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ORIGINAL RESEARCH PAPER

Ethnic variation of uric acid level among population in greater Kamrup district

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ABSTRACT

Introduction: *In about 16th century gout sounded like a disease out of a novel. Purine leads to high level of uric acid which are deposited in the joints and causing the attack of gout. Gout which is the disease since antiquity is an acute, often recurrent arthritis mediated by the crystallization. Genetic or other influences are important modulator for the serum uric acid level. Many studies have been conducted worldwide to identify the risk factors for hyper uricemia including ethnic, enzymatic and environmental predisposition.* ***Materials and methods:*** *The present study was conducted among different communities in Greater Kamrup District. Samples were collected by stratified random sampling technique. Communities selected were Ahom; Adivasi; Bodo, Bengali, Karbi, Manipuri and Marwari. Serum uric acid level in different communities were evaluated and compared.* ***Results:*** *Uric acid level of Boro community is higher in comparisons to other communities. Uric acid level of Ahom community is found higher in comparison to Manipuri, Bengali, Adivasi and Marwari. Sex wise uric acid level is high in case of males 5.69 mg/dl, compared to females 4.95mg/d1.* ***Conclusion:*** *From the present study, it can be concluded that different communities of Greater Kamrup district depicts different uric acid levels and association with sex. This finding can be associated with dietary habits of different communities. It can be placed in the context of overall health promotion, disease prevention and disease treatment with appropriate attention to nutritional needs in different communities.*

Keywords: *Gout; uric acid; community; purine.*

INTRODUCTION

In about sixteenth century gout sounded like a disease out of a novel.[1] That is probably because this joint disease famously afflicted many luminaries from the past. It has been theorized these historical figures had gout because they had money to enjoy red meat, sea food and all other food rich in purine.[2] Purine leads to high level of uric which are deposited in the joints and causing the attack of gout. Gout which is the disease since antiquity is an acute, often recurrent arthritis mediated by the crystallization.[3]

Some indigenous people such as Polynesians of Pukapuka in the Cook Island have relatively high serum uric acid level despite on traditional diet that is low in red meat.[4] So, genetic or other influences that are also an important modulation of the serum uric acid level.[5] Many studies have been conducted worldwide to identify the risk factors for hyper uricemia including ethnic, enzymatic and environmental predisposition.[6] Among the acquired factors, reversible life style factor contribute to increased blood uric acid concentration. These factors were suggested to be higher Purine diet, alcohol consumption and obesity.[7]

Objective is to evaluate serum uric acid level in different communities of Greater Kamrup District and compared.

MATERIALS AND METHODS

The present study was conducted among different communities in Greater Kamrup District. Samples were

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collected by stratified random sampling technique. Communities selected were Ahom, Adivasi, Bodo, Bengali, Karbi, Manipuri and Marwari. Serum uric acid level in different communities were evaluated and compared.

The study was carried out over a period of 2 years with total number of 280 subjects. 40 subjects from each community consisting of equal numbers of males and females (1:1). They belong from the different community with different occupations and socio-economic status, food habits. They gave informed consent to participate in the study. Subjects are evenly distributed in the age group of 25 years to 70 years.

Estimation of serum uric acid was done within 48 hours of collections of the blood samples. Using a calorimeter the biochemical estimations was done. Uricase converts uric acid to allantoin and hydrogen peroxide. The hydrogen peroxide formed further reacts with a phenolic compound and 4 aininoantipyrine by the catalytic action of peroxidase to form a red coloured quinoneimine dye complex. Intensity of the colour formed is directly proportional to the amount of uric acid present in the sample.

RESULTS

280 patients of Gout were included in this study, out of which 140 were males and 140 were females. Subjects are evenly distributed in the age group of 25 years to 70 years.

