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RESEARCH ARTICLE

DESIGN OF DRUG MOLECULES FOR CRI DU CHAT SYNDROME USING BIO-INFORMATIC TOOLS

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ABSTRACT

Our study shows that in addition to proportion and position of the 5p deletion, of the factors may alter the brain function of patients with the 5p deletion. cri du chat syndrome, or 5p deletion syndrome, is a raremedicalconditionthataffects1in50,000newborn. Mental illness depends on the approximate proportion and position ofthe5pdeletion, but in most cases the mental illness is a normal negative for the 5p deletion. He has a soft, gentle voice like a cat. One of the characteristics of new burns is a loud catchy, and this is often considered a diagnosis of illness. However, meowing behaviour observed in individuals whose deletion was limited to 5p15.3 but without the dysmorphic and growth –like condition. Although the size of the deletion varies, in anycasethemainpart deleted is 5p15.2 This paper suggests the type of chemical compound to support the behaviour of the patient includes loudcrying, psychomotor retardation, microcephaly, growth retardation, and craniofacial abnormalities including round face, protrusion, broad nasal bridge and downward-sloping palpebral fissures. We present Some clinical features such as elongated face, large stoma and scoliosis have been reported. This study provide drug, MR level, population genetic and telomere length. Diagnos is may be difficult in some patients with advanced age at first presentation. Some of these have craniofacial features similar to Angelman syndrome. Patients of ten experi encetrauma, self-harm, and violence

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INTRODUCTION

Cri du chat syndrome is a one of the rare genetic disorder due to some errors in the chromosomes (22q11). It is named as cri du chat syndrome as it was first discovered by Jerome Jejune in 1963.So, this is also known as 5p-syndrome. He named this disorder called as cry of the cat, because the people with this disease make sound like cry of the cat. It is a *hereditary congenital syndrome*. (1) It affects one in 50,000 peopleacross the world. It frequently observed in female by a 4:3 ratios. After some research it is know that-this disorder caused by error occur at the end of the short (p) arm of chromosome 5 and a small section of the long arm (q) of human chromosome 22 being present 3times (trisomy) or 4times (tetratomic) instead of the usual 2times. By this deletion multiple genes are missing or deleted. This condition happens randomly during to the formation of reproductive cells in early fatal stage. most of the cri du chat disorder is not inherited. Another cause of this disorder is unbalanced translocations which further cause birth defects and other health problems. (1) The protein name telomerase reverse transcriptase (hTERT) is affected by this syndrome. Cri du Chat Syndromes (CdCs) are treatableconditions with an incidence of 1in15,000 to 1in50,000. The description of this material and its 5p deletion characteristics may help further refine the phenotype-genotype relationshipbetweenCdC and autism spectrum disorder.

SYMPTOMS

Deletions of many genes will affect the phenotype and evidence. The main symptoms of speech syndrome are:

Abnormal growing head.

- Forehead is colossal in size.
- Delay in growth of the body.
- Cardiovascular abnormalities.
- A high pitched cat like cry.
- Broad spaced eyes i.e. HYPERTELORISM.
- Abnormally shaped or ears are small in size.
- A tiny jaw i.e. MICROGNTHIA.
- Delicate muscles tonieri.e. HYPOTONIA.
- Anal atresia. (Abnormal obstruction of the anus).

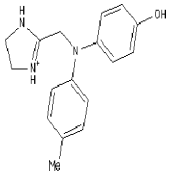
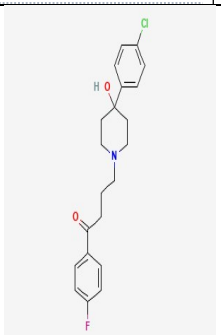
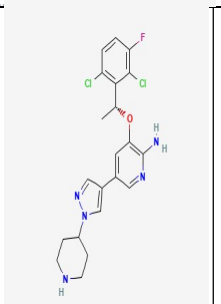
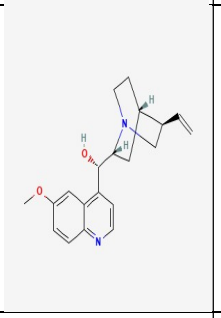
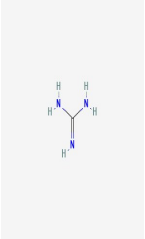
Other symptoms like

- Moderate hearing.
- Cleft palate means incomplete closure of the roof of the mouth.

