that sleep disturbances were found in approximately 50 % of children with CDC. Sleep complaints in children with CDC include difficulty in settling, sleep anxiety, night waking, insomnia, poor sleep quality and sleep-disordered

breathing (**Xavier, S. D *et al*., 2024).** When 8 individuals suffering from CDCS were studied, the results found that in 4 patients, the 3 sleep-related genes (SLC6A3, ADCY2, and TERT) were deleted in 5p. However, there was no significant correlation between the size of the deletion and the severity of sleep problems (**Kloster *et al*., 2025**). Patients with Cri-du-chat syndrome showed different brain metabolism patterns depending on severity, with reduced activity in parts of the temporal lobe, frontal lobe, caudate, and cerebellum. Abnormally increased activity in certain frontal areas was seen only in those with the severe phenotype, suggesting that hypermetabolism may be linked to more severe symptoms (**Cistaro *et al*., 2020).** Comparing the phenotype of patients at several ages, a change of their phenotype was noted. The clinical diagnosis should be confirmed as soon as possible with cytogenetic investigation to provide specific support, prevention, and treatment of complications beforetime **(Van Buggenhout *et al*., 2000).** Studies suggest adaptive skills and language tend to improve with age unlike other symptoms that show progression overtime. Longitudinal follow-up shows overall stability, but outcomes vary widely, emphasizing the need for individualized assessment and intervention (**Cochran, L *et al*., 2019).** Most children with Cri-du-Chat syndrome are born small, and as they grow, many develop significant microcephaly and low weight for age, with height often less affected **(Marinescu, R. C *et al*., 2000).** Patients with Cri-du-Chat syndrome have a higher prevalence of specific congenital heart defects, compared with the general CHD population. However, the genomic basis for this increased risk remains unclear, emphasizing the need for careful cardiac assessment in CdCS **(Hills, C *et al*., 2006).** limited parental awareness of recurrence risk highlights the need for clearer communication and ongoing genetic counseling to improve understanding of CdCS and its familial implications (**Honjo, R. S *et al*., 2018).**

Characterisation of CDCS by using novel technology: Genetic expressions such as TERT, SEMA5 A, CTNND2, TPPPpresent on chromosome 5p arm are expressed in the brain that play a key role in the development of the nervous system, oligodentrocytes and in the regulation of glutamatergic and dopaminergic synaptic transmission. It thus becomes necessary to understand the role of these genes in diseased patients in order to get properly acknowledged of syndrome. A research was carried out to compare the normal induced pluripotent stem cells (iPSCs) as a control to CDC-iPSCs (pathologically established) in order to study the neuronal development in patients affected by CDCs. In CdC-neurons, TERT gene expression is half as compared to HD, CDNND2 value is four times lower, SEMA5 A gene expression is half and TPPP about ten times less. These changes in gene expressions lead to the changes in brain functionality of patients resulting in significant symptoms like mental retardation,diificulty in concentrating etc. It helps us to study the pathological aspects of cdc patients by differentiating neuronal subtypes of diseased patients to those of normal patients **(Piovani, G *et al*., 2025).**

Genotype-Phenotype correlation: There has been a number of studies that attempt to link genomic changes such as deletion, reduplication, or silencing of genes to cognitive and behaviour outcomes: in essence to link genotype to phenotype **(Cornish, K *et al*., 2002).** Genotype broadly reflects the genetic framework of organism whereas, phenotype depicts the physical appearance. In order to get deep and clear insight of a genetic disorder, it is mandatory to study the genotype-phenotype relation. Changes in genes causes broad differences in phenotypic occurrence when an individual develops a certain disorder. In case of Cri Du Chat syndrome, a specific gene codes the characteristic information for a particular occurring symptom **(Ajitkumar A *et al*., 2022).** Larger 5p deletions, especially involving the 5p15.2 region, are associated with more severe speech and language impairments in CdCS, while proximal 5p15.3 deletions correlate with better outcomes.Specific genes like CTNND2 are frequently implicated, but detailed genotype–phenotype maps linking individual genes to distinct speech deficits remain lacking (**Iloanusi, N. J. R., 2025**). Cases of siblings with different features like growth and development have been observed, despite having inherited the same deletion. Affected Members of families in which deletions were genetically inherited from father resulted in more growth and developmental delay as in the affected members of families in which deletions were inherited maternally **(Lojo Iglesias., 2022).**

