Once again CGG Repeat Patients, Hypospadia: A Systematic Review

Peni K Samsuria Mutalib[1*], Indranila Kustarini Samsuria[2*]

[1]Medical Physics Department, Medical Faculty, University of Indonesia
[1]Medical Technology Cluster, IMERI, Medical Faculty, University of Indonesia
[2]Clinical Pathology Department, Medical Faculty, University of Diponegoro
*Corresponding Author

Received:- 29 December 2021/ Revised:- 08 January 2022/ Accepted:- 16 January 2022/ Published: 31-01-2022
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Abstract— *High prevalence of hypospadias is only the peak of the iceberg, because there are stigma and isolation, which make not all patients seek a doctor to check up and do counseling. However, failure of psychical, anatomical and metabolomic development should be faced from the childhood age, adolescent, through the puberty years. One hundred years of congenital adrenal hyperplasia (CAH) in Sweden, open the failure of this labium minor fusion is associated with hypermethylation which have many names. Familial cases, in female, bring this case a gender reversal and reconstructive urology repair, were successful, while the cause, CYP21 mutation/blockade/deficiency also known as cytochrome P450 deficiency is neglected. In prevention, lose with reconstruction, psychologic and environmental which reported due to pesticide are favorite. Digging the cause of labium minus fusion failure, which given the real cause, is need to be chased for prevention in the population.*

Method: Systematic review (SR) using Science Direct search engine cross by PubMed, preferable SR and meta-analysis (MA) design than the other. Keywords: hypospadia-fragile (10), -CYP21 mutation (2). CYP21 deficiency-CAH is the core of this study.

Result: Twenty-one references flowchart and table with 4 references in SR and MA which supported Hypospadia-CYP21 deficiency-CAH. More than 3126 cases were studied.

Discussion: The association of CAH hormone and behavior (family-genetic), hypospadia-Parkinson (12), -pesticides, gen chromosome 6p, -autism (59), -bipolarism (22) bring to epigenetic hypermethylation cases. The CGG repeat-hypermethylation-gene silencing which produce protein enzyme is the cause of hypospadia. Geographical of Brazil, Latin American, incl. Argentine, SEA such as Thailand, Indonesia, and also Sweden, which all are in wet and warm climate area, has high hypermethylation prevalence due to RNAi in GMO green activity.

Keywords— CAH, gene silencing, Martin-Bell syndrome, Escalante syndrome, FRAXA.

I. INTRODUCTION

It is already known that CGG repeat large amount give FMR1 full mutation, while 55-200: permutation associated with psychological and behavior disorder, and FMR1 intermediate, grey zone permutation, and small CGG repeat has also been studied. This epigenetics hypermethylation cases underlie many diseases such as Fragile-X Syndrome, parkinson,[1] bipolar,[1]

autism,[1,2] etc. due to silence of DNMT enzyme.[3] Hypospadia cause by hormonal disorder, have a Congenital Adrenal Hyperplasia (CAH) disorder (CYP21 deficiency),[4] is reported genetics,[5] but never epigenetic. Hypospadia could be associated with CGG repeat/ CpG island hypermethylation, -FMR1, -CYP21 mutation. The later is cause by failure of neurosteroid production.[6] Hypospadia is a structural marker of FX syndrome also in CAH, and CAH 100 year in Sweden has been reported.[7] The high prevalence of hypospadias is only the tip of an iceberg, because the stigma and exclusion, prevent most sufferers from getting checked by a doctor.[8] They avoid seeking medical advice. However, psychological disorder, and fail in anatomical development, as well as metabolism, must be faced by the subjects since childhood, adolescence through puberty.[9,10,11,12] Familial, in Congenital Virilizing Adrenal Hyperplasia (CVAH) women the case of gender reversal to male in male rearing are successful managed as male,[13] and three reconstructive pediatric urological condition: hypospadia, CAH, and bladder exstrophy have been reported from the perspective of changing expectations and outcomes,[14] while the main cause of Cyp21 mutation/blockade/deficiency or cytochrome P450 deficiency is underestimated and become inferior than reconstruction handlers. The psychological and environmental prevention are mentioned due to pesticide in this epigenetics cases.[15,16] whereas knock out the enzyme production give hypospadia[2] and antenatal androgen excess.[17] Exploring the labium minus cause of failure to adhere (hypospadia), the real cause needs to be pursued for mainly prevention purposes.

