Format for ANSWERING REVIEWERS

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7688-review.doc).

Title: Genetic Polymorphisms of Cytokine Genes in Type 2 Diabetes Mellitus

Author: Monisha Banerjee and Madhukar Saxena

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 7688

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewers	Comments	Clarifications
02453123	The authors have reviewed the role of cytokine polymorphisms in diabetes in an extensive manner. The article underscores the importance of recognizing the genetic polymorphisms in the pathogenesis of diabetes. We suggest having a separate paragraph explaining the pathogenesis for the ease of readership.	Thanks for your appreciation. We have added the figure 2 to understand the pathogenesis of T2DM
	We also suggest that authors review the effect of anti-inflammatory markers in improving the glycemic control. As most of the studies reviewed by the authors explored the role of inflammation, the data on the role of anti inflammatories in improving the glycemic control would substantiate the subject explored a,b,c	We have included both pro and anti inflammatory markers in the review. The literature are focused on genetic polymorphisms of inflammatory markers, if we include the data on the role of anti inflammatories in improving the glycemic control then the theme of the review will deviate. We will try to focus the same in next article.
	A schematic diagram of how the interleukins work would be more useful to the readers not familiar with the inflammatory pathway	A simplified figure 2 of how some of the interleukins work and lead to T2DM.
	The role of genetic polymorphisms in the development of micro-vascular complications from diabetes has been explored in the past and review of few of them would add more support to the article.	We have includes all the articles available on genetic polymorphism and T2DM in the present report. If we include micro-vascular complication from diabetes in the current manuscript then it will more complicated for the reader. We have tried to compress more in less in this review and focus of the theme should be maintained. Important ones have already been in the manuscript [86, 95, 101, 102, 104, 111, 112, 114, 115, 116, 122, *etc*]
	The article reads well and does not have any major grammatical errors	Thanks for your appreciation.
01404215	Major Points 1. The authors have not performed specific experiments to correlate mutational polymorphisms and the incidence of type 2 diabetes. They have only taken data from other authors and presented them in a systematic reviewed form.	This is a review article and not a research article. However the review article includes the published work of all our experiments [4, 9, 10, 11, 12, 17].
	2. The resulting manuscript is like a review on the topic, but if that is the case, the length and depth of the article are insufficient for the purpose.	Yes, the manuscript is a review and in our opinion is quite exhausted with more than 160 references. As per other reviewers, the review of such a complicated topic is enough for the

		readers' interest and comprehension.
	3. A detailed interpretation of the molecular mechanisms relating the polymorphic change and the induction of type 2 diabetes is lacking. As a consequence, the manuscript is too descriptive and readers do not learn the mechanistic effects of single mutations on cytokine transcription and translation and the final outcome, i.e., the appearance of type 2 diabetes.	The molecular mechanism relating to the polymorphic changes can be a review in itself. The purpose of this review is to throw light upon the role of cytokine gene polymorphisms in T2DM and to provide the readers a lead for future research.
	4. Fig 1 (displaying a scheme of the relationship between cytokines and metabolic induction of type 2 diabetes) does not show the biochemical correlation between causes and effects, and as a result, the specific transcription factors interacting with specific parts of cytokine gene promoters are lacking.	A separate figure showing biochemical correlation has been incorporated (Figure 2)
	Minor Points 1. Captions of Tables are too simplistic and do not help the reader to understand the results presented.	All necessary correction have been incorporated in table 1.
	For example, in Table 1 the meaning of VNTR is not given. The redundant IL-18 in the penultimate line is difficult to understand.	The necessary correction have been made and highlighted in yellow.
	The occurrence of 5 SNPs (without detailing the mutations) has not been clarified.	The necessary correction have been made and highlighted in yellow.
	The meaning of capitals S or NS used in column 4 has not been explained	The necessary correction have been made and highlighted in yellow.
	2. Table 3 shows two references to the same populations (the KORA Survey). Detailed polymorphisms are lacking	The same group illig et al, 2004, 2005 have worked on Il-6 polymorphisms in the same population. The polymorphism is -174G/C mentioned in the column 1 of table 3.
	3. Table 4. It would be of interest to explain how the same polymorphism (-1082 G/A), produced different effects in Indian populations. The same applies to polymorphism (-592 A/C) in the Taiwanese groups (S versus NS). A comment about these points would have been useful.	Since the manuscript is a review the results of different groups have been incorporated as such. There are many factors which result in the same polymorphism producing different effects in different population.
	4. Table 5. A T at the beginning of line	The necessary correction have been made and

	1 is lacking (Tarragonan rather than Arragonan).	highlighted in yellow.
00597793	The title of the paper suggests that the authors will discuss the effects of variants of cytokines with DM and its complications. This is not done in the text of the paper. There is some information like this in the Tables. The text of the article is a general discussion of cytokines which does not comport with the title.	With due respect to the reviewer we wish to clarify that the text of the paper exactly complies with title as confirmed by other reviewers.
	The INTRO is diffuse and does not add anything to the paper and is off subject. The first 3 paragraphs can be deleted.	We thing that the first paragraphs in introduction are important since they include prevalence of diabetes, cytokines and their role in T2DM before coming to the genetic studies. It is for the convenience of readers and also for budding researchers in this field.
00106462	Nicely organized and well written review of a complicated topic	Thank you.
01692833	This manuscript represents an interesting effort to connect polymorphisms of interleukins and inflammatory factors with type 2 diabetes. Indeed there is an extensive literature covered to yield the tables shown in the manuscript; however, what is lacking is the comparison with a number of other diseases (MS is mentioned in one table) in which inflammation plays a major role, such as: verious types of arthitis, Crohn's disease, ulcerative colitis,type 1 diabetes, etc.The point made is the following: how specific are these SNPs for T2DM? the manuscript does not yield information in this respect, but this is the most important point.	Inflammation is common to several diseases but our focus is on type 2 diabetes. Since T2DM is a part of metabolic syndrome and reference 151 showed the association of adiponectin with MS which included T2DM subjects. Only the association of these SNPs with other diseases as per learned reviewer can throw light on their specificity to T2DM. This can be good topic for review.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Diabetes*.