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Thalassemia Major and Intermedia Patients in East Java do not Show Fetal Hemoglobin Level Difference in Relation to XMNI Polymorphism

Retno Dwi Wulandari^{1,2}, Diana Lyrawati³, Fatchiyah Fatchiyah⁴, Loeki Enggar Fitri⁵

ABSTRACT

Introduction: Thalassemia is a genetic disorder, which shows, varies phenotype due to genetic modifier. *Xmnl* is one of the genetic modifiers which affect clinical severity in thalassemia. *Xmnl* polymorphism may increase HbF production beyond fetal life, thus ameliorating the clinical phenotype. **Aim:** this study aimed to investigate the difference in HbF level and the relation of HbF level and *Xmnl* polymorphism in Thalassemia Major (TM) and Thalassemia Intermedia (TI) patients. **Methods:** forty-eight beta thalassemia patients (28 males and 20 females), consists of 16 TM and 32 TI; mean age, 25.30 year old. Hemoglobin Fetal and HbA₂ level were determined using High performance Liquid Chromatography (HPLC), and *Xmnl* polymorphism was confirmed by PCR-RFLP. **Statistical analysis was done using** T-test, Mann-Whitney and Pearson Chi-square. **Results:** The frequency of heterozygote (+/-) *Xmnl* polymorphism in TM and TI patients was 56.25% vs 71.87%, while the frequency of homozygote (-/-) in TM and TI was 43.75% vs 28.13% with p value >0.05. The insignificant difference also found in HbF level between *Xmnl* +/- and -/- in TM and TI patients. **Conclusion:** This study revealed that thalassemia major and thalassemia intermedia patients in East Java showed similar *Xmnl* polymorphism. These phenomena also showed by HbF level in relation to *Xmnl* polymorphism in the phenotype groups (TM and TI).

Keywords: thalassemia, major, intermedia, HbF level, *Xmnl*.

1. INTRODUCTION

Thalassemia is one of the common genetic diseases in the world that characterized by chronic hemolytic anemia. Thalassemia patients with severe condition that needs regular blood transfusion were categorized as thalassemia major (TM), while those with milder disease severity are considered as thalassemia intermedia (TI). Thalassemia intermedia patients usually need medical attention later in childhood, or adulthood and do not need regular transfusion to survive (1).

The clinical severity in thalassemia depends on three different mechanisms of genetic modifiers. The first modifiers represent the inheritance of beta globin mutation, which affect beta globin gene production, from slightly reduced to totally absent beta chain production (finally, these determine the degree of alpha/beta globin imbalance). The second modifiers are the co-inheritance of alpha gene mutation (which decreases the unbound alpha globin chain). Similarly, the imbalance in globin chain

production could be reduced by over expression of gamma globin gene that elevates HbF level in the adult. The third modifiers included those which affect the complication of the disease but not related with globin chain production (1).

In adult, the predominant gene is alpha and beta globin to form HbA ($\alpha_2\beta_2$) while in newborn baby. The 60-80% of total hemoglobin is HbF ($\alpha_2\gamma_2$). Although HbF was found abundant in fetal life, but before two years, its level decrease to less than 1% until adult life (2, 3). The switch occurs just before birth, when beta globin replaces fetal gamma globin, which involves the same alpha globin (4). The switch mediated by Locus Control Region (LCR) on beta globin gene. Physical bending of chromatin needed to bring the LCR promotor first to gamma globin gene before switched to the beta globin gene (4). In beta thalassemia, there is delayed switch from gamma globin to beta globin expression, and as consequently HbF levels remain above normal in most patients. Beta thalas-

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semia patients usually clinically present after 2 year of age (5), following the decrease in HbF production as the switch occur (6).

XmnI polymorphism was one of the genetic modifier known, which can modified gamma chain production. The polymorphism result in highly expressed gamma globin gene leading to increasing HbF level in adult life (7). The elevated HbF production may compensate for the low HbA level which caused by the abnormal beta globin chain. The polymorphism site located in -158 promoter HBG2 gene will change C > T. Some studies reported significant association between the *XmnI* polymorphism and HbF level (8, 9). Carriers of the T allele of *XmnI* have shown to be more possible having a milder disease course (4). Research showed that the increasing of HbF production beyond fetal life has been a benefit for beta thalassemia patients as it can ameliorate the thalassemia phenotype (2) although negative relation also reported (10).