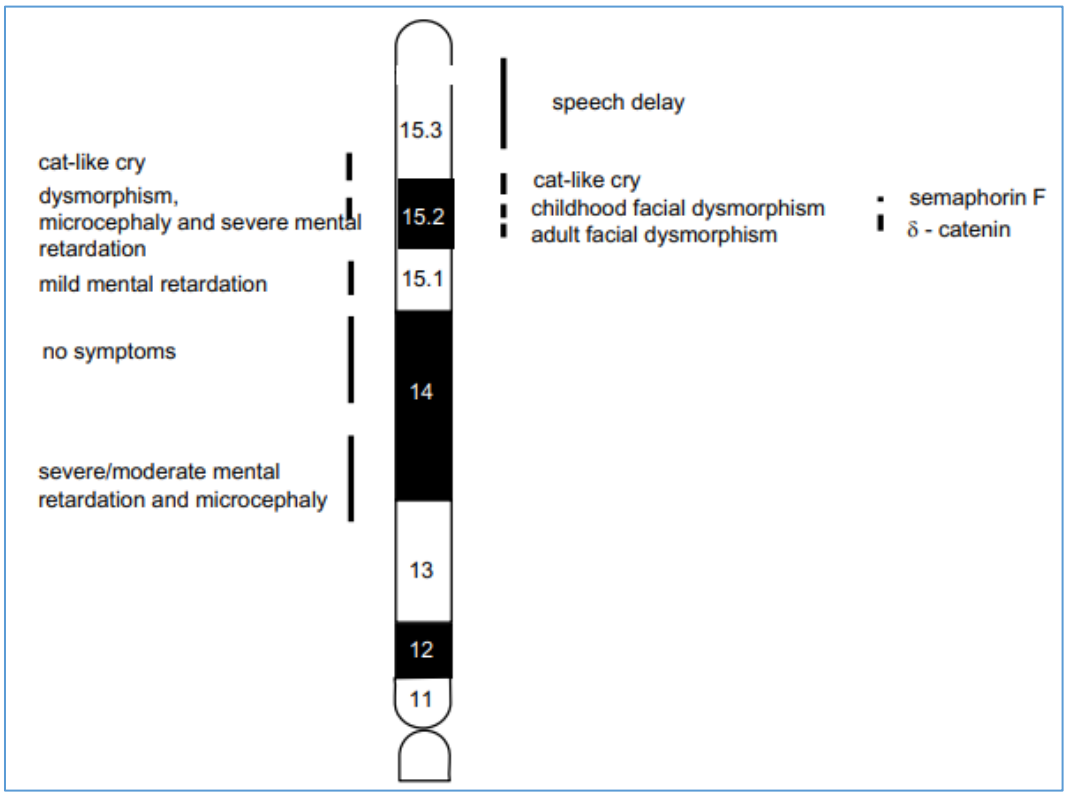

Figure 1: Phenotypic map of 5p. Vertical lines indicate the critical regions for the cry in p15.3, and for the other signs of Cri du Chat syndrome in p15.2. Vertical lines in p15.1, p14 and p13 refer to clinical symptoms. It depicts appearance of symptoms as per the changes in size of chromosomal segment and changes in genes responsible for it (**Cerruti Mainardi, P., 2006**).

