Appendix 1: Ethical Approval from the Ethics Committee, UMMC

JAWATANKUASA ETIKA PERUBATAN
PUSAT PERUBATAN UNIVERSITI MALAYA
ALAMAT: LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA
TELEFON: 03-79494422 FAKSIMILI: 03-79545682

NAME OF ETHICS COMMITTEE/IRB:
Medical Ethics Committee, University Malaya Medical Centre

ADDRESS: LEMBAH PANTAI
59100 KUALA LUMPUR

PROTOCOL NO:

TITLE: Single Nucleotide Polymorphisms (SNPs) And Pharmacogenomics Of Diabetes Mellitus In Malaysia

PRINCIPAL INVESTIGATOR: Prof. Dr. Nor Azizan Abdullah

TELEPHONE: KOMTEL:

ETHICS COMMITTEE/IRB REFERENCE NUMBER:
6314

The following item [✓] have been received and reviewed in connection with the above study to be conducted by the above investigator.

✓ Borang Permohonan Penyelidikan
✓ Study Protocol
✓ Investigator Brochure
✓ Patient Information Sheet
✓ Consent Form
✓ Questionnaire
✓ Investigator(s) CV’s (Prof. Dr. Nor Azizan Abdullah)

and have been [✓]

✓ Approved
✓ Conditionally approved (identify item and specify modification below or in accompanying letter)
✓ Rejected (identify item and specify reasons below or in accompanying letter)

Comments:

i. Investigator is required to follow instructions, guidelines and requirements of the Medical Ethics Committee.

ii. Investigator is required to report any protocol deviations/violations through the Clinical Investigation Centre and provide annual/closure reports to the Medical Ethics Committee.

Date of approval: 30th January 2008

s.k Ketua
Jabatan Farmakologi

Timbalan Dekan (Penyelidikan)
Fakulti Perubatan, Universiti Malaya

Setiausaha
Jawatankuasa Penyelidikan Pusat Perubatan
Fakulti Perubatan, Universiti Malaya

PROF. LOOI LAI MENG
Chairman
Medical Ethics Committee

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Appendix 2: Presentation at WorldPharma 2010, Copenhagen, Denmark