The term CAH covers a number of people of disruptions caused by imperfection in hydroxylation of cortisol precursors. The missing enzyme could be 21-hydroxylase, 17- hydroxylase, 18-hydroxylase, etc. The CYP21 is the mainly steroid missing enzyme gene due to mutation, hypermethylation on CpG islands, blocking, or deficiency. Extremely increasing rate 90% of CAH subjects are made by the alteration of the CYP21 gene on a DNA double helix in 6p21.3.[18,19]

When a serious autosomal recessive (AR) disorder, which results in influenced homozygotes, has a large occurrence of wide scope population, the account that makes something clear must lie in either a very high mutation rate or in heterozygote advantage. Yupik Eskimos has been reported resistance or advantage in Influenza B in CAH disorder, an AR genetic disorder.[19] The art icon mask of Yupik Eskimo depicting the bad spirit of the mountain/river, is similar with Escalante syndrome in Argentina

(https://commons.wikimedia.org/wiki/File:Mask_depicting_the_Bad_Spirit_of_the_Mountai n,_Yupik_Eskimo,_Yukon_Riv er_area,_probably_St._Michael,_late_1800s,_wood,_paint,_f eathers_-_Dallas_Museum_of_Art_-_DSC04535.jpg).

Deficient cortisol production, induce/increased secretion of corticotropin (ACTH). Overproduction of ACTH causing adrenal hyperplasia (CAH). The net effect is a build-up in the adrenal gland of cortisol precursors and androgens.[20] The production of more of adrenal androgens is an additional ordinary aspect of it. This hormone amount that is more than necessary results make greater physical size, hairy body, deep voice and double meaning in external genitalia.[20] Hypersecretion of adrenal androgens during intrauterine life cause masculinization of the female external genitalia. Increased body growth at an accelerated rate and show advanced skeletal maturation. However, because of premature closing of the epiphyses, their ultimate height is below average.[21] Hypospadia 46,XX successfully with reconstruction urology repair,[12,13] whereas hypospadia 46,XY reared male or female can lead to successful long-term outcome for the majority of cases.[22]

II. METHOD

Systematic review (SR) using Science Direct search engine and cross checked by PubMed. Two times collected articles and extracted data independently. The SR and meta-analysis (MA) references are preferable than the other methods. PRISMA design has used to get flowchart and table of references that support hypospadia-CAH (189) caused by CYP21 or CytP450

deficiencies to support hypermethylation which already report in Fragile-syndrome, Parkinson, autism and bipolar cases.[1,3,23] Keywords: hypospadias- CGG repeat (0), -fragile (10), -CYP21 mutation (2). Hypospadias-CYP21 deficiency (1), hypospadia-CytP450 (1), - cytochrome P450 (25), hypospadia-fragile (10). Hypospadia-Parkinson (12): pesticide, -autism (63), - bipolar (23); CAH-Parkinson (11), CAH-autism (58), CAH-bipolar (12). Change the keywords to CAH-CYP21 (72), CAH-CytP450 (0), CAH-Cytochrome P450 (139). The 100 y CAH and associated with syndrome hypermethylation is clinical in high prevalence in wet and warm climate area, will be the Bayesian network and analysis. Included the CytP450 deficiency and excluded the genetic but epigenetic cases.

III. RESULT

Twenty-one references supported FMR1 intermediate and Small CGG expansion associated with neurosteroid direct via hypermethylation, or indirect via Fragile-X syndrome (FMR1)/Parkinson/autism/bipolar which have more CGG repeat / CpG islands and hypermethylation patient or pedigree. This stable and unstable hypermethylation is associated with silence genetic of CYP21 or high production of hormonal androstane group (C19). Four designs of the references are SR/MA, 1 clinical trial, 1 cross-sectional, 5 case-control, 1 cohort, 1 retrospective, 3 distribution, 5 reviews. At least 3126 cases of CGG repeat expansion were studies.