2. AIM

In this study we aimed a) to investigate the frequency of *XmnI* polymorphism in thalassemia major and intermedia; b) to investigate the HbF level difference according to gender and the *XmnI* polymorphism of phenotype group in both thalassemia major and intermedia; and c) to determine difference of HbF level in relation to *XmnI* polymorphism between thalassemia major and thalassemia intermedia patients in East Java, Indonesia.

3. MATERIAL AND METHODS

This research study approved by Ethical Committee of Health Research of Medical Faculty Wijaya Kusuma Surabaya University (No.10198/SLE/FK/UWKS/2018).

Patients

The thalassemia patients were member of Indonesian thalassemia's parents association (POPTI). Thalassemia major (TM) patients were those who started transfusion before 5 year old with the needs regular (6-12 times per year) transfusion. Thalassemia intermedia patients started transfusion at 5 years old and after, with transfusion rate 0-12 times per year.

Sample preparation

After signing an informed consent, 10 ml blood was obtained from peripheral blood and collected in vacutainer for hematologic analysis including High Performance Liquid Chromatography (HPLC) assays. Hematologic analysis was taken by using Advia 2120 Siemens. HPLC analysis was conducted using VariantTM II Thalassemia Short Program (Bio-Rad Laboratories, Hercules, CA, USA). The VARIANT II β -thalassemia Short Program utilizes principles of ion exchange high performance liquid chromatography (HPLC). The samples are automatically mixed and diluted on the VARIANT II Sampling Station (VSS) and injected to the analytical cartridge. The VARIANT II Chromatographic Station (VCS) dual pumps deliver a programmed buffer gradient of increasing ionic strength through the cartridge, where the HbA2/F are separated based on their ionic interactions with the cartridge material. The separated HbA2/F then

pass through the flow cell of the filter photometer, where changes in the absorbance at 415 nm are measured. An additional filter at 690 nm corrects the background absorbance. The VARIANT II Clinical Data Management (CDM) software performs reduction of raw data collected from each analysis. One-level calibration is used for adjustment of the calculated HbA2/F values. A sample report and a chromatogram are generated by CDM for each sample.

We used a solvent reagentse.i. Elution buffer 1 and 2 (containing sodium phosphate buffer), Whole Blood Primer (containing lyophilized human red blood cell hemolysate with gentamicin, tobramycin and EDTA as preservatives), HbA2/HbF calibrator/diluent set (lyophilized human red blood cell hemolysate containing gentamicin, tobramycin and EDTA as preservatives), and Diluent (contains deionized water with less than 0.05% sodium azide as a preservative).

Running method: HbA2/HbF calibrator reconstituted with calibrator diluent. The Whole Blood Primer prepared by adding deionized water to the vial. Vials prepared for Variant whole blood primer, deionized water, Variant A2/F calibrator, positive and negative control, stop tube and vials for samples/patients. Vial 1 contains primer, vial 2 contains deionized water, vial 3 and 4 contain HbA2/HbF calibrator, vial 5 and 6 contain control level 1 and 2, vial 7 to N contain patient samples, N+1 and N+2 contain control level 1 and 2, N+3 is stop tube. The result will be printed out from the HPLC.

PCR analysis of *XmnI* polymorphism

The *XmnI* was identified using PCR with primer pair: Forward (5'-AACTGTTGCTTTATAGGATTTT-3') and Reverse (5'-AGGAGCTTATTGATAACTCAGAC-3') and PCR profile as described by Said & Abdel-Salam (2015) (2). PCR was performed using Veriti (Applied

Parameter	N(%)	Mean (\pm SD)	Range	p-value
Gender	48			
Male	28(58.33)	10.8(9.8)	2.7-45.8	0.184
Female	20(41.67)	8.8(8.9)	1.1-37.5	
<i>XmnI</i> polymorphism				
Heterozygote (+/-)	32(66.7)	11.86(10.88)	1.1-45.8	0.058
Homozygote (-/-)	16(33.3)	6.27(3.45)	2.7-15.5	

Table 1. Comparison of Mean HbF level (%) in Relation to Gender and *XmnI* polymorphism