Table 1 High uric acid level among respondents of different community

Community	Total respondent	High uric acid
Boro	40	13
Ahom	40	6
Karbi	40	6
Adivasi	40	5
Bengali	40	2
Manipuri	40	2
Marwari	40	0

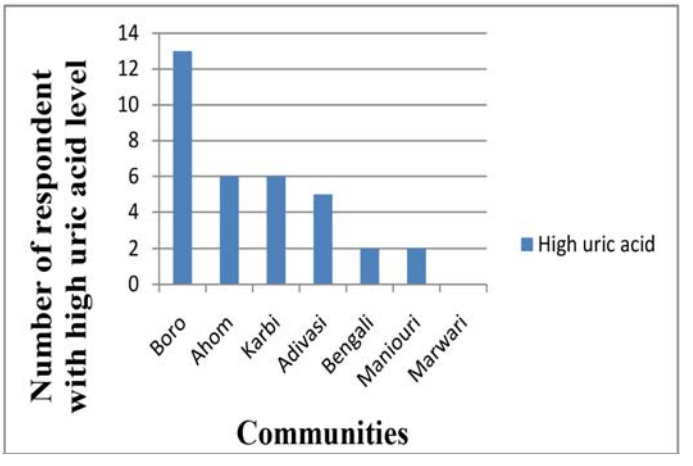

Figure 1 Distribution of high uric acid level among the respondents of different communities

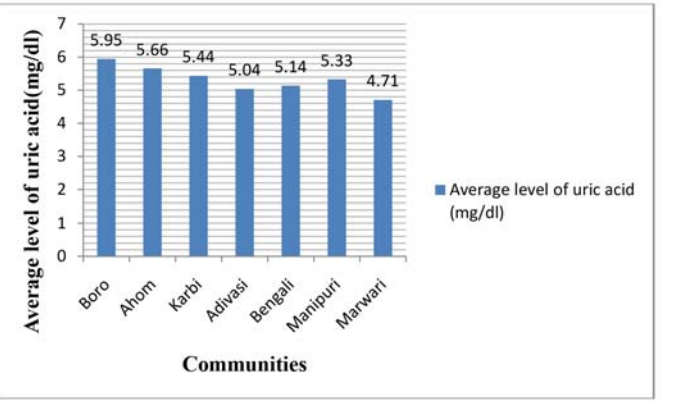

Figure 2 Average uric acid level of different community

Figure 2 Depicts uric acid level of Boro community is higher in comparisons to other communities. Uric acid level of Ahom community is found higher in comparison to Manipuri, Bengali, Adavasi and Marwari.

Table 2 Variation of uric acid level of different community

Source of variation	SS	df	MS	f
Between groups	40.43	6	6.73	5.64
Within group	325.84	273	1.19	
Total	**366.27**	**279**		

Table 2 depicts variation in high uric acid level recorded among the Boro community followed by Ahom, Karbi, Adivasi, Bengali, Manipuri significantly. No cases of high uric acid level were recorded in Marwari community.

Table 3 Uric acid level of different community vs sex

Community	Male (mg/dl)	Female (mg/dl)	t value (mg/dl)
Boro	6.69	5.22	4.1
Ahom	6.02	5.29	3.09
Karbi	6.09	4.79	3.75
Adivasi	5.43	4.65	2.3
Bengali	5.74	4.53	3.75
Manipuri	4.8	5.85	3.8
Marwari	5.09	4.34	3.57
Overall	5.69	4.95	6.12

Significant at 5% level of significance

Table 3 depicts Sex wise uric acid level is high in case of males 5.69 mg/dl, compared to females 4.95mg/d1. The average difference of uric acid level of male and female is found to be statistically significant. t - value is 6.12 mg/dl. Incidence of high uric acid level recorded among the Boro community followed by Ahom, Karbi, Adivasi, Bengali, Manipuri significantly. No cases of high uric acid level were recorded in Marwari group.

Table 3 also illustrated comparative tendency of high uric acid level is more among males as compared to females except among the Manipuri community.

DISCUSSION

It was observed in categories wise distribution the incidence of high uric acid level was nil in vegetarian categories. In Marwari, out of 40 respondent there is no record of high uric acid. Uric acid in Marwari community is 4.71 mg/dl, much less than other communities. The beneficial effect of dairy proteins relates to the fact that this type of protein cause excretion of urate and contain much lower level of purine. The findings are found to be in consistence with study carried out at different parts of the world.[8,9]

In the non-vegetarian group, often they consumed alcohol daily according to the social customs and religious rituals. It was observed that serum uric acid level in Boro community i.e. 5.95 mg/dl which was comparatively more than the other communities and this finding are similar with studies carried out by different workers.[6,10,11]

Sex wise differences have often been observed and the differences are reported to result from differences in sex hormones. Uric acid level is higher in male is 5.69 mg/dl when compared with female is 4.95 mg.