(a) Programme book cover
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Title</th>
<th>Presenters</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:30 - 09:45</td>
<td>YI.01</td>
<td>Free Communication Presentation: Reversible allosteric inhibition of RGS GAP activity by small molecules reveals a general mechanism for inhibition of protein-protein interactions</td>
<td>Levi Blazer, (USA), B Greedy, S Husbands, R Neubig</td>
</tr>
<tr>
<td>09:45 - 10:00</td>
<td>YI.02</td>
<td>Free Communication Presentation: Intranasal delivery of mesenchymal stem cells to the brain</td>
<td>Lusine Danielyan, (Germany), R Schäfer, A van Ameln-Mayerhofer, F Bernhard, S Verleysdonk, M Buadze, B Proksch, GH Buniatian, M Schwab, WH Frey II, CH Gielert</td>
</tr>
<tr>
<td>10:00 - 10:15</td>
<td>YI.03</td>
<td>Free Communication Presentation: Functional and structural analysis of NO production by equine and naturally occurring estrogens</td>
<td>Ana Paula Dantas, (Spain), L Novensa, J Selent, M Pastor, K Sandberg, M Heras</td>
</tr>
<tr>
<td>10:15 - 10:30</td>
<td>YI.04</td>
<td>Free Communication Presentation: The impact of TCF7L2 variants on antidiabetic treatment regime selection: a Malaysian perspective</td>
<td>Muhammad H Haron, (Malaysia), R Pendek, Z Mohamed, Vl. Raj, NA Abdullah</td>
</tr>
<tr>
<td>10:30 - 10:45</td>
<td>YI.05</td>
<td>Free Communication Presentation: The ryanodine receptor – BKCa channel signaling in erectile function</td>
<td>Shreena Joshi, (UK), M Werner, M Nelson</td>
</tr>
<tr>
<td>10:45 - 11:15</td>
<td></td>
<td>COFFEE BREAK</td>
<td></td>
</tr>
<tr>
<td>11:15 - 11:30</td>
<td>YI.06</td>
<td>Free Communication Presentation: Lipocalin-2, an inflammatory adipokine, uncouples endothelial nitric-oxide synthase and enhances endothelial dysfunction caused by dietary obesity</td>
<td>Jacky TC Liu, (PR China), X A Xu, TW Mak, CF Liang, ICM Law, RYK Man, PM Vanhouffe, Y Wang</td>
</tr>
<tr>
<td>11:30 - 11:45</td>
<td>YI.07</td>
<td>Free Communication Presentation: Association between Pro12Ala polymorphism of the PPAR-gamma2 gene and insulin sensitivity in Iranian patients with type II diabetes mellitus</td>
<td>Azadeh Motavallian Naenei, (Iran), H Mirmohammad Sadeghi, M Amini, F Moazzen</td>
</tr>
<tr>
<td>11:45 - 12:00</td>
<td>YI.08</td>
<td>Free Communication Presentation: Co-administration of ondansetron reduces the analgesic efficacy of tramadol in postoperative pain in humans</td>
<td>Ana Carolina Pereira do Vale, (Portugal), MFSC Oliveira, JPFC Assunção, CF Ribeiro, FC Pereira</td>
</tr>
<tr>
<td>12:00 - 12:15</td>
<td>YI.09</td>
<td>Free Communication Presentation: Molecular predictors in dhfr and dhps genes and in vivo response to antifolate in Plasmodium falciparum malaria in Nigerian children</td>
<td>Ernest Tambo, (Benin), CT Happi, GO Gbotosho, OA Folani, A Sowunmi, MJ Oduola</td>
</tr>
<tr>
<td>12:15 - 12:30</td>
<td>YI.10</td>
<td>Free Communication Presentation: Identification of a small molecule inhibitor of the PICK1 PDZ domain that inhibits hippocampal LTP and LTD</td>
<td>Thor G Thorsen, (Denmark), KL Madsen, N Rebola, MA Rathje, V Anggono, A Bach, IS Moreira, N Stuhr-Hansen, T Dyhring, D Peters, T Beuming</td>
</tr>
</tbody>
</table>
Appendix 3: Presentation at 26th Scientific Meeting of MSPP 2012, Penang, Malaysia

(a) Cover of Programme Book
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(b) Poster schedule

<table>
<thead>
<tr>
<th>MSPP2012</th>
</tr>
</thead>
</table>

### List of late breaking abstracts

**Presentation time:** Day 3, 20th May 2012, 1200 pm-1300 pm  
(Serial number/Program number)

0104/P087  
THE EFFECTS OF BLOCKING TREM-1 ACTIVATION ON THE HISTOPATHOLOGICAL CONDITIONS OF MAJOR ORGANS DURING MALARIA INFECTION  
Afia Asyran Yusof1, Herni Taib2, Rusliza Basir1, Sabariah Mohd Noor2, Fauziah Othman1, Marzieh Jabbarzadeh1  
1Department of Human Anatomy, Faculty of Medicine & Health Sciences, Universiti Putra Malaysia, Malaysia, 2Department of Pathology, Faculty of Medicine & Health Sciences, Universiti Putra Malaysia, Malaysia

000/P068  
In Vivo Investigation of Geraniin's Effects on High-Fat Diet-Induced Metabolic Factors Associated with T2DM and Its Complications in Rodent Models  
Alexis Y. S. Chung1, Sunil Gurtu,1 Ton So Ha,1 Uma D. Palanisamy1  
1 School of Medicine and Health Sciences, Monash University, 46150, Bandar Sunway, Selangor, Malaysia.