Variable	All samples	TM (n=16)	TI (n=32)	p value
HbA ₂ level (%)				
Mean	31.28	25.93	33.95	0.225
Median	27.9			
Range	6.2 – 69.8			
HbF level (%)				
Mean	9.99			
Median	7	6.48	11.76	0.060
Range	2 – 45.8			

Table 2. The level comparison of HbA2 and HbF on TM and TI

Phenotype	<i>XmnI</i> -/- (n=16)	<i>XmnI</i> +/- (n=32)	p value
TM (n=16)	7(43.75%)	9(56.25%)	0.279
TI (n=32)	9(28.13%)	23(71.87%)	

Table 3. The Frequency of *XmnI* -/- and *XmnI* +/- polymorphism in TM and TI

Phenotype	Level of HbF		P value
	<i>XmnI</i> -/- Mean (\pm SD)	<i>XmnI</i> +/- Mean (\pm SD)	
TM	5.71(3.44)	7.07(4.71)	0.536
TI	6.70(3.61)	13.73(12.07)	0.122
P value	0.470	0.157	

Table 4. The Level of HbF in homozygote (-/-) and heterozygote *XmnI* Polymorphism between TM and TI

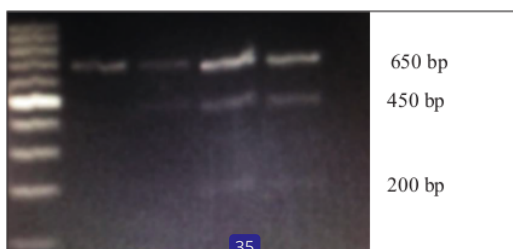


Figure 1. Gel electrophoresis of G gamma gene (-158 C>T) PCR-RFLP with *XmnI* restriction enzyme. Lane 1 (left side): DNA marker 100 bp, lane 2: 650 bp band from patient with *XmnI* (-/-) polymorphism, lane 3-5: 650bp, 450 bp and 200 bp bands from patients with *XmnI* (+/-) polymorphism.

Biosystem, USA). The PCR product was then run in 2% gel electrophoresis.

If there was band, the process continued to digest the PCR product with restriction enzyme.

RFLP analysis of *XmnI* polymorphism

The PCR product was then digested using *XmnI* restriction enzyme (Biolabs) following its instruction, yielding +/- genotype as indicated having 450 and 200bp, heterozygote genotype (+/-) showed 3 bands at 650, 450 and 200bp and -/- genotype showed only band at 650 bp at 13 run in 2% agarose gel electrophoresis (Figure 1)

Statistical analysis

Data are presented as mean \pm SD, range and percentage. T-test was performed to analyze the difference of the mean, first transfusion age and transfusion rate per year between phenotype groups (TM and TI). Hemoglobin Fetal level difference according to sex and *XmnI* (-/- and +/- polymorphism) was analyzed using Mann-Whitney test. The Mann-Whitney test also used to analyze the difference of HPLC results (HbA₂ and HbF) between phenotype groups as well as the relation between HbF level and *XmnI* polymorphism in TM and TI. Pearson's Chi-squared was used to compare between *XmnI* -/- and *XmnI* +/- polymorphism in TM and TI. P value < 0.05 was considered statistical significant. Data were analyzed using SPSS 20.

4. RESULTS

A number of 48 patients which 28 (58.35%) were males and 20 (41.7%) were females involved in this study. Although the number of female patients in this study was lower than male, but since thalassemia inherited as autosomal recessive, means that female and male have the same chance to get the disease. The sample's age data (mean age 25.30 yo) with the difference of mean age between male (24.45yo) and female (27.1yo) was not significant (p=0.24). In this study, *XmnI* gene polymorphism was only found in heterozygote form with overall frequency was 66.7%. Mean HbF level comparison between heterozygote (+/-) *XmnI* polymorphism and homozygote (-/-) genotype showed nearly significant difference, while comparison between male and female showed no significant difference (Table 1).

After grouped into TM and TI, the mean age of TM was 21.75yo and TI 27.08yo (p value = 0.052); mean age of 1st transfusion was 2.59yo vs. 11.68yo (p value = 0.00), while mean transfusion rate/year 9.52 vs. 7.7 (p value = 0.169).