Sex wise incidence high uric acid was recorded among males in all the communities except the Ahom community. These findings are in consistence with observations of different workers.[4,12,13]

The strength of this study is that it gives some general clue over the altered serum uric acid level in relation to diet. In conclusion it is observed that intake of alcohol and not the purine intake is a strong risk for hyperuricaemia and for the development of gout. And vegetables which are rich in dietary fibres are protective against hyperuricaemia and gout.

CONCLUSION

Serum uric acid level shows significant variation in different communities like Boro community have high uric acid level in comparison to other communities. Because of their dietary habits. It was seen that there is no significant rise of high uric acid level in Marwari who are strictly vegetarian.

Sex wise high uric acid level is found in males compared to females and the average difference is statististically significant which is similar to all the community except Manipuri.

Serum uric acid may be a marker for the presence of an adverse cardiovascular diseases and it is strongly related to hypertension; hyperlipidemia; diabetes mellitus.

So, from the above study it can be concluded that different communities of Greater Kamrup district depicts different uric acid levels and association with sex. These findings can be associated with dietary habits of different communities. It can be placed in the context of overall health promotion, disease prevention and disease treatment with appropriate attention to nutritional needs in different communities.

A further bio-chemical analysis of blood in persons of different communities, both vegetarian and non-vegetarian dietary habit may help us to know different health problem in our society. Also, a thorough study is needed regarding the quantitative and qualitative evaluation of the constituent of non- vegetarian diet in different community without changing their dietary habit.

So, the above study reflects obvious scope for further work on this observation.

Conflict of interest: None declared.

Ethical clearance: Taken.

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Role of KIR gene cluster in susceptibility to rheumatoid arthritis

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ABSTRACT

Introduction*: Rheumatoid Arthritis (RA) is an autoimmune and chronic inûammatory disease of unknown etiology whose pathogenesis is not fully understood. Small joints in the hands and feet are involved the most. Genetic risk association of RA with HLA-DRB1 gene is the most significant. Women are more affected than men. Natural killer cells and CD28 null T-cells present in synovial membranes of joints of RA patients express Killer cell immunoglobulin-like receptors on its surface. KIR gene cluster has a strong association with autoimmunity as found in various studies.* ***Objective****: To investigate the role of various genes of KIR gene cluster in the pathogenesis of RA.* ***Materials and methods****: Blood samples from 80 cases (following ACR/ EULAR criteria-2010) and 80 controls were collected in EDTA vials using* standard venipunture procedure. *DNA was extracted from each of the collected blood samples and KIR genotyping was done by molecular techniques using SSP kits.* ***Results****: The presence of KIR2DS1, KIR2DS3, KIR2DS4, KIR2DS5 and KIR3DL1 genes among RA patients showed risk association. Using standard statistical tools results were validated.* ***Conclusion****: Some of the KIR genes have risk association with occurrence of RA. Individuals carrying these genes are suspected to be more susceptible to develop RA.*

Keywords*: Pathogenesis; genotyping; risk association; susceptible.*

INTRODUCTION

Rheumatoid Arthritis (RA) is an auto-inflammatory disease whose progression is chronic in nature. It mainly attacks synovial joints but extra-articular involvement can also be seen. Pain, swelling, and stiffness of the joints are the most common signs and symptoms. Most often small joints in the hands and feet are involved, although larger joints may also be involved. Typically joints are affected in a symmetrical pattern; for example, if joints in the right hand are affected, left hand also tends to be involved. It affects approximately 1% of the population distributed worldwide. The prevalence of RA is higher in women as compared to men.[1] Depending on the age of onset, it reduces the lifespan of the patient by 5-10 years.[2] Pathogenesis of RA has not been fully elucidated till now, even though many researches have been done. As the immune system attacks the body's own tissues and organs, and, due to the presence of autoantibodies like rheumatoid factor (RF) and anti-cyclic citrullinated antibodies (Anti-CCP), it is considered to be an autoimmune disease. As both genetic and environmental factors are involved, it is considered a multifactorial disease. Etiology of the disease comprises of 60% of genetic factors.[3] Variations in human leukocyte antigen (HLA) genes, especially the HLA-DRB1 gene is the most significant genetic risk factors for rheumatoid arthritis. It has been documented that shared epitope (SE) alleles, such as HLA-DRB1*01 and DRB1*04, some HLA alleles like HLA-DRB1*13 and DRB1*15 are connected to RA susceptibility.[4]

