Decitabine Self Monitoring in Unstable Methylation of DNMT Patients: A Quasi Systematic Review

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Abstract—

Background: *Grey zone or intermediate zone CGG repeat in Pre-mutation FMR1 gene become in high prevalence in tropical rainforest area.*

Problem: *Bipolar disorder and Major depressive disorder used epigenetic drugs inhibitor to ameliorating their mood as well anticancer agent, decitabine are broadly used. Meanwhile, basic knowledge remains largely unknown.*

Objective: *Demethylation effect in grey zone methylation instability has to be controlled whereas up till now are to be disturbing the social behavior activities.*

Hypothesis: *Demethylation drive through, from >34 to <26 CGG repeat has behavior abnormalities.*

Method: *Quasi-Systematic Review with Bayesian network analysis using Science Direct and Ebsco-host search engine.*

Result: *One PRISMA Systematic Review flowchart to got the references and one table of 16 references to answer the methylation and demethylation in global living related to decitabine are recorded.*

Discussion: *Decitabine effect in epigenetic memory in mammals and neuro developmental, cognitive, behavioral and physical changes in grey zone and carrier permutation FMR1 gene are scanned.*

Conclusion: *Demethylation to high as well low grey zone CGG count could be self monitor due to instable methylation*.

Keywords: decitabine, hypomethylation, CGG repeat, tremor, cognitive, epigenetic instability.

I. INTRODUCTION

1.1 Background

Unstable methylation in pre-mutation and grey area on CGG repeat DNMT gene for brain and behavior abnormalities[1] are in high prevalence of Decitabine using for antidepressant and controlling epigenetic mood disorder, except for anticancer drug.

1.2 Problem

Psychiatry and Psychology of bipolar, autism, tremor/ataxia, LGBTQ are in high prevalence in tropical rainforest area taken decitabine but demethylation drive through (epigenetic instability) small CGG repeat below normal (5-50 CGG repeat)[2] is unexplored till date.[3] A neurodegenerative disorder caused by the expansion of 55-200 CGG repeat (carrier pre-mutation FXS) sequester one or more RNA-binding proteins and impairing their function.[4]The micro-RNA (miRNA) and RNA interference (RNAi) induce CGG repeat over expansion and Trichostatin A, a histone deacetylase inhibitor show a reactivation of the silence promoter (CpG island methylation to be demethylation).[5] RNA-directed DNA methylation has been used in plant,[6] and CRISP to be used in Maize.[7] In human pluripotent stem cells paired-Knock Out[8] Cytosine methylation is a significant and widespread regulatory factor in plant system and a previously acquired through sequencing plant methylomes, remaining challenge to open the mistery.[9] Low homocysteine and B vitamin treatment are involved in the production of SAM, a universal methyl donor essential for DNA methylation, has been reported to protect declining cognitive health.[10]Decitabine demethylation (methylation inhibitor) are a strength CpG and CGG repeat demethylation on DNMT gene.[11,12,13] How about driven through decitabine to below normal or normal lower number on CGG repeat?[14] This Quasi Systematic Review study, show the drive through of demethylation normal low which could be done self control by the user, to gain the demethylation effect of decitabine.[14]This kind of demethylation is beyond Arsenic-demethylation.

1.3 Objective

Methylation and drive through demethylation have to be self controlling or use in combination with several issues reported not to be disturbing in social and economic behavior.[3]

Hypothesis: RNAi-hypomethylation or RNAi-demethylation in epigenetic instability. Decitabine-Demethylation drive through, from >34 to <26 CGG repeat has a behavior abnormalities.

II. METHOD

Quasi-Systematic Review PRISMA design with Bayesian analysis network using keyword: decitabine-demethylation. Science Direct and EBSCO host, binomial 0 or 1 to answer methylation and demethylation effect in each study. Amount of >200 CGG repeat are excluded. All decitabine derivate are included due to methylation inhibitor effect. The same binomial record for depressive and mood disorder. Normal 5-50 CGG stable methylation vs. unstable low and high grey zone (41-60) CGG repeat are used for cut off. Small CGG repeat (55-200) have a late onset, where 41-55 had been poorly defined.[15]

III. RESULT

One flowchart has identified 91 references, which support decitabine^demethylation (139 references for RNAi^demethylation, RNAi^methylation 982). Flowchart or 16 references supported DNMT demethylation in several cases in plants to cancer therapy. Permanent hypermethylation to gene silencing due to RNAi and DNA demethylation which reactivated gene up-regulated and get to mutation by decitabine, open the relation of methylation instability in global living.