0111/P089  
ON THE ANTI-TB ACTIVITY OF NANOPARTICULATE DRUG FORMS OF RIFAMPICIN AND GATIFLOXACIN.  
Renad Alyaudin1,2, Galina Mozhokina2, Jihad Maghrabi2, Ervand Oganesyan1  
1UTM, Malaysia, 2I.M. Sechenov MSMU, Russia

0014/P090  
DENTATIN-INDUCED APOPTOSIS IN PC-3 PROSTATE CANCER CELLS: ROLE OF REACTIVE OXYGEN SPECIES, NUCLEAR FACTOR-KB, MITOCHONDRIAL MEMBRANE POTENTIAL (ΔΨM) AND CYTOCHROME C  
Aqdren Zaini1, Ismail Adam Arbab1, Ahmad Bustamam Abu1, Mohd Aspoliah Sukari2, Rasedee Abdullah1, Syyam Mohan3, Suvitha Syam3, Manal Mohamed Elhassan Taha3, Siddig Ibrahim Abdewahab1, A Hamid A Hadi1  
1Cancer Research Laboratory, Institute of Bioscience, University Putra Malaysia, Malaysia, 2Department of Chemistry, Faculty of Science, University Putra Malaysia, Malaysia, 3Department of Pharmacy, Faculty of Medicine, University of Malaya, Malaysia, 4Department of Chemistry, Faculty of Science Building, University of Malaya, 50603 Kuala Lumpur, Malaysia

0092/P091  
TCF7L2 POLYMORPHISMS AND THEIR IMPACT ON DIABETES AND ITS TREATMENT  
Muhammad Huzaimi Haron1, Zahurin Mohamed1,2, Nor Azizan Abdullah1,2  
1Universiti Teknologi MARA, Malaysia, 2Universiti Malaya, Malaysia

Late Breaking Abstracts
P091

**TCF7L2 POLYMORPHISMS AND THEIR IMPACT ON DIABETES AND ITS TREATMENT**

Muhammad Huzaimi Hanon¹, Zahurn Mohamed¹,², Nor Azizan Abdullah¹,²

Univeriti Teknologi MARA, Malaysia, ¹Universiti Malaya, Malaysia

Single nucleotide polymorphisms (SNPs) in TCF7L2 predispose to type 2 diabetes (T2D). Furthermore, these SNPs have also been implicated in impairing treatment response with sulfonylureas. The SNPs are thought to impair the pancreatic beta cells’ response to glucose by interfering with incretin signalling, specifically GLP-1. Most oral antidiabetic agents modulate insulin secretion and sensitivity, which could be affected by the effect of the SNPs. The objective of our study was to observe the effect of the SNPs on T2D treatment in a Malaysian population. 483 Malaysian subjects were recruited from T2D patients attending UMMC during 2008 until 2010. DNA was extracted from their leukocytes and were genotyped for the SNPs in TCF7L2 (rs7903146, rs12255372, rs1196205, rs7901695 and rs4506559) using TaqMan SNP genotyping assays (Applied Biosystems) on StepOne real-time PCR system. Cross-sectional data regarding treatment regime and HbA1c levels were obtained from their UMMC medical records. Anthropometric and personal data were obtained via interviews. Subjects were divided into 2 broad treatment groups, depending on the presence or absence of insulin therapy. In subjects treated with oral antidiabetic agents only, there were no significant differences of HbA1c between the different genotypes of all the SNPs examined. In those treated with insulin, the variant TT genotype of rs4506559 was associated with a higher mean HbA1c compared to the AA genotype (p=0.03). In a subset of subjects treated with either metformin or sulfonylurea alone, there were no significant differences in HbA1c noted among the genotypes. However, the subset that was treated with the metformin-sulfonylurea combination demonstrated a significantly higher HbA1c in the heterozygous carriers of 4 of the SNPs examined after adjusting for age and BMI. Carriers of the variant genotypes in TCF7L2 are associated with higher HbA1c, which probably reflects increased T2D severity, rather than treatment failure.