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The Immune system distinguish the body's own proteins from proteins made by foreign invaders with the help of the proteins produced from HLA genes which is estimated to be 11–37 %.[5] Other genetic risk factors for RA are PTPN22, CD40, CTLA4 and also genes coding elements of NF- êB signaling pathway like TNFAIP3 and TRAF1.[6] Natural killer (NK) cells, which are bone marrow derived large granular lymphocytes, mount early immune responses in an antigen independent manner by direct cytotoxicity.[7] NK cells display Killer cell immunoglobulin-like receptors (KIRs). Located on chromosome 19q13.4, the KIR gene cluster spans about 150–200 kb in the Leukocyte Receptor Complex. By interacting with MHC class I molecules, which are expressed on all cell types, KIRs regulate the killing functions. This interaction allows them to detect virally infected cells or tumor cells that have a characteristic low level of Class I MHC on their surface. The KIRs comprise a multigene family of receptors. KIR gene cluster consists of inhibitory genes, viz., KIR2DL1, KIR2DL2, KIR2DL3, KIR3DL1, KIR3DL2, KIR3DL3, KIR2DL4, KIR2DL5; activating genes, viz., KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DS1 and pseudo genes, viz., KIR2DP1 and KIR3DP1.[8] KIR genes like KIR2DL2, KIR2DS2, KIR3DS1 and KIR2DS4 are found to be associated with RA in Iranian, Mexican, Polish, Caucasian, Taiwanese and North Indian populations.[8-13] Studies on the relationship of KIR and RA are inconsistent and contradictory.[14]

In the Northeastern parts of India, only a few studies related to association of genetic factors related to RA, have been done. A recent study found TNF-á –308 variant GA genotype was higher in RA (46.03%) than in control (25%). The presence of TNF-á –308 variant A allele was associated with increased risk of RA susceptibility.[15] Till date, not a single study examining the KIR gene cluster in relation to RA, has been done in this part of India i.e., the Northeastern parts. Hence, the present, study aims to examine the role of various KIR genes in the susceptibility to rheumatoid arthritis among the population of Assam, which is one of the most important states of North East India.

MATERIALS AND METHODS

The study was conducted in a tertiary care government hospital situated in Guwahati, which is the gateway to Northeast India and where the capital of Assam (Dispur) is situated. This hospital caters to a large number of patients from every region of the state. A total number of 80 cases were taken from the Rheumatology OPD, Department of Medicine, Gauhati Medical College and Hospital, Guwahati, Assam, following the ACR/EULAR criteria (2010), during the period from 2017 to 2019. Four to six milliliters of blood were obtained, from patients diagnosed with RA as per the standard venipunture procedure and transferred into EDTA vials. Similarly blood samples were also collected from 80 controls who were individuals neither having any history of RA nor any other autoimmune diseases. DNA was extracted from all samples using standard (Manatis, et al) technique.[16] Quality and quantity was checked using Multiscan Go (Spectrophotometer/ Nanodrop). Purity ratio of DNA samples were found to be between 1.8- 2.0 using wavelength 260/ 280 nm.[17] Concentrations were found to be above 200 ng/ µL. PCR amplification of DNA samples of both patients and controls groups for KIR genes were performed using Sequence-Specific Primer (SSP) technique. The amplified products were subsequently loaded in 2% agarose gel submersed in 0.5X Tris buffer in a gel electrophoresis system. After running the electrophoresis for the required period, the 2% agarose gels were documented under gel documentation system. Intercalating agent ethidium bromide was used to tag the DNA in the gels viewed under UV rays using gel documentation system. KIR genes were identified, using appropriate tools, for the KIR genes responsible for inhibitory signals (KIR2DL1, KIR2DL2, KIR2DL3, KIR3DL1, KIR3DL2, KIR3DL3, KIR2DL4 and KIR2DL5), activating signals (KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5 and KIR3DS1) and two pseudo genes (KIR2DP1 and KIR3DP1). Results were validated using statistical tools like Fisher's exact test and Chi square test for independence and the findings less than P value- 0.05 were considered as statistically significant.