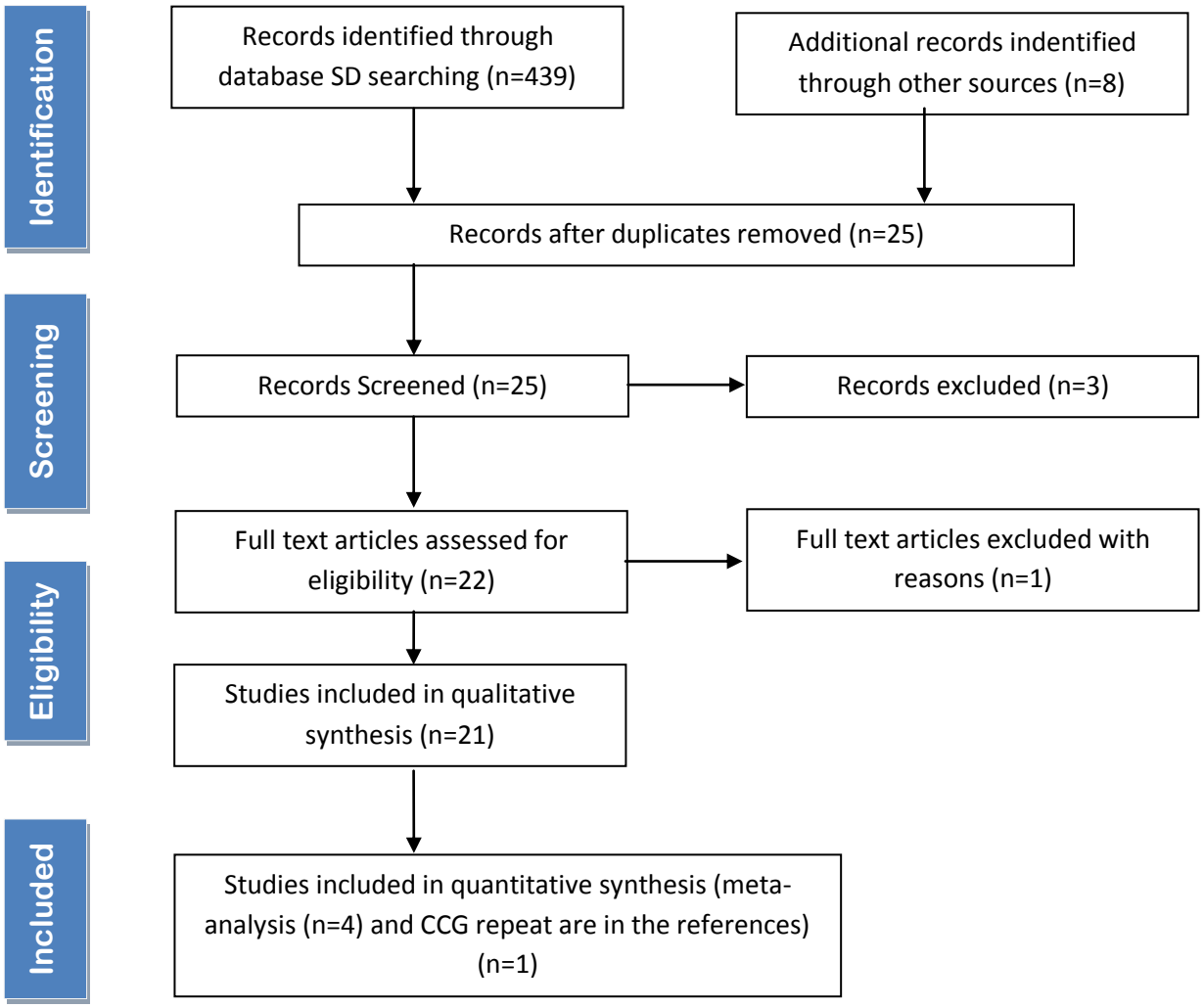

FIGURE 1: Twenty-one references flowchart which support hypospadia-CAH-CYP21 deficiency in association with hypermethylation cases in intermediate/ Small CGG neurosteroid.