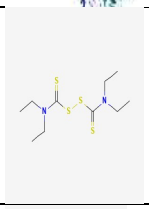
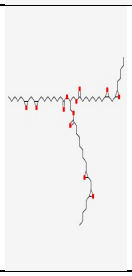
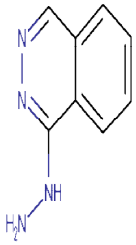
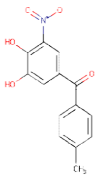
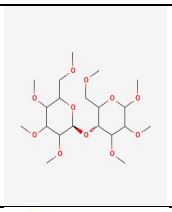
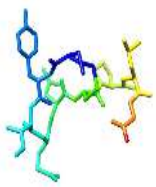
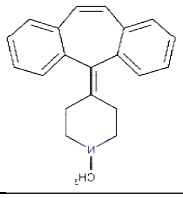
Nephrological problems

- Scoliosis or skeletal problems.
- Short stature.

Table 1. Molecular Drug

SL NO.	NAME OF THE DRUGS	MOLECULAR FORMULA	MOLECULAR STRUCTURE	SOURCE	DRUGBANK ACESSION NO.	URL
1	Bitter DB 389				ChemDB7597489	NIH Clinical Collection via Pub Chem SAM003107541 ○ SAM003107541
2	Haloperidol	$C_{21}H_{23}ClFNO_2$		Haloperidol is a phenylbutylpiperidine derivative with antipsychotic, neuroleptic and antiemetic activities. It is a very potent first generation (regular) antipsychotic and one of the most commonly prescribed antipsychotics worldwide.	DB00502	https://go.drugbank.com/drugs/DB00502
3	Crizotinib	$C_{21}H_{22}Cl_2FN_5O$		Crizotinib is an oral aminopyridine receptor tyrosine kinase anaplastic lymphoma kinase (ALK) and hepatocyte growth factor receptor (HGFR) inhibitor with antineoplastic activity. Binds and inhibits ALK in ATP competition kinase and ALK fusion proteins.	DB08865	https://go.drugbank.com/drugs/DB08865
4	Quinidine	$C_{20}H_{24}N_2O_2$		Quinidine is an alkaloid extracted from the bark of cinchona with anti- malarial effects. It also stabilizes neuronal membranes by binding to and inhibiting voltage- gated sodium channels.	DB00908	https://go.drugbank.com/drugs/DB00908
5	Rumex crispus top			Rumex crispus top allergenic extract which is used in allergenic testing.	DB14167	https://go.drugbank.com/drugs/DB14167
6	Durvalumab			Durvalumab is an anti-cancer antibody. It blocks the action of PD-L1 by which activation of the T-cell increases, enhancing detection of tumour cells.	DB11714	https://go.drugbank.com/drugs/DB11714
7	Guanidine	CH_5N_3		Guaniidine is a uremic toxin.It is an Acetylcholine Releasing Agent. The physiologic effect of this is by means of Increased Acetylcholine Activity.	DB00536	https://go.drugbank.com/drugs/DB00536

Continue ….