RESULTS

After analyzing the data of the study group it has been found that the frequency of female RA patients was higher (**Figure 1**) than male patients (P value<0.0001, OR- 9.0, 95% CI- 4.7450-17.0706). Females were found to be more predominant in terms of disease acquirement.

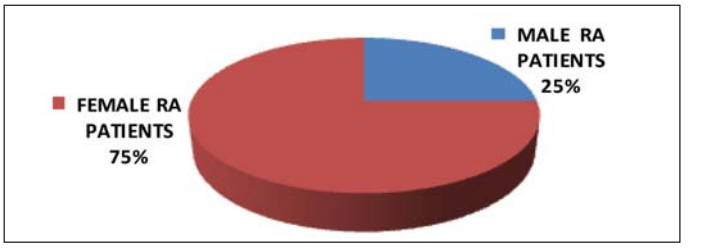

Figure 1 Sex distribution among RA patients

Associations of 16 KIR genes have been portrayed in **Table 1.** Considerable difference in the occurrence of KIR2DS3 gene between the patient and the control group was found during the study. From the univariate analysis comparing RA patient with healthy controls it was found that KIR2DS3 may have a significant role in increasing the susceptibility to RA (P value- < 0.0001, OR- 4.4211, CI- 2.1912 to 8.9200). Apart from that, few other genes from the KIR cluster were found to have risk associations with RA. Those activating genes were KIR2DS1 (P value- 0.0372, OR- 2.0636, 95% CI- 1.0904 to 3.9056), KIR2DS4 (P value- .0072, OR- 4.7500, 95% CI- 1.5115 to 14.9269) and KIR2DS5 (P value- 0.0092, OR- 2.6667, 95% CI- 1.3147 to 5.4091). Moreover, it was found that the incidence of inhibitory gene KIR3DL1 was higher in frequency among the RA patients than the controls in the study population (P value- 0.0446, OR- 2.8141, 95% CI- 1.0965 to 7.2222). The protective functionality of KIR genes in RA as reported in different populations [8-13] was not observed in this study group.

Table 1 Distribution of the KIR genes in patient and control group

Genes	Patients (n)	Controls (n)	P value	Odds ratio	Confidence interval
KIR2DL1	78	75	0.4426	2.6000	0.4893 to 13.8145
KIR2DL2	64	56	0.1074	1.7143	0.8285 to 3.5473
KIR2DL3	60	64	0.5704	0.7500	0.3558 to 1.5811
KIR2DL4	80	80	-	-	-
KIR2DL5	72	64	0.1198	2.2500	0.9029 to 5.6069
KIR2DS1	53	39	0.0372*	2.0636	1.0904 to 3.9056
KIR2DS2	68	65	0.6734	1.3077	0.5692 to 3.0043
KIR2DS3	64	38	< 0.0001*	4.4211	2.1912 to 8.9200
KIR2DS4	76	64	0.0072*	4.7500	1.5115 to 14.9269
KIR2DS5	64	48	0.0092*	2.6667	1.3147 to 5.4091
KIR3DL1	73	63	0.0446*	2.8141	1.0965 to 7.2222
KIR3DL2	80	80	—	—	—
KIR3DL3	80	80	—	—	—
KIR3DS1	73	71	0.7930	1.3219	0.4671 to 3.7414
KIR2DP1	80	80	—	—	—
KIR3DP1	77	75	0.7194	1.7111	0.3949 to 7.4144

*Statistically significant.

Distribution of the KIR genes in patient and control group in terms of frequency of occurrences has been illustrated in **Figure 2**.