The comparison of HbA₂ and HbF level between TM and TI patients presented in Table 2 where the insignificant difference found in both mean HbA₂ and HbF level between TM and TI patients.

Among TM and TI patients, more patients showed heterozygote *XmnI* polymorphism than homozygote (-/-). The frequency of heterozygote *XmnI* polymorphism was 71.87% in TI group compared to 56.25% in TM group. The difference of *XmnI* polymorphism's frequency between TM and TI presented in Table 3, which showed that there was no significant difference between the homozygote (-/-) and heterozygote (+/-) *XmnI* polymorphism in TM and TI patients (p=0.279).

HbF level comparison between phenotype (TM and TI) and *XmnI* polymorphism are presented in Table 4.

The mean HbF level both in TM and TI patient with heterozygote *XmnI* polymorphism was higher compared to those with the absence of polymorphism, but the difference was not significant (p = 0.536 and p = 0.122); the mean HbF level difference between TM and TI with homozygote (-/-) and heterozygote *XmnI* polymorphism also did not showed significant difference (p = 0.470 and p = 0.157) respectively.

5. DISCUSSION

Thalassemia major patients refer to those who need regular transfusion which started before 2 year old, but occasionally the presentation could be delayed until 4-5 years (11, 12).

In this study, patients got transfusion before 5 year old, as there were possibilities delayed which may be due to factors such as: a) the lack of parents' knowledge or caring for their children; b) socioeconomic factor; c) the knowledge of health worker about the disease; d) the limitation of thalassemia prevention program in identifying thalassemia earlier. While to be survive, patients with thalassemia intermedia usually do not need regular transfusion, or only occasional and can be even more frequent in certain condition (13). We found that

some TI patients got 12 times per year although the first transfusion received later in age. The possibilities were: a) transfusion needed for growth and development; b) recurrent infection (patients with middle-low economic status); c) social purposes, if it needed for activity.

In the case of relation to activity needs, some mothers asked for transfusion before their child started to have exam. Taher, et al (2015) (14) reported that there was possibility that some HbE/ β thalassemia (TI) patients got unnecessary transfusion as severe anemia and acute haemolysis exacerbated by infection.

Beta thalassemia patients usually show increasing HbA₂ and HbF level. By examination using HPLC, hemoglobin variants such as HbS, HbE, and Hb Lepore result in higher HbA₂ levels compared to those using capillary electrophoresis (CE) due to co-elution (15). Our data showed that the level of HbA₂ in TI was higher than TM although the difference was not significant. Khera, et al (2015) (16) also reported that it might be caused by more HbE variant in TI than TM.

Although there is elevation of HbF production in beta thalassemia, this study showed that the mean HbF level was not different in relation to gender. This result in line with study by Lim, et al. (17). We also found that the overall positive heterozygote XmnI polymorphism frequency was quite high (66.7%), although there was no difference between homozygote (-/-) and heterozygote XmnI polymorphism in TM and TI. This result confirmed the earlier studies by Neishabury, et al (2010) and Said & Abdel-Salam (2015) which showed no relation between C to T substitution in XmnI polymorphism with phenotype severity (thalassemia major and intermedia) (2, 18).

Research showed that the increasing of HbF production beyond fetal life has been a benefit for beta thalassemia patients as it can ameliorate the thalassemia phenotype (2) by reducing the imbalance in alpha/beta globin chain synthesis. This would lead to a milder phenotype, thalassemia intermedia, despite similar beta genotype and no co-inheritance of alpha mutation (2, 5, 17). Although in this study HbF level in TI was higher than in TM but the difference was not significant. As presented in Table 3, the polymorphism was only found in heterozygote form, while among +/- XmnI polymorphism, the number of TI patients showed higher percentage compared to TM (p value >0.05). This was one of few studies, which found that XmnI polymorphism difference between TM and TI was not significant. This result in line with previous study by Tyagi, et al (2003) which resulted no statistically significant difference between positive heterozygote XmnI polymorphism in thalassemia major and thalassemia intermedia (10).