8	Human immunoglobulin G	$C_{6332}H_{9826}N_{1692}O_{1980}S_{42}$		Human Immunoglobulin G is a pure form of human Immunoglobulin G and other proteins used in the treatment of immune system diseases and many autoimmune diseases..	DB00028	https://go.drugbank.com/drugs/DB00028
9	Disulfiram	$C_{10}H_{20}N_2S_4$		Disulfiram is an orally bioavailable carbamoyl derivative which is used in the treatment of alcoholism,.It act as an antineoplastic agent and a ferroptosis inducer. It is an organic disulfide and an organosulfur acaricide.	DB00822	https://go.drugbank.com/drugs/DB00822
10	Soybean oil	$C_{57}H_{98}O_{12}$		.Soybean oil is a vegetable oil and a source of polyunsaturated and saturated fatty acids. It is used as a source of calories and essential fatty acids in patients selected for total parenteral nutrition (TPN) therapy and prevention of essential fatty acid deficiency.	DB09422	https://go.drugbank.com/drugs/DB09422
11	Hydralazine	$C_8H_8N_4$		Hydralazine is an oral anticonvulsant that works by causing peripheral vasodilation. It is a member of the phthalazines, azaarenes, ortho- fused heteroarenes and hydrazines.	DB01275	https://go.drugbank.com/drugs/DB01275
12	Tolcapone	$C_{14}H_{11}NO_5$		Tolcapone is a benzophenone derivative, a member of 2-nitrophenols and a member of catechols. It is a catechol-O-methyltransferase (COMT) inhibitor. It is used to treat Parkinson's disease.	DB00323	https://go.drugbank.com/drugs/DB00323
13	Methylcellulase	$C_{20}H_{38}O_{11}$		Methylcellulose is **a** methyl ether of cellulose **and has** laxative **properties. It** is a polymer **that has many connections between sugar** molecules **and is** used as a **stabilizer,** thickener and emulsifier **in food** and **cosmetics.**.	DB11228	https://go.drugbank.com/drugs/DB11228
14	Oxytocin	$C_{43}H_{66}N_{12}O_{12}S_2$		Oxytocin **has** 9 **amino acids** with a **disulfide bond** between Cys **1 and 6** residues. It is an **oxytocin hormone that acts** as a vasodilator and a **heterocyclic** peptide. It plays an important role in **coordination,** social **cognition,** and even fear **control. It** also **plays** a role in metabolic homeostasis and cardiovascular **regulation.**.	DB00107	https://go.drugbank.com/drugs/DB00107
15	Cyproheptadine	$C_{21}H_{21}N$		Cyproheptadineis a H1-receptor antagonist, an antipruritic drug, an anti-allergic agent and a gastrointestinal drug. It is a 1st generation member of piperidines and a tertiary amine. It is a combine of serotonin and histamine antagonist.	DB00434	https://go.drugbank.com/drugs/DB00434

Continue ….

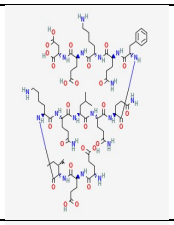
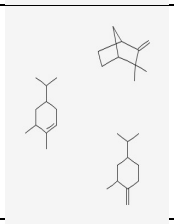
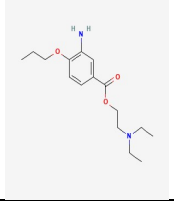
16	Human interferon beta	$C_{72}H_{115}N_{19}O_{26}$		Human interferon beta is a **peptide** drug. It is currently **studying the** treatment **of** COVID-19, the **disease caused by the new** 2019 SARS-CoV-2 virus.	DB14999	https://go.drugbank.com/drugs/DB14999
17	Nutmeg	$C_{32}H_{56}$		Nutmeg is an extract from Nutmeg used in allergy testing.	DB10676	https://go.drugbank.com/drugs/DB10676
18	Proparacaine	$C_{16}H_{26}N_2O_3$		Proparacaine **yog** benzoic acid derivative anesthetic **uas inhibits** voltage- gated sodium channels .		
19	Corifollitropin alfa **(Elonva)**	Not found		It can only be used by typing. It is used together with a gonadotropin-releasing hormone (GnRH) antagonist, which is also used in the treatment of female fertility.	DB09066	https://go.drugbank.com/drugs/DB09066

Table 2. Score Count

NAME OF THE DRUGS	SEQUENCE ID		SEQUENCE ALLIGMENT SCORE						REMARK
	1st ID	2nd ID	RMSD	TM SCORE	SEQUENCE IDENTIFICATION	EQUIVALENT RESIDUE	REFERENCE COVERAGE	REFERENCE COVERAGE	
Bitter DB 389	4A04	6R2U	4.24	0.14	6%	51	28%	19%	
Crizotinib	4A04	3ZBF	5.66	0.13	7%	62	34%	22%	NOT SUITABLE
HaloperidoL	4A04	**6**DJZ	4.52	0.23	4%	71	39%	33%	
Quinidine	4A04	**6LQA**	3.04	0.03	4%	31	17%	3%	
Rumex crispus top	4A04	5V7C	1.17	0.08	13%	15	8%	10%	
Durvalumab	4A04	5X8M	3.8	0.32	4%	84	46%	72%	
Guanidine	4A04	4D50	1.09	0.05	0%	16	9%	6%	
Human immunoglobulin G	4A04	1LVE	3.57	0.33	6%	84	46%	74%	
Disulfiram	4A04	**6LS5**	6.75	0.19	5%	104	57%	32%	
Soybean oil	4A04	6EMM	1.37	0.06	11%	18	10%	7%	
Methylcellulase	4A04	1A7S	4.75	0.17	5%	57	31%	26%	
Tolcapone	4A04	4D7B	4.66	0.12	3%	37	20%	32%	
Cyproheptadine	4A04	5AYF	4.46	0.11	2%	38	21%	16%	
Human interferon beta	4A04	1N6U	3.6	0.27	8%	79	44%	37%	
Nutmeg	4A04	1BX4	4.76	0.12	6%	59	33%	17%	
Propantheline	4A04	1X9Q	3.26	0.27	4%	80	44%	35%	
Oxytocin	4A04	6TPK	3.23	0.06	8%	34	19%	7%	
Corifollitropin alfa	4A04	2WKL	6.2	0.11	2%	77	43%	16%	