TABLE 1
TWENTY-ONE REFERENCES WHICH SUPPORT HYPOSPADIA-CAH-CYP21 IN ASSOCIATION WITH HYPERMETHYLATION DIRECT OR HYPERMETHYLATION CASES ON ANDROGEN BULK

Study, year	Design	Population	Hypospadia/CAH*/CYP21/ Cyt P450	Hypermethylation/ CGG repeat#/CpG island/Journal (J**)
[24]Richards G, 2020	SR/MA	CAH 2D/4D	Hypospadia-CAH	J: Hormones and Behavior
[25]Parsa AA, 2017	Review	CAH	CYP21 varying degree-CAH	J: Steroid Biochem Mol Biol 6p chromosome
[26]Mutalib PKS, 2002	Review	Sport Women	Gender Verification-CAH in Competition	J: Dexa Media. Majalah Kedokteran dan Farmasi
[15]De Jaeger C, 2012	Distribution	Parkinson	Hypospadia	Parkinson: pesticides, sante et longevite
[27]Sharma S, 2013	Review	Parkinson	CAH	Parkinson[#]
[28]May T, 2020	SR & MA	Autism	Sex hormone levels or response	Autism
[29]Knickmeyer R, 2006	Cross sectional	Autism	CAH, Androgens	Autism
[30]Tordjman S, 2018	Review	Autism	Behavioral Syndrome	Reframing Autism 16p11.2 deletion syndrome
[31]Johansson AG, 2012	Case-Control	Bipolar	DHEAS[+] and progesterone	Paranoid, bipolar, mania hypomania[#]
[32]Walsh MJM, 2021	SR	Autism	MRI, fMRI, DTI findings	Autism: Brain-based sex differences
[33]Zhang O , 2016	MA	Bipolar	CAH, Reproductive abnormalities	Valproate in Bipolar, Total and Free Testosterone treated> Non treated Valproate
[34]Joffe H 2006	Clinical Trial	Women Bipolar	Hyperandrogenism	Valproate treated Women with Bipolar disorder
[35]Cesta CE, 2016	Cohort	Nationwide Swedish	POS[++]	Psychiatric disorders, patients and family need mental health care
[36]Rahman Q, 2003	Retrospecti ve	Human sexual orientation	Born Gay Childhood Gender nonconformity	Psychobiology Neurobiological female homosexuality
[37]Okten A, 2002	Case-Control	2D-4D CAH	CYT-21 deficiency, androgen prenatal	J: Early human development
[38]Ingudomnuku l E, 2007	Case-Control	Women ASC	Elevated testosterone	Women Autism Spectrum Conditions (ASC)
[39]Ruta L, 2011	Case-Control	Adult ASC	Increased and rostenedione (precursor of testosterone and estrogen)	Adult with ASC
[40]Rivet TT, 2011	Review	ASD	Gender differention	Autism spectrum disorders (ASD)
[41]Henningsson S, 2009	Case-Control	ASD	Androgen receptor gene -, CAG repeat Prenatal brain expose by Androgen	Autism spectrum disorder (ASD)
[42]Goldman S, 2013	Distribution	Autism	A biosocial ASD	Sex, gender and the diagnosis of autism
[43]Wang C, 2017	Distribution	Human	CAH-CytP45021A2 variant	J: J of biol chem

CAH: Congenital Adrenal Hyperplasia **J: Journal [#]fragile-X/parkinson/autism/bipolar-neurosteroid [+]DHEAS: Dehydroepiandrosterone sulfate (androgen) [++]POS: Polycystic Ovary Syndrome

IV. DISCUSSION

Hypospadia associated with CAH could be seen in table 1). Over 90% CAH individuals are caused by the mutating of the gene on chromosome 6p21.3 which produce 21-hydroxylase.[18,19] The CAH peoples extend over a number of subjects with illness or condition that disrupt due to the systematic function of cortisol precursors hydroxylation. The missing enzyme could be 21-hydroxylase, 17-hydroxilase, 18-hydroxilase, etc. CYP21 is the mainly steroid missing enzyme gene due to mutation, hypermethylation on CpG islands, epigenetic non coding RNAs. The CYP21 mutation or deficiency is in broad spectrum. Similar to blocking, or deficiency in CGG repeat in autism, could be an autism spectrum conditions (ASC) and autism spectrum disorders (ASD).