Symptoms and Epigenetic changes: Cri du chat syndrome has shown various symptoms ranging from mild like changes in physical appearance to severe like mental retardation. Facial shape in CDCS shows consistent, characteristic change with age, mainly varying in severity rather than pattern. Multiple critical regions on 5p (5p15.33–15.32) influences facial features **(Vanneste, M *et al*., 2026).** At birth**,** the skull is massive, in contrast to the round, full face along with other noticeable symptoms like cyanosis, inadequate sucking, and hypotonia. During the first year of life, They have a short, ordinary neck, spontaneous fractures, inguinal hernia, myopia, small hands, flat feet, slow and incomplete development of motor skills, skin excrescence just in front of the ear, a sunken root of the nose, inwardly adducted thumb, cleft lip and palate, a characteristic pouting mouth, absence of spleen and kidney, clubfoot etc **(Rodríguez *et al*., 2025).** Individuals with Cri-du-Chat syndrome demonstrate distinct vocal characteristics, with significant acoustic differences in sustained vowel production, particularly among older males.These findings support that voice features may reflect underlying biological and clinical traits, reinforcing the characteristic vocal phenotype of CDCS (**Sforza, E *et al*., 2024**). Individuals with CDCS took more frequent, shorter steps than normal; maintaining similar walking speed, but showed limited adjustment when performing a complex task. This suggests difficulty in coordinating movement or responding to additional task demands (**Abbruzzese, L. D *et al.,* 2016**). Congenital dislocation of the hips and knees in these patients is particularly rare and has not been described in the medical literature among CDCS patients (**de Jesus Graça *et al*., 2025).** Scoliosis is another notable condition must be taken under consideration while studying CDCS.The condition shows progression upon aging of affected individuals (**Takebayashi *et al*., 2006**). Affected children showing terminal deletions, a negative correlation was found between the size of the deletion and the individual's intelligence quotient. Moreover, patients accounted

direct proportionality of deletions with respect to growth retardation **(Wolf, B *et al*., 1983).** one notable feature is a delay in the onset of spoken words. children affected by CDCS begin to produce their first spoken words between 2.5 and 5 years of age, which is significantly delayed compared to the typical speech development of around 12 months (**Papadopoulou, S *et al*., 2024**). No such correlation between the clinical features and localisation of deletion has been determined **(Niebuhr, E *et al*., 1978).** DNA methylation analysis of eight patients affected by syndrome was carried out to rule out the epigenetic changes that result in particular signs and symptoms.changes in methylation of CpG sites on p arm of chromosome 5 of patients were identified.Gene set enrichment analysis was performed which suggested that The genes with altered promoter methylation are enriched for genes involved in embryonic development and are also linked to clinical features that are very common in Cri du chat syndrome, specifically developmental delay and microcephaly.This confirmed the involvement of epigenetics in the study of syndrome **(Holland, P *et al*., 2022).** According to the % evaluated from Italian CDCS registry following data has been received for occurrence of symptoms **(Cerruti Mainardi P., 2006).**

Table 1: Symptoms of CDCS (%) as per their occurrence according to Italian CDCS registry [*source: Googlescholar*]

Features	**159 patients at diagnosis**	**%**	**49 patients at diagnosis**	**%**	**49 patients at diagnosis >15 years**	**%**
Round face	96/115	83.5	29/31	93.5	1/48	2.1
Broad nasal bridge	102/117	87.2	31/35	88.6	28/43	65.1
Lateral downward slanting	70/123	56.9	21/38	55.3	14/47	29.8
Hypertelorism	105/129	81.4	34/41	82.9	29/46	63.0
Down turned corners of mouth	81/100	81.0	31/32	96.9	27/42	64.3
Low-set ears	81/116	69.8	21/30	70.0	15/46	32.6
Typical cry / acute voice	141/147	95.9	46/48	95.8	30/45	66.7
Short neck	41/73	56.2	7/15	46.7	10/39	25.6
Transverse flexion creases	103/112	92.0	38/40	95.0	38/40	95.0
Small pelvis	31/42	73.8	4/7	57.1	13/24	54.2
Hypotonia	78/108	72.2	34/35	97.1	1/40	2.5
Diastasis recti	43/56	76.8	5/8	62.5	20/27	74.1
Epicanthal fold	119/132	90.2	39/43	90.7	27/48	56.2
High arched palate	62/74	83.8	13/14	92.9	23/40	57.5