Interestingly, this study found a new frequency of heterozygote polymorphism. The frequency of heterozygote polymorphism in this study was different from previous study done on HbE/ β and β thal/ β thal patients in Central Java, Indonesia, which found +/+ polymorphism in 3.7% and +/- polymorphism in 20.6% samples (8). The difference from previous study may be due to difference frequency in the different population.

Patients with heterozygote XmnI polymorphism showed higher expression of HbF compared to those without polymorphism with nearly significant difference (p value = 0.058). The insignificant difference also showed when HbF level in homozygote XmnI (-/-) and heterozygote (+/-) polymorphism compared between phenotype group (TM and TI). This showed that HbF level and XmnI polymorphism could not make the significant difference between TM and less severe TI phenotype. The most possibility for main contributor was the inheritance of mild beta mutation in TI than XmnI polymorphism.

To our knowledge, this is the first study that reports the frequency of XmnI polymorphism and HbF level comparison in relation to XmnI polymorphism in Thalassemia Major and thalassemia intermedia in East Java, Indonesia.

6. CONCLUSION

This study demonstrates that thalassemia major and intermedia patients in East Java do not show homozygosity (+/+) of XmnI polymorphism, while the heterozygous state (+/-) shows the highest frequency. There is no XmnI (-/-) and (+/-) polymorphism difference between thalassemia major and thalassemia intermedia patients. The HbF level in relation to XmnI polymorphism between thalassemia major and intermedia patients do not show difference as well. It needs further research to determine the main contributor to the less severe phenotype in thalassemia intermedia patients.

Limitation of the study: According to small patient population, it limits us to draw general conclusion, that it may needs further study to prove the finding with larger sample size and different population for thalassemia major and thalassemia intermedia patients.

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REFERENCES

1. Musallam KM, Sankaran VG, Cappellini MD, Duca L, Nathan DG, Taher AT. Fetal hemoglobin levels and morbidity in untransfused patients with β -thalassemia intermedia. *Blood*. 2014; 119(2): 364-367.
2. Said F, Abdel-Salam A. XmnI polymorphism : Relation to β -thalassemia phenotype and genotype in Egyptian Children.

