

Response Form for the Final Performance Review Report*

1. Name of Grantee: National Disease Research Interchange
2. Year of Grant: 2008 Formula Grant

A. For the overall grant, briefly describe your grant oversight process. How will you ensure that future health research grants and projects are completed and required reports (Annual Reports, Final Progress Reports, Audit Reports, etc.) are submitted to the Department in accordance with Grant Agreements? If any of the research projects contained in the grant received an “unfavorable” rating, please describe how you will ensure the Principal Investigator is more closely monitored (or not funded) when conducting future formula funded health research.

Future health research grants and projects will be completed and required reports (Annual Reports, Final Progress Reports, Audit Reports, etc.) will be submitted to the Department in accordance with Grant Agreements, exactly as they have been previously. NDRI’s policies and procedures and oversight process in this regard have ensured timely submission of all reports to date using the required formats.

For each research project contained in the grant, please provide a response to items B-D as listed on the following page(s). When submitting your response please include the responses for all projects in one document. The report cannot be submitted as a ZIP file, because the Department’s exchange server will remove it from the email. If the report exceeds 2MB, please contact the Health Research Program for transmittal procedures: 717-783-2548.

* Please note that for grants ending on or after July 1, 2007, grantees’ Final Performance Review Reports, Response Forms, and Final Progress Reports **will be made publicly available on the CURE Program’s Web site.**

Project Number: 0864201

Project Title: Genetic Susceptibility for Microvascular Complications in Patients with Type 1 Diabetes

Investigator: Lonsdale, John T.

B. Briefly describe your plans to address each specific weakness and recommendation in Section B using the following format. As you prepare your response please be aware that the Final Performance Review Report, this Response Form, and the Final Progress Report will be made publicly available on the CURE Program's Web site.

Reviewer Comment on Specific Weakness and Recommendation (*Copy and paste from the report the reviewers' comments listed under "Specific Weaknesses and Recommendations"*):

Reviewer 1:

1. It is unclear whether much has been done other than sending out letters to study participants. At least a summary of the results of those letters could be presented.
2. Results of Aim 1 met only the most liberal criteria for acceptance, as being genetically associated with the diabetes complications.
3. The sample sizes for the subjects with complications are small. Thus, the dataset will likely only be useful in concert with other samples from other studies. Some effort is being made (i.e., the consortium grant), but this has not yet materialized.

Reviewer 2:

It would be nice to see the results of Specific Aim 3.

Reviewer 3:

1. The response rate for the follow-up survey (Aim 2) was significantly lower than the stated goal of 25%, which could impact statistical power and generalizability. In the final report, the researchers did not discuss their actual efforts to increase response rates and whether or not they have used any new methods to do so. It is recommended that the researchers indicate what, if any, methods they are (or will be) using to increase response rates. Some possible methods might include additional follow-up contacts, incentives, and mailings to other additional family members. Other possible methods might include alternative data collection methods such as making phone calls or using the internet. Although some of these methods may not be ideal for the kind of data being collected, there should be more detail regarding efforts to maximize the response rate and more discussion of the potential impact of a low response rate.
2. The investigators did not provide a focused statement on how the findings specifically contributed the changes in outcome, impact and effectiveness of research in this area. Instead they provided a brief and general discussion of the potential impact very much like the one provided in the strategic research plan prior to conducting the research. A more detailed

explanation of the impact of the actual results would have been helpful for evaluating the true impact of the study.

3. There were no publications at the time the final report was generated. The lack of publications is not unreasonable given the length of the project, but it is a slight weakness because it makes it difficult to ascertain the full impact of the project. There is no way to know whether this article will be submitted and/or accepted for publication. It is recommended that the investigators discuss any progress that has been made in writing articles for submission to journals.
4. This project did not appear to enhance the quality and capacity for research at the grantee's institution. This is a slight weakness because the extent to which there was potential to use project funds to hire and train new investigators is unclear. The investigators should provide comments on why aims under this criterion were not achieved.