Behavioural changes:Patients suffering from Cri Du Chat syndrome also administer hyperactivity or attention deficit hyperactivity disorder (ADHD) and characteristics of autism spectrum disorders (ASDs) with 5p deletioins.This results in behavioural changes such as attachments to unusual objects,hand movements such as shaking or twirling etc. However, simultaneously receptive skills are more developed in people affected by Cri Du Chat syndrome **(Lojo Iglesias., 2022).** Beside, developmental changes such as ablility to communicate their needs, socially interact with others, and have some degree of mobility were noticed **(Cornish, K. M *et al*.,1996).** Adoptive behaviour was noticed when sample size of 10 children and

adolescents were studied for their maladaptive and adaptive behaviours **(Teixeira *et al.*, 2011).** Self-injurious behaviors commonly reported were- striking the head against objects, hitting the head with body parts, and self-inflicted injuries through biting.however, self destructive behaviour decreases with aging **(Collins *et al.*,2002)** Early intervention strategies such as occupational therapy, psychological support, and parental counseling have effectively eradicated these issues **(Papadopoulou, S *et al.*, 2024).** They also show marked sense of humor, being affectionate, scary, and shy. Studies suggested that there was no correlation found between the aggressive behaviour and age **(Bel-Fenellós, C *et al.*, 2023).**

Diagnosis: DNA clone mapping of chromosomal critical region (5p13-15) showing cat like cry feature can be performed. The presence of the cat-like cry should not lead to a diagnosis of cri-du-chat syndrome. Only if deletion including 5p15.2 is observed, the presence of the cat-like cry may lead to the diagnosis of cdcs else better cytogenetic analysis is suggested **(Gersh, M *et al.*, 1995).** Accurate cognitive assessment is essential in CdCS patients, as severe speech and gestural dyspraxia can mask true intellectual abilities, guiding appropriate diagnosis and intervention strategies (**Marignier *et al.*, 2012**). Differentiating between types of 5p deletions is important, as deletions including the typical Cri-du-chat region cause severe cognitive impairment, while distal deletions lead to milder impairment and better prognosis **(Cornish, K. M., *et al.*, 1999).** Early diagnosis is important to avoid any critical circumstances in later stage of life. Research suggests mostly this syndrome occurs in females however, there is no proper scientific reason estimated behind it till date. The research is still ongoing. Prenatal diagnosis of CDCS is possible via findings such as- absent nasal bone, ascites or other duplication syndromes. Combining typical karyotyping with chromosomal microarray analysis (CMA) is definitive method for precise diagnosis **(Zhao *et al.*, 2025).** Whereas amniocentesis is the widely used clinical method for detection of genetic disorders **(Su, J., Fu, H., Xie, B. *et al.*, 2019)**. Other methods include chorionic villus sampling or cordocentesis, even in rare presentations such as fetal hydrops (**Tullu, M. S *et al.*, 1998).** Careful second-trimester ultrasound, including fetal biometry and soft markers, can help detect Cri-du-Chat syndrome even when first-trimester screening appears low risk (**Teoh, X.H *et al.*, 2009**).