14. [10](#) *pt J Med Hum Genet.* 2015; 16: 123-127.
3. Mosca A, Paleari R, Leone D, Ivaldi G. The relevance of hemoglobin F measurement in the diagnosis of thalassemias and related hemoglobinop [32](#) es. *Clin Biochem.* 2009; 42(18): 1797-1801. Available from: <http://dx.doi.org/10.1016/j.clinbiochem.2009.06.023> [31](#)
4. Guha BG, Sharma SK. Raised Haemoglobin F (HbF) Level in Haemoglobinopathies : an Indicator of Polymorphism. *Int J [20](#) Res.* 2014; 3(7): 532-536.
5. Sripichai O, Fucharoen S. Fetal hemoglobin regulation in β -thalassemia : heterogeneity, modifiers and therapeutic [44](#) p-approaches. *Expert Rev Hematol.* 2016; 9(12): 1129-1137. Available from: <http://dx.doi.org/10.1080/17474086.2016.1255142>
6. Musallam KM, Taher AT, Cappellini MD, Sankaran VG. Clinical experience with fetal hemoglobin induction therapy in patients with β -thalassemia. *Blood.* 2013; 121(12): 2199-2212.
7. Danjou F, Anni F, Perseu L, Satta S, Dessì C, Lai ME, et al. Genetic modifiers of β -thalassemia and clinical severity as assessed by age at first transfusion. *Haematologica.* 2012; 97(7): [4](#)9-993.
8. Rujito L, Basalamah M, Siswandari W, Setyono J, Wulandari G, Mulatsih S, et al. Modifying effect of Xmn1, BCL11A, and HBS1L-MYB on clinical appearances : A study on β -thalassemia and hemoglobin E / β -thalassemia patients in Indonesia. *H [30](#)tol Oncol Stem Cell Ther.* 2016; (1): 1-9. Available from: <http://dx.doi.org/10.1016/j.hemonc.2016.02.003>
9. Dadheech S, Jain S, Madhulatha D, Sharma V, Joseph J, Jyothy A, et al. Association of Xmn1 -158 γ G variant with severity and HbF levels in β -thalassemia major and sickle. *Mol Biol Reports Vol.* 2014; 41: 3331-3337. doi:10.1007/s11033-014-[12](#)5-5.
10. Tyagi S, Kabra M, Tandon N, Saxena R, Pati HP, Choudhry VP. Clinico-Haematological Profile of Thalassemia Intermedia Patients. *Int J Hum Genet.* 2003; 3(4): 251-258.
- [8](#)
11. Hassan T, Badr M, El Safy U, Hesham M, Sherief L, Zakaria M. β -Thalassemia: Genotypes and Phenotypes. In: *Epidemiology of Communicable and Non-Communicable Diseases - Attributes of Lifestyle and Nature on Humankind.* 2016: 113-[28](#).
12. Badens C, Joly P, Agouti I, Thuret I, Gonnet K, Fattoum S, et al. Variants in genetic modifiers of β -thalassemia can help to predict the major or intermedia type of the disease. *Haematologica.* 2011; [2](#)(11): 1712-1714.
13. Musallam K, Rivella S, Vinchinsky E, Rachmilewitz EA. Non-transfusion-dependent thalassemias. *Haematologica.* [16](#)3; 98(6): 833-844.
14. Taher AT, Radwan A, Viprakasit V. When to consider transfusion therapy for patients with non-transfusion-dependent [11](#)assaemia. *Vox Sang.* 2015; 108(1): 1-10.
15. Hafiza A, Malisa M, Khiretdin A, Azlin I, Azma R, Thong M, et al. HbA2 levels in normal -thalassaemia and haemoglobin E carriers by capillary electrophoresis. *Malaysian J Pathol.* 2012; [5](#)(2): 161-164.
16. Khera R, Singh T, Khuana N, Gupta N, Dubey AP. HPLC in Characterization of Hemoglobin Profile in Thalassemia Syndromes and Hemoglobinopathies : A Clinicohematological Correlation. *Indian J Hematol Blood Transfus.* 2015; 31(1): [18](#) 115.
17. Lim WF, Muniandi L, George E, Sathar J, Teh LK, Lai MI. HbF in HbE; β -thalassemia: A clinical and laboratory correlation. *[41](#)matology.* 2015; 20(6): 348-353.
18. Neis [1](#)bury M, Azarkeivan A, Najmabadi H. Frequency of Positive Xmn1 G γ polymorphism and coinheritance of common alpha thalassemia mutations do not show statistically significant difference between thalassemia major and intermedia cases with homozygous IVSII-1 mutation. *Blood Cells Mol Dis.* 2010; 44(2): 95-99.

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35 Fariz Kahhaleh, M Ameen Sulaiman, Faizeh Alquobaili, Yaşam Kemal Akpak. "Association of Xmn1 polymorphism and consanguineous marriage with fetal hemoglobin in Syrian patients with sickle cell disease", Cogent Medicine, 2019
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36 Neishabury, M.. "The modifying effect of Xmn1-HBG2 on thalassemic phenotype is associated with its linked elements in the beta globin locus control region, including the palindromic site at 5'HS4", Blood Cells, Molecules and Diseases, 20120115 <1 %

37

Sneha Dadheech, Suman Jain, D. Madhulatha, Vandana Sharma, James Joseph, A. Jyothy, Anjana Munshi. "Association of Xmn1 -158 γ G variant with severity and HbF levels in β -thalassemia major and sickle cell anaemia", *Molecular Biology Reports*, 2014

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M Kent Ranson, Tara Sinha, Mirai Chatterjee, Fenil Gandhi, Rupal Jayswal, Falguni Patel, Saul S Morris, Anne J Mills. "Equitable utilisation of Indian community based health insurance scheme among its rural membership: cluster randomised controlled trial", *BMJ*, 2007

Publication

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41

Prasing, W., T. Odawara, P. Traisathit, Y. Yamashiro, Y. Hattori, and S. Pornprasert. "Analysis of the Xmn 1-G γ polymorphism in β -thalassemia/hemoglobin E (HbE) and homozygous HbE patients with low and high levels of HbF", *International Journal of Laboratory Hematology*, 2014.

Publication

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42 Tian, H.. "Evaluation of Silica Resins for Direct and Efficient Extraction of DNA from Complex Biological Matrices in a Miniaturized Format", *Analytical Biochemistry*, 20000801
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