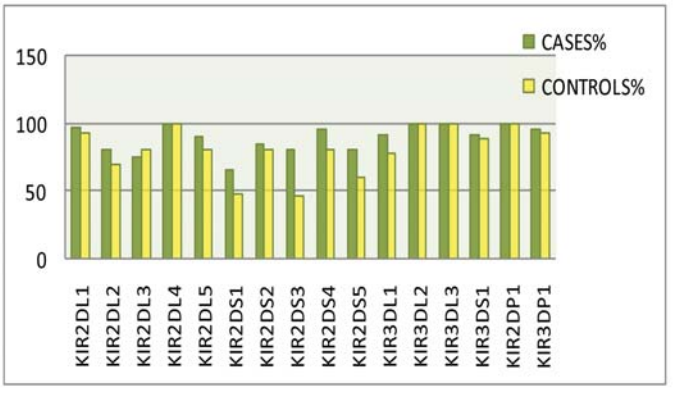

Figure 2 Distribution of the KIR genes in patient and control group in terms of frequency of occurrences

DISCUSSION

RA is an autoimmune disease with immunocomplex mediated hypersensitivity. It drastically involves the synovial joints and has a prevalence of approximately 1%. It affects generally the people of age group 30 to 60 years. Though its etiology is not fully understood still polygenic involvement is suspected to be associated. Whereas KIR has been seen to be associated with various autoimmune diseases and viral complications. The multiallelic diversity of KIR has made it the prime candidate for disease association studies. In this study, an approach has been made to elucidate the relationship between KIR and RA. After investigating the cases and controls drawn from homogenous population of Assam, it has been seen that the incidence of RA is higher in females as compared to

males (P value- < 0.0001, OR- 9.0, 95% CI- 4.7450-17.0706), such findings based on gender variation are also reported in studies conducted on other populations.[1]

Upon univariate analysis of individual KIR genes in the study group, it has been found that KIR2DS1 (P value- 0.0372, OR- 2.0636, 95% CI- 1.0904 to 3.9056), KIR2DS3 (P value- < 0.0001, OR- 4.4211, CI- 2.1912 to 8.9200), KIR2DS4 (P value- 0.0072, OR- 4.7500, 95% CI- 1.5115 to 14.9269), KIR2DS5 (P value- 0.0092, OR- 2.6667, 95% CI- 1.3147 to 5.4091) and KIR3DL1 (P value- 0.0446, OR- 2.8141, 95% CI- 1.0965 to 7.2222) genes have risk associations with RA. Out of these five genes, KIR2DS3 has been found to be highly associated with susceptibility to RA in terms of frequency. A similar finding from Taiwanese population has also been reported where KIR2DS4 was found to be associated with RA.[12] In contrary to our findings, risk association and protective functions of KIR genes are contradictory and inconsistent in different populations. In Mexican population, KIR2DL2 and KIR 2DS2 have risk associations with RA whereas KIR2DL3 seems to confer protection against RA.[9] In Polish population,[10] it has been found that frequencies of KIRs in patients with RA are similar to the frequencies in controls whereas in Iranian population KIR2DL2, KIR2DL5, KIR2DS5 and KIR3DS1 are found to be protective against RA.[8] In North Indian population also KIR association with RA has been studied where they observed KIR3DS1 and KIR2DS2 have risk association however KIR2DL2, KIR2DL3 and KIR3DL1 have protective function.[13]

Another observation was made where KIR3DL1, which is normally classified under inhibitory signaling genes,[8] has been found to be higher in patients than in controls, thus contraindicating its inhibitory role in the population in Assam. Other KIR genes viz., KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL4, KIR2DL5, KIR2DS2, KIR3DL2, KIR3DL3, KIR3DS1, KIR2DP1, KIR3DP1 were found to have similar frequencies in both cases and controls and their relationship with RA could not be statistically proven.

CONCLUSION

In this study it has been seen that there is an activating role of KIR2DS1, KIR2DS3, KIR2DS4, KIR2DS5 and KIR3DL1 in RA and the individuals with these genes are more susceptible to develop RA. The actual mechanism behind their role in susceptibility is through various cascades of pathways involving the KIR receptors in NK cells, further to validate the findings comparison and confirmation from various independent cohorts is needed. Despite of everything, irreconcilability has been seen in the effort of replicating the result.

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