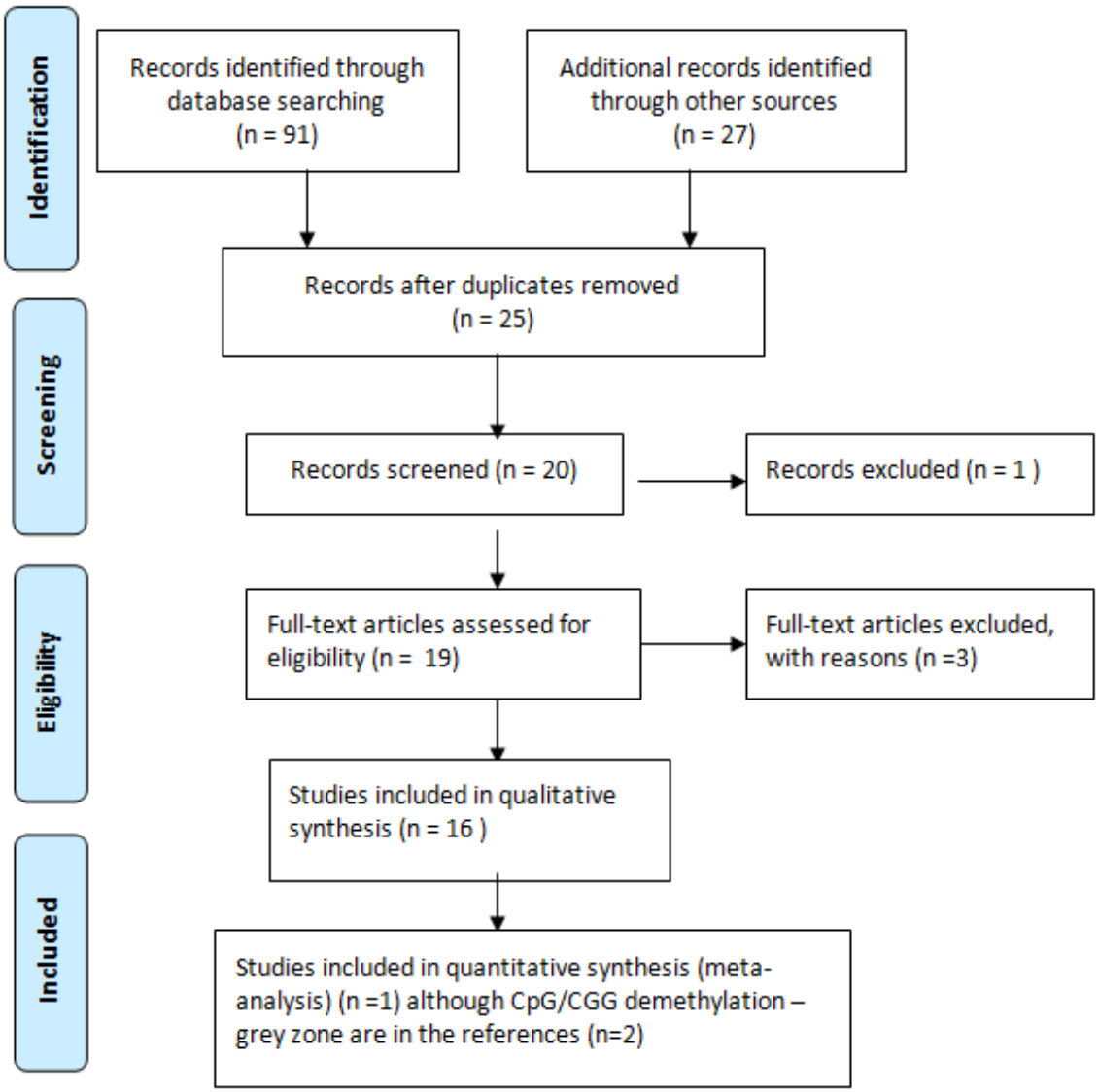

FIGURE 1. Flowchart 16 references of RNAi /decitabine)-demethylation

As antianxiety and anticancer therapy, decitabine give drive through demethylation until low normal whereas in methylation instabllity has an effect and poor prognosis in RNAi anticancer therapy.[16]Ameliorating Neurodegenerative disorder related Number of CGG repeat give human different cells Epigenetic changes.[17]