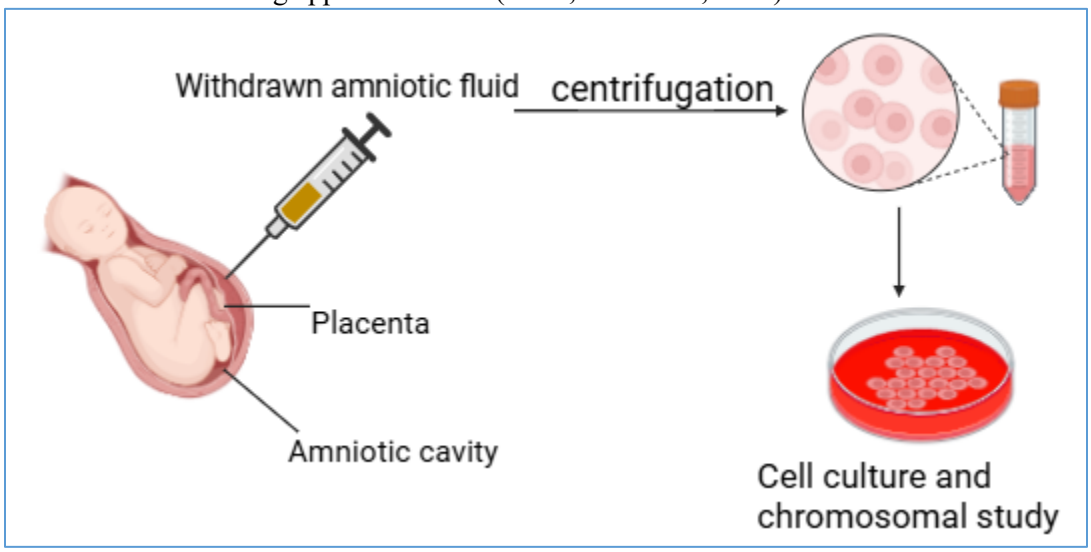

Figure 2: Amniocentesis used for detecting chromosomal abnormality occurring as a result of rarely occurring Cri Du Chat syndrome.

*Limitation of Amniocentesis:*It can be done only after 12-16 weeks after conception. Analysis of the culture will take another 2-6 weeks. Therefore, if any kind of abnormalities are found and the mother is asked for abortion it will be too late. Amniocentesis will give a mild shock to the foetus affecting its growth. Postnatal diagnosis of CDCS include examining the symptoms such as cat like cry within one year of birth, low birth weight, distinctive facial features, change in language and speech, late development etc. [**source: microscopia IWM**] specific tests can be carried out for confirmation like fluorescence in situ hybridization

(FISH), comparative genomic hybridization (CGH), or quantitative polymerase chain reaction (PCR) (**Danijela Krgovic *et al*., 2014**).

Treatment: It is a genetic disorder hence, no specific medical treatment is available. However, effects of syndrome can be minimized using different ways like- corrective surgery, communication aids, regular follow up, educational intervention etc. Children with Cri-du-Chat syndrome should have regular eye exams to check for amblyopia**,** strabismus**,** high refractive errors**,** cataracts**,** lid/adnexal disease**,** or optic nerve problems, and therapy can help with visual-spatial and kinesthetic difficulties (**Sweeney, S. 2012**). Experimental trials on treating Cri Du Chat syndrome are being carried out by using a novel technology like CRISPR cas9.Methods such as Programmable Addition via Sitespecific Targeting Elements (PASTE) by using viral integrase proteins instead of Cas double-strand breaks to deliver DNA can be used for addition of deleted genes: tested on mouse liver cells.Similarly, transposons(jumping genes) can also be employed **(Japson, E., 2026).** A novel CdCS rat model with a 2q22 deletion is developed that represents chromosomal abnormality similar to patients suffering from cdcs. AAV vectors can deliver functional genes that show potential for enhancing cognitive function by addressing the loss of synaptic components like δ-catenin. However, the effectiveness of this therapy is confined to the early developmental stages and does not fully restore all CdCS symptoms. **(J. Shen, Y *et al*., 2025).** Thus, soon with emerging technologies and effective experiments it would be possible to treat such life threatening rare genetic disorders.