4.1 Genetic, epigenetic or Pesticide

When a serious autosomal recessive (AR) disorder, which results in affected both alleles, has a high occurrence in a big population, the explanation must lie in either a very high mutation rate or in heterozygote advantage. Yupik Eskimos has been reported resistance or advantage in Influenza B in CAH disorder, an AR genetic disorder.[19]

The sexual orientation based on 46XX for female and 46XY for male, maybe also from the anatomical of urological structure,[12,13,14] and androgen-brain level.[37,41,42] Sexual orientation is the psychological hypospadias-bipolarism is associated with epigenetic hypermethylation. Androgen, disturbance of epigenetic inheritance arranging of gene silencing or enzyme down regulating during development is associated with hypospadias.[2] The human androgen synthesis disruption in CAH associated with cytochrome P450 mutation has been analyzed.[17]

Parkinson, Alzheimer, reproductive tracts, DNA damage, to alter the expression of the gene at the stage of non-coding RNAs, histone deacetylase, DNA methylation system, suggesting their role in epigenetics, and epigenetic cases of Parkinson is reported cause by pesticide.[16] Geographically, in Brazil, Martin-Bell-Renpenning Syndrome; in South American Countries, Escalante's Syndrome; has the clinical figures as this neurosteroid destruction,[1,3] and anatomical face and ear, also 100 years CAH in Swedia[7] and the important of mental health care POS and family in Sweden Cohort Nationwide.[35] Brazil, South America incl. Argentina, South East Asia i.e.: Thailand, Indonesia has a wet and warm climate, also Sweden in North Europe, has rich of lakes and located in peninsula surrounding with water. The CGG repeat expansion – hypermethylation means silence off the gene for protein enzyme incl. hydroxylase or monooxygenase (cytP450), one of the specific isoforms are CYP21. Cytochrome P450-term since the enzyme was find when it was recognized that composing of microsomes that had been chemically reduced and then substituted to carbon monoxide, display a definite peak at 450 nm. The distinctive P450s are then autocratically allocated to Arabic numeral, e.g., CYP21, with the gene encoding CYP21 is *CYP21*, in italic.[20]

4.2 Hormonal level in CYP21 mutation/deficiency

Hypospadia and neurosteroid production is due to CYP21 mutation or CYP21 deficiency.[6] Hypospadia–enzyme hydroxylase 21 deficiency give Congenital Adrenal Hyperplasia has high level of androgen hormonal production. The CGG repeat spectrum-hypermethylation is associated with off gene which produce protein enzyme such as CYP21. Hypospadias – enzyme hydroxylase 21 deficiency which cause CAH (hormonal) is associated with CYP21-CAH neurosteroid production,[25] whereas over 90% CAH is caused by CYP21 deficiency.[18,19]

Made from cholesterol, the cholesterol side-chain split is associated to basic steroid hormone structures. The commons sterol closed chain are recognized by the letters A to D known as cyclopentanoperhydrophenanthrene nucleus. The carbon elements are numbered 1 to 21, beginning from the A ring. A brief record of facts, the estrane classification has 18 carbons (C18). Cortisol (C21H305) and progesterone has 21 carbons known as pregnane group, Testosterone has C19 (androstane group).[20,44] With the 21-hydroxylase, pregnane group go the pathways to become cortisol and aldosterone. With deficiency of 21-hydroxylase (CYP21 gene mutation or methylation), C21 produce androstenedione (C19) a precursor of testosterone (C19) and estrogen (C18). The 21-carbon steroid involves sequential hydroxylation in this adrenal steroidogenesis.