Table 3. Classification of MR

ME LEVEL	DESCRIPTION	IQ	PHENOTYPE	
			Child	Adult
0	Normal	-	No MR	No MR
1	Borderline	<70	Normaldevelopment; Mino growth retardation occurs in the first year.	Yearsspent in standard school; Small/large need support
2	Very mild	<65	Growthisnormalin the first few years of life; Mildgrowth retardation occursat2-3 years ofage.	Severalyears in the school model;theneed for reinforcement; basic reading, writing and math skills
3	Mild	<50	Asignificant delaying growthforseveralmonths; Significantgrowth retardation at1-2 years	Understand everything, including long sentences; have very basic reading, writing and math skills
4	Moderate	<35	delayed significantgrowthfor several months; Significant growth retardation from 1 year ofage	Know almost everything; use smaller sentences and more characters
5	Severe	<20	Significantgrowth is delayed from months to a year; MR occurs before 1 year ofage	Easy-to-understand everyday sentences and words; Use2-3word sentences and lots of characters; Walk
6	Very severe	<10	Significantgrowthhaslowedover the years; MRI apparently 6 months ago	I understood a few words; usually walk regularly if supported; no speech or just a few words
7	Profound		5-year-old can't standonhisownfeet	Show little or no response; can sit and stand independently; rarely travel

Table 4. Cytogenetic Analysis

PATIENT	AGE(YEARS)	KARYOTYPING	TELOMERE LENGTH	HTERTmRNA INDUCTION
1	0-1	46,XY,del(5)(p13)	-	-
2	1	46,XX,del(5)(p15.1)	20,638 ± 6,141 (43,904 ± 546)	
3	4	46,XY,del(5)(p13)	15,819 ± 1,206 (46,549 ± 4,006)	.6 (3.1)
4	8	46,XY,rec(5)dup(5q)inv(5)(p14q35)	12,339 ± 3,901 (36,240 ± 2,290)	1.6 (1.7)
5	8.5	46,XX,del(5)(p13)	12,684 ± 1,886 (30,720 ± 1,080)	6.0 (5.4)
6	8.8	46,XX,del(5)(p15.1)	7,520 ± 1,823 (36,976 ± 5,230)	.5 (2.1)
7	10	46,XX,del(5)t(5;3)(p14;q31)	6,552 ± 635 (22,912 ± 3,030)	.7 (2.1)
8	12	46,XY,del(5)(p14)	13,461 ± 3,419 (26,146 ± 2,944)	3.2 (6.6)
9	14	46,XX,del(5)(p15.1)	4,337 ± 864 (30,223 ± 3,254)	.9 (3.0)
10	35	46,XX,del(5)(p14)	-	-

- Facing difficulties in swallowing and sucking.
- Low weight during birth.
- Flat nose.
- Multiple size fingers.
- Unusualface changes.
- Extra folding skin.
- Delay while talking.

The cri du chat syndrome cause due to disorder of two amino acids– HISTIDINE & TYROSINE.

Diagnose: There are normally three genetic tests use to diagnose the cri du chat syndrome. Such as

- **Karyotype:** It is a karyotype chromosomal analysis which express the child's chromosomes, by which we know that about the missing or deflectionor addition ofthe chromosome.
- **FISH testing:** The full form of the FISH is 'Fluorescence In Situ Hybridization'. This test looks for the specific changes of the gene on their positions in the child's cells.
- **Chromosome microarray analysis:** It is attest which is used to identify the extra duplicated and deleted the chromosomal segment of the person. (Table 1) It is also used to recognised the genetic irregularity and the condition of the disease.