Case studies: A 6year old male child was diagnosed with Cri Du Chat syndrome in Nepal when brought to outpatient department of the tertiary care center by his parents. Mother was 21 years old and Father's age was 32 years. Both were phenotypically normal. However the child was reported to have high pitched cry after birth having weight of around 2.5kgs and showed symptoms like delay in speech and self-injurious behaviour in later stage of life. There was no family history of developmental delay. Expressive language was delayed as compared to receptive language. On physical examination symptoms like elongated face, epicanthal folds,large ears and microcephaly were noted. Chromosomal study revealed a segmental loss on chromosome 5 (25.4 Mb) at the cytoband region 5p15.33- p14.1, indicating monosomy. Physiotherapy, occupational and behavioral therapy were advised as a part of treatment. The parent's karyotype was normal, indicating de novo mutation in the child. This was the first genetically confirmed case of Cri-du-chat syndrome reported from Nepal.The case highlighted the importance of early detection of syndrome ,leading families to seek beforehand support (**Surabhi Arya *et al*., 2025).** A prenatal SNP-array study in China identified Cri-du-Chat syndrome (CdCS) in 12 of 35,233 pregnancies (0.034%). Half of the cases involved isolated terminal 5p deletions, and the other half were due to unbalanced translocations, with a female-to-male ratio of 7:5, similar to postnatal patterns. First-trimester screening was largely uninformative, but cerebral abnormalities on ultrasound were the most consistent finding (42%) in fetuses with 5p15.2 deletions, highlighting abnormal brain development as a key prenatal marker of CdCS **(Su J *et al*., 2014**). In a case of an infant with Cri-du-Chat syndrome (CdCS), early general movements assessment (GMA) at 14 weeks showed absent fidgety movements, a limited motor repertoire, and monotonous movement patterns. Despite early intervention from 14 weeks and some progress in developmental milestones, Bayley-III scores did not reflect these gains. This case highlights that abnormal GMA patterns in CdCS may signal early neurodevelopmental challenges, and early intervention can support milestone achievement even if standardized scores show limited change (**Yardımcı-Lokmanoğlu, B. N *et al*., 2021).** In a study of 12 prenatal Cri-du-Chat syndrome (CdCS) cases, karyotyping and SNP-array analysis were used to assess clinical and molecular characteristics. Nine cases had terminal 5p deletions and three had interstitial deletions; seven were de novo and the rest inherited. Phenotypically, seven of the nine fetuses with deletions showed signs of neurodevelopmental abnormalities, while two appeared normal. Ultrasound findings included growth retardation (3 cases), cerebellar hypoplasia (5), congenital heart defects (2), hypospadias (2), and lung dysplasia (1), illustrating the wide spectrum of prenatal features and emphasizing the importance of detailed genetic and imaging evaluations in early detection of CdCS **(Peng, Y *et al*., 2020).**11month old male infant administered to a medical consultation due to a reflection of symptoms like dysmorphism and psychomotor delay. Delivery was conducted vaginally and birth weight

was 2.4kg. The infant had a kitten cry and experienced feeding difficulties, leading to weight at 2.4 kg until 3 months of age. Facial dysmorphism was evident, including a round face, orbital hypertelorism, mandibular hypoplasia, a wide and flat nasal bridge, a globular nasal tip, epicanthus, and eyebrows slanting towards the middle of the face. The fourth toes of both feet consistently rested on fifth and fourth toes figure 2(a). The remainder of the clinical examination showed no abnormalities. Metaphase karyotyping of patient revealed a 5p deletion 46, XY, del (5) (p13p15) figure 2(b) (**H. Bella *et al*., 2024**).