4.3 Cyp21 deficiency and T Cell finds with Science Direct (16)

CAH-severe infection (T cell), and autoimmune-CAH are not the core of this research, but could be a greater amount in many broad spectra of CAH in clinical and population cases. Interactions between sex steroids (androgens, estrogens, progestogens)-corticosteroids and 25- hydroxycholecalciferol, and the immune system may reveal novel approaches as putative treatments of immune-driven disease.[45]

The term activated immunity describe the epigenetic and metabolic medium-term rearranging of the peripheral tissues or in the bone marrow stem cell niche strong related with antigen presentation to T cells, in innate immune cells.[46] Single-walled carbon nanotubes (SWCNTs) inhibit heat shock protein 90 (HSP90) instruction in human keratinocytes and lung fibroblasts,

influencing T cell proliferations.[47] Like in Yupik-Eskimo, who have genetics of resistance to Influenza B in CAH disorder infectious disease,[19] chicken MHC gene has the gene and their contribution in immune responses.[48]

4.4 Hypermethylation and Hypospadia

Geographical Brazil, South America incl. Argentina, SEA incl. Thailand and Indonesia, have a wet and warm climate, has a high prevalence of hypermethylation associated with CGG repeat cases.[3] FMR1 gene 10 y 10-month girl with a history of precocious puberty and a family history of Fragile-X syndrome,[11] is associated with CGG repeat expansion, CpG islands and hypermethylation. A mutual relationship of CpG island and CGG methylation show a knock out of the FMR1 genes, extensively known full mutation have 200-4000 CGG repeat in FMR1 gene are reported as Fragile-X Syndrome subject. A 55-200 CGG repeat size known as permutation is associated with psychiatric disruption, weaken of cognitive proficiencies.

Hypermethylation of CGG repeat represent of the methylated CpG islands.[3] Upstream CGG repeat in FMR1 gene, known as the 65-75 CpG, become stable DNA methylation boundaries, in premutation carriers. Cases of hypermethylation as LGBT in high moisturized and warm countries have high prevalence including Sweden Europe with much lakes and the land located surrounding sea water (peninsula). Transexual operation are high in Bangkok.[3] In both gender, homosexuality is correlated with childhood sexual difficult to determinate. The neurobiological underlying support of preferred gender targets and strongly associated of female homosexuality.[36] Hypermethylation associated with CGG repeat has been reported in many cases incl. LGBT, Fragile-X Syndrome, Parkinson, psychiatric diseases.[1,3,23] Repeat CGG associated with Parkinson, bipolar, autism support epigenetic change of DNA methylation is strong related with hypospadias in a case-control study.[2]

V. LIMITATION

The psychosocial and biosocial of psychological, culture, religion, childhood, puberty, adolescence should have been analyzed in cases associated with hypospadias to find the submerge of the ice berg. This study also not totally have done it, however, sentential logic (nominal and ordinal)[49] approach has been used for supporting the Bayesian analysis, and network (interval) scale which is a sentential calculus. The other limitation is that the role of wet climate correlated with tropical health and infectious diseases is not yet known widely especially in the transgenic technology.[50] Large natural incubator like tropical rainforest area with high relative humidity climate condition is not mystic and need to be disseminated especially in accordance with climate change, global warming, carbon tax, carbon trading, and green activity.

VI. CONCLUSION

Hypermethylation, CGG repeat, CpG island is associated with steroid genes silencing, is the cause of hypospadias, psycho, neuro, metabolism in wet and warm countries high prevalence, which hide by culture, religion and high social stigmatization.

CONFLICT OF INTEREST

The author declares nothing.

ACKNOWLEDGEMENT

Akademi Ilmu Pengetahuan Indonesia (AIPI) 12 April 2021, which has been brough up the submerged ice berg by saying sexual development disorders is only as the tip of an ice berg. CRID-TROPHID who ask physics department to participate in infectious diseases and tropical health in fighting these health burden. IMERI catalog which launch XGA10053 High Relative-Humidity as the basic condition which should be disseminated to industrial countries. IJSER who published carbon nano tube in industry 4.0 should be support with sociology 5.0 in wet and warm climate area.

FUNDING

CRID-TROPHID which support the funding to complete the practice measurement instrument to high relative humidity for all.

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