Response (Describe your plan to address each specific weakness and recommendation to ensure the feedback provided is utilized to improve ongoing or future research efforts):

Reviewer 1:

1. We have made significant efforts to track our families through follow-up emails and phone calls, with over 600 emails sent and 100 phone calls made from the time period of 10/11/2010-12/31/2010. We have made contact with over 400 families at this point and continue to reach out to our families for follow-up. A summary of the efforts (mail, email, and calls) to contact families after this years mailing will be provided in future annual and final reports.
2. We feel our analysis demonstrated an important biological point in that there is a genetic risk not only to developing T1D but to developing complications to T1D that is independent of the genetic risk of developing T1D itself. Our research continues to address this important concept.
3. Much effort has been applied to the creation of a genetic database to allow for power calculations and linkage analysis. The power calculations have shown that the sample size is adequate to perform these studies. We will report more on this in this years' annual and final report.

Reviewer 2:

A set of 95 cases with retinopathy, 38 cases with nephropathy, 31 cases with neuropathy and 167 controls without microvascular diabetic complications were selected from the HBDI cohort genotyped by T1DGC. The SNP saturation study demonstrated a significant region within the gene selected for study that was associated with the presence of retinopathy (p-values ranging from 0.0002391 – 0.009694, OR 1.69-1.864). Additional analysis will provide useful information on linkage. Additional results of the SNP analysis will be included in the annual/final reports this year.

Reviewer 3:

1. We have made significant efforts to track our families through follow-up emails and phone calls, with over 600 emails sent and 100 phone calls made from the time period of 10/11/2010-12/31/2010. We have made contact with over 400 families at this point and continue to reach out to our families for follow-up. A summary of the efforts (mail, email, and calls) to contact

families after this years mailing will be provided in future annual and final reports. Efforts that have been used to increase the response rates will also be discussed.

2. The important impact of these studies is the potential discovery that there are genetic factors that predispose diabetes to develop complications or to be protected from such complications. This finding could potentially lead to better screening and/or monitoring of diabetics at risk and a lowering of the occurrence or severity of the complications that are so detrimental to the quality of life of diabetics. We will provide a more detailed discussion of the important impact of these findings in the annual and final reports.

3. Unfortunately, we have had difficulty finding an available set of samples/data that will allow us to perform the replicative studies that need to be performed to publish this work. We require a data set with concurrent available DNA samples that has paired T1D siblings with confirmed presence or absence (at least 10 years) of complications. This has prohibited our ability to publish this work. However, the linkage analysis that we are now able to do will allow us to publish this work. We will also continue to search for an available replicative data set to confirm these studies with.

4) We have addressed the lack of training by including volunteer research aides in this years work.

a) Ms. Barbara Corso. Ms Corso is a graduate student from Columbia University. She has volunteered her time to work on assisting in the development of the T1D complication genetic database. The database allows for the power calculations and linkage analysis to be performed. She will continue to be involved in the statistical analysis for this project as she works towards attaining her PhD.

b) Ms. Cheryl Tang. Ms Tang is a high school student who volunteered over the summer of 2010. Ms. Tang was introduced to the project, discussions as to the importance of the research to the diabetic community and society as a whole were carried out. Ms. Tang spent a significant amount of her time compiling potential new contact information for the 6600 families in the Genetics Family Registry, including address, phone, email, and facebook/twitter accounts. Thru her efforts we were able to reach out to individuals for follow up that we had not been able to previously reach. Ms. Tang is interested in returning to volunteer next summer as well and shows promising interest in focusing on a career in research.

C. If the research project received an “unfavorable” rating, please indicate the steps that you intend to take to address the criteria that the project failed to meet and to modify research project oversight so that future projects will not receive “unfavorable” ratings.

Response: NA

D. Additional comments in response to the Final Performance Review Report (OPTIONAL):

Response: NA