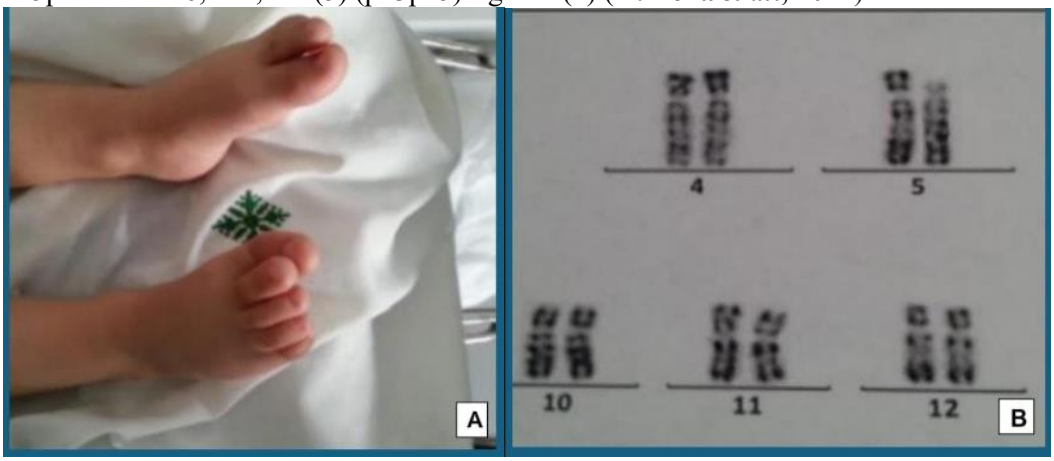

Figure 3. (a) The fourth toes of both feet consistently rested on fifth (b) Metaphase karyotyping of patient revealed a 5p deletion 46, XY, del (5) (p13p15) [source: SAS journal of medicine].

As the child ages, the face becomes long and thin. Decreased muscle tone is constant in the neonatal and early childhood period but disappears later. Psychomotor milestones are delayed, with independent sitting achieved after the age of 2 years and independent walking rarely before the age of 4. Language is usually limited to a few words or absent. Intellectual delay is evident from the first months and ranges from severe to profound. Behavioural problems were observed like- self-destructive activities, anxiety and aggression etc (**H. Bella *et al*., 2024**).

CONCLUSION

Despite name is given as cri du chat based on cats cry symptom, ample of research papers says that CDCS diagnosis is not confirmed by cat like cry but it is only a suspicious aspect of evaluation.cat like cry occurs due to improper development of larynx resulted from abnormal size of chromosome 5p.Thus, normal crying sound appears as if cats cry.Not all patients suffering from CDCS reflect same symptoms. It depends upon the phenotype and genotype of person. Case studies revealed that Most common symptom found is cat's cry hence, name given Cri Du Chat (French term).According to Italian CDCS registry, order of symptoms based on the most observed to least is as follows: Microretrognathia (96%) > Cat's cry(95%) > Transverse flexion crease(92%) > epicanthal fold (90%)> broad muscle bridge (87%)> high arched palate(83%) > hypertelorism(81%) >diastasis recti(76%) > small pelvis (73%) > hypotonia(72%)> prominent metapoic bossing(70%) > short neck(56%) Extends of deletion may vary from person to person accordingly symptoms can be seen based on change of size of chromosome 5p.Different research papers show variant occurring frequencies of respective syndrome. However, average 1 in 15,000 – 50,000 could be considered. Prenatal diagnosis is better than postnatal as early diagnosis will result in manageable symptoms. Research on treatment is still ongoing for genetic disorders. However, there is no proper treatment investigated till date. Research suggest that Amniocentesis is most easy and common method used for Prenatal diagnosis of genetic disorders like CDCS wherein amniotic fluid is extracted consisting of fetus cells that hold chromosomes. Abnormalities beside CDCS symptoms may occur like overlapping of toes as revealed from recent case study.

FUTURE SCOPE

As per the research papers reviewed it has been clear that due to advancement in technology and scientific approaches, scientists are more willingly working on finding new ways either to tackle effects of syndromes or striking hard to treat genetic disorders. Current research on cri du chat focuses on physiotherapy, speech therapy, communication alternatives early schooling, occupational therapy and oral stimulation. Technical areas where upcoming research fellows can work are- genomic editing like CRISPR for potential therapeutic applications, neuroimaging for brain development and epigenetic biomarkers for diagnosis and treatment monitoring. Factors affecting patients with CDCS could be studied rather than those considered by researchers like aging, cancer studies etc. Moreover, research in personalised medicine would pave an excellent path as a specific treatment for this syndrome. Research could be carried out to study in detail about the person-to-person genetic framework and functioning in correlation with family's medical background and inheritance. Accordingly, treatments could be formulated with proper experimentation. Targeted therapies could be another alternative for carrying out research by addressing a specific symptom and working on it. Stem cell therapy can be used to repair and replace the damaged tissues. Alternatively artificial tissues could be invented for the same purpose. Broad research in hormonal therapies could be carried out to improve the hormonal misbalance thus managing the symptoms effectively like- aggression, depression, loneliness, anxiety, mood swings etc. Thus, the future scope for cri du chat syndrome is promising.

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