TABLE 1
Sixteen references supported RNAi /decitabine)-demethylation

Study, year	Design	Population	RNAi/methylation inhibitor	Hypo/hyper
Usdin 2014[17]	Review	Human different cells Epigenetic changes	Number of CGG repeat	Ameliorating Neurodegenerative disorder Hyper to hypo?
Movahedi 2015[6]	Epigenetic	Plants	siRNA	DNA methylation
Hardcastle 2013[9]	Epigenetic	Plant DNA	Acquired plant methylome	DNA methylation
Muthusamy 2010[18]	Epigenetic	Cancer in mammal cells	Two recent GW RNAi screens	DNA methylation
Ma 2015[19]	Epigenetic	Flower development	Low temperature	hypermethylation (silencing)
Lev 2017[20]	Epigenetic	Permanent RNAi-met not terminate>F30	siRNA	Permanent hypermethylation
Chandler[5] 2003	Epigenetic	Lined promotor	Unstable CGG repeat to > 200 Cause unknown	Methylation and RNA silencing Cause unknown
Biancalana 2015[21]	Epigenetic	FXS	Unstable CGG repeat	FX associated disorder Abnormal methylation
Indah Winarni 2012[22]	Epigenetic	Language development ↑	Sertaline vs. no medication for children under 5 y	Autism disorder
Paluszczak 2010[23]	Low doses in diet	MCF7 BC cells	Decitabine DNMT inhibitor	CpG demethylation reactivation p53
Bracht 2012[11]	Epigenetic Control trial	Somatic and germline cell	Azacitidine and decitabine vs. Trifallax	DNMT demethylation
Linnekamp 2017[12]	Systematic Review	Solid tumors	Azacitidine, decitabine etc.	Demethylation, overall response is limited
Wong 2013[16]	Epigenetic Treatment Record	Myelodysplastic syndrome	Prolonged Decitabine in nano-molar dosage	Demethylation in promoters and Gene-Bodies
Geng 2016[24]	Epigenetic Control Trial	Myelodysplastic syndrome (AML)	Decitabine combination	But not demethylation and DNMTs mRNA expression
Flitton 2019[10]	Cohort	DNMT3L brain atrophy in mild cognitive impairment	SAM donor and B vitamin treatment	Visuospatial associative memory ↑
Chatterjee 2018[25]	Epigenetic	Immune checkpoint	Marked Global DNA hypomethylation	PD-L1 Expression

IV. DISCUSSION

In table1, three groups of references which supported decitabine-demethylation: 1) the using of methylation in environment and human; 2) decitabine and derivate to be methylation inhibitor and 3) other methylation-demethylation evidence.

This table, are relevance to healthcare providers, users, and policy makers in methylation and demethylation interverences, whereas prevention is better than treatment.

Epigenetics and Psychiatric Disease, CNS-hypomethylation, progress and invasiveness of Cancer supported the decitabine-demethylation benefit and problem.

DNMT Enzymes that establish and maintain DNA methylation using methyl-group donor compounds or cofactors. The main mammalian DNMTs are DNMT1 and DNMT3. DNMT1 maintains methylation state across DNA replication, and DNMT3 perform de novo methylation. With the silencing of DNMT1 due to methylation of CpG island or CGG repeat common in FXS, this epigenetics are related to psychiatric disorder and other neuro development and neurofunction diseases. Epidemiologic worldwide psychiatric disorder: whereas major depressive disorder beyond schizophrenia and bipolar are in high prevalence especially in tropical rainforest area. Hypomethylation are related to CNS disorder are reported in gene binding protein.[26] And demethylation in Akt/p53 is related to the progression and invasiveness of Cancer.[27]