There is no cure for Chatter syndrome. Treatments designed to support children and help them reach their potential include: Physical therapy to improve muscle weakness. speech therapy. The above chemical compounds used to prepare the drug molecules. On the basic of sequence identification score, equivalent residue, reference coverage and reference coverage drug molecules are selected (Table 2). In children, CdCs is defined by microcephaly, mental illness and disability. Psychotic symptom such as tantrums, self-harm, aggressive behaviour and feelings of abuse, hallucinations, depression, and self-hatred. (2) Mental illness depends on the approximate proportion and position ofthe5pdeletion, but in most cases the mental illness is a normally negative for the 5p deletion. He has a soft, gentle voice like cat. One of the characteristics of new-born is a loud cat cry, and this is often considered a diagnosis of illness. However, meowing behaviour was observed in individuals whose deletion was limited to 5p15.3 but without the dysmorphic and growth-like condition. (3) It has been shown that the ROPN1L gene is affected by fragmentation. Patients often experience trauma, self-harm, and violence. Cytogenetic analysis revealed a deletion at the end of chromosome 5p14, insistent with the cri-du-chat locus. (4,5) The prongs is for mental illness depends on the extent and location of the 5p deletion, but in many cases the mental illness is a normally poor due to the 5p deletion. All 15 patients (about two-thirds of patients with severe autism) were found to have numerical deviations in addition to the 5p deletion. (6,7) Limiting the analysis to only patients with the 5p deletion illuminates the effect of the deletion and shows that the reared 3 regions with different hysteresis, designated MR-I, MR-II, and MR-III. Subtraction includes MR-I, a 1. The 2-Mb region overlaps with the previously identified cri-du-chat core region, but excludes MR-II and MR-III, resulting in a delay. (Table 2) Deletion of MR-II, which is confined to the immediate adjacent MR-I, causes slight delay, whereas deletion confined to the more recent MR-III does not produce the phenotype.(8,9) However, while deletions including MR-I gradually progress to MR-II and MR-III, dementia increases and becomes severe when all 3 regions are deleted.(Table 3)

Population Genetics: Meowing syndrome appears to be one of the most common human withdrawal symptoms, occurring in between 1 in 20,000 and 1 in 50,000. The frequency of people with severe intellectual disability (IQ less than 20) is about 1%. An important chromosomal region involved in cryogenic depression was identified at the corresponding 5p15.3 (D5S727 probe), while a chromosomal region involved in the main features of the condition resulted in a small region in the middle of 5p15.2 (D5S721 probe).(10,11) The size of the second region is about 2 Mb. Deletions that exclude both chromosomal regions present a wide range of clinical phenotypes, from severe mental retardation and microcephaly to clinically normal enotypes. (12,13) The breakpoint was located in the 5p15.2 regions, indicating that the other gene for the disease is adjacent to this region. cDNA was isolated from the critical cri-du-chat region by direct sequencing of a chromosome 5-specific cDNA library.

METHODS

Patients: The present study included 10 patients with ranging from 1 month to 35 years. The diagnosis of CdCS was based on clinical characteristics and cytogenetic analysis. h TERT status is +/− . The karyotyping data from all the patients are presented in Table3. The TERT gene is located on chromosome 5p (e.g., 5p15.33) and is the rate limiter of telomerase activity, which is important for maintaining telomere length and promoting cell proliferation. The study found that the TERT allele was deleted in every 10 patients with meowing syndrome they tested. (13,14,15) Five of seven patients had lower TERT mRNA. levels in proliferating lymphocytes than unaffected individuals. (Table 4) Patient lymphocytes exhibited shorter telomeres than individuals of the same age (P < 0.0001). Shortened replicative survival and increased chromosomal fusion rates were observed in cultured patient fibroblasts. Reconstitution of telomerase activity by ectopic expression of TERT extends telomere length, increases population doubling, and prevents end-to-end fusion of chromosomes. (14,15) It has been shown that haploid insufficiency of telomere maintenance in vivo may be one of the genetic factors that cause phenotypic changes in cridu-chat syndrome.

CONCLUSION

We found that three regions of chromosomes in patients had different MR levels. Deletions containing all or part of these three regions interact with other abnormalities in the genome to produce the full MR phenotype. Finally, our high-resolution data allowed us to advantage of areas associated with crying, facial expressions, and slow speech in "chats."

Conflict of interest: The authors have no conflict of interest to disclose.

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