4.1 Methylation and cognitive function impairment

CpG methylation related to ataxia[28] and childhood autism risks from CGG repeat and environment (CHARGE) study[29]There are 3 groups of 5-55 CGG repeats:<26, normal (26-34) and small CGG expansion (35-54 repeats).[14]Mid-size CGG repeat (50-141) has the greatest risk of psychiatric disorder development.[30]

4.2 DNA Methyl Transferase (DNMT) 1, 3 and memory

DNMT 1 and DNMT3 have a role in resetting epigenetic Memory in mammals cellular memory.[31]DNA methylation regulate gene expression and play a crucial role in minimize learning and memory deficits in Down Syndrome.[32]Better visuospatial associative memory reported the role of DNMT3L-mediated DNA methylation which influence cognitive decline.[10]

4.3 Decitabine for Bipolar, peculiar reaction, tremor

Decitabine for Cancer Drugs CGG repeat polymorphism should have neuropsychiatric risk as a routine test.[14] Pre-mutation carrier with 55-200 CGG repeat have tremor/ataxia,[33]Those alleles with a CGG repeat number ranging between 41-55 are relatively poorly defined and known as Grey Zone.[15]The grey zone also has neuro developmental, cognitive, behavioral and physical changes[33] and small CGG repeat expansion is link with Parkinson's disease.[34]The carriers of pre-mutations in the mid-size CGG repeat range (50-141) may be at greatest risk for the development of psychiatric disorder,[30]but in women, cognitive function or executive function are not significantly different,[35]while the cognitive impairment in men is correlated in more CGG repeat in pre-mutation (55-200 CGG repeat).

4.4 Decitabine and derivate for demethylation effect

Reactivation of DNMT related to cognitive decline,[10] and the impairment in the cognitive functioning with FXTAS and was greater for men with more CGG repeats, although number of repeats was not associated with age of onset of either tremor or ataxia.[36]In women, where the pre-mutation (55-200 CGG repeats) are relatively in high prevalence, and these pre-mutation carriers reported higher levels of obsessive compulsive symptoms, depression, and anxiety, has no significant deficits in global cognitive or executive function compared to the control group.[35]

4.5 Decitabine Stop or in combination

Decitabine in combination with homoharringtonine had no enhanced effects on hypomethylation and DNMT1, DNMT3A and DNMT3B mRNA expression in SKM-1 cells.[24]

A routine epigenetic changes is also should be cover for this repeat instability to be ameliorating this molecular aspect of small CGG repeat,[17] especially <26 and >34.[14] Hematological toxicity or relapses[37,38] and how to induced pluripotent stem cell including reprogramming strategies[39] to methylation de novo of CGG repeat and downstream DNA especially p53 where DNMT 3a represses p53 which this DNA demethylation in tumorigenesis has been demonstrated in global, and regional hypermethylation in regional CpG island of tumor suppressor genes.[40,41]

V. LIMITATION

At study and outcome level (risk and bias) have minim discuss the 19-56 CGG repeat which though to be normal but successfully described have the genetic background of AGG interruptions in CGG repeat.[42]Three subgroup of 5-55 CGG repeat: Low numbers of CGG repeat (<26 repeats), normal CGG count (26-34 repeats), and small CGG expansion (35-54 repeats)[14] has been revealed to some diseases but not associated with methylation and demethylation directly. Low numbers has been related to premature ovarian failure. Small expansion has significant influence on Male Parkinsonism cohorts, mental retardation and repeat instability.[14]

After advancing NG drug discovery neuropsychiatry disorder with stem cell technology.[43] the retrieval on the impact of DNA-Methylation on stress-related pathogenesis of mental health outcome associated with cancer therapy.[44]DNA methylation and post-translational histon modification which play a crucial role in the development of the cognitive deficits in Down Syndrome with large CGG repeat has not been included in this study although the prevalence and theoretically has been increased.[32] Social behavior and brain & behavior is also depend on demethylation stage[45] mix with sex hormone since in uteri[46]

VI. CONCLUSION

The methylation RNAi and demethylation in global living related to decitabine using are recorded, and demethylation to high as well to low in grey zone CGG count could be self monitor by mental health due to instable methylation as an implications for future research.

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CONFLICT OF INTEREST

None declared till now.

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