P092

**INTERLEUKIN-18 ANTAGONISM IMPROVED HISTOPATHOLOGICAL CONDITIONS OF MALARIA INFECTION**

Marzieh Jabbarghan1, Hamid Tabib1, Rezaliza Basir2, Sabarina Mohd.Noor1, Fauziah Othman1, Mohammad Reza Rezai1, Mohd. Aliq Asryan Mohd. Yusof1

1Pharmacology Unit, Department of Medicine & Health Sciences, University Putra Malaysia, Malaysia, 2Department of Pathology, Faculty of Medicine & Health Sciences, University Putra Malaysia, Malaysia, 3Department of Medicine, Faculty of Medicine, Tehran University of Medical Sciences, Iran

Interleukin-18 (IL-18) is an important mediator that functions as an immune regulator and inducer of pro-inflammatory cytokines release and has diverse involvement in many disease conditions. Many studies have demonstrated the promising therapeutic potential of modulating IL-18 bioactivity especially in inflammatory related diseases. In this study, we investigated the effects of modulating IL-18 release on the histopathological conditions during malaria infection. Plasmodium berghei infection in ICR mice was employed as a model for malaria. Mice were inoculated intraperitoneally with 2 x 10⁷ parasitized red blood cells (0.2ml). Control uninfected mice received an equivalent volume and dilution of normal red blood cells. Treatment with IL-18 antagonist, rmIL-18Fc chimera (binding protein), were initiated on day 1 post infection and continued until day 4. On day 5, five major organs including the brain, liver, lungs, spleen and kidneys were collected from the animals and histopathological study was conducted on all the organs. Results showed that all tissues from the organs of malarial mice treated with rmIL-18Fc chimera were presented with significant improvement on their histopathological conditions as compared to the untreated malarial mice. From the results, it can be concluded that IL-18 is involved in mediating the pathological conditions associated with malaria infection and the host may benefit from its antagonism.

**Late Breaking Abstracts**
TCF7L2 polymorphisms: Their IMPACT on DIABETES and its TREATMENT

Muhammad Huzaimi Haron¹, Zahurin Mohamed² & Nor Azizan Abdullah²

¹Discipline of Pharmacology, Faculty of Medicine, Uitm
²Department of Pharmacology, Faculty of Medicine, Um

INTRODUCTION

Single nucleotide polymorphisms (SNPs) are common DNA variations occurring at a single nucleotide base pair (i.e., a cytosine to guanine switch). SNPs have been implicated in the differences in phenotypes observed between individuals of a similar biologic background, e.g., of similar ethnicity.

SNPs in TCF7L2 gene predispose to type 2 diabetes (T2D) in various populations globally (Grond et al., 2012; Palmer et al., 2011). Moreover, SNP rs7903146 was also found to be associated with type 2 diabetes in various populations (Grond et al., 2012; Palmer et al., 2011). Furthermore, these SNPs have also been implicated in imparting treatment response with sulfonylureas (Shoham et al., 2011).

Most oral antidiabetic agents modulate insulin secretion and sensitivity, which could be affected by the effect of the SNPs.

The objective of our study was to observe the effect of the SNPs on T2D treatment in a Malaysian population.

RESULTS

A total of 483 Malaysian subjects were recruited from patients with type 2 diabetes that attended UM taking medications between 2006 and 2012. DNA was extracted from their leukocytes and were subsequently genotyped for the SNPs in TCF7L2 (rs7903146, rs12255373, rs1119205, rs7901645 and rs4126853) using Taqman SNP genotyping assays (Applied Biosystems) on the Applied Biosystems 7500 Fast Real-Time PCR system. Cross-sectional data regarding treatment regime and HbA1c levels were obtained from their UM’s medical records. Anthropometric and other data were obtained via interviews.

Subjects were divided into 2 broad treatment groups, depending on the presence or absence of insulin therapy in their regimen.

Table 1: Characteristics of subjects according to various treatment regimes

<table>
<thead>
<tr>
<th>GENOTYPE</th>
<th>Metformin only</th>
<th>Metformin+SU</th>
<th>Other combo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>7.06±1.83</td>
<td>7.04±1.85</td>
<td>7.42±1.77</td>
</tr>
<tr>
<td>CG</td>
<td>7.02±1.79</td>
<td>7.04±1.86</td>
<td>8.14±1.49</td>
</tr>
<tr>
<td>GG</td>
<td>6.95±1.75</td>
<td>6.96±1.80</td>
<td>6.91±1.35</td>
</tr>
</tbody>
</table>

Adjusted p-value (A): 0.81 (0.81) 0.0002 (0.0002)

Table 1: Characteristics of subjects according to various treatment regimes

<table>
<thead>
<tr>
<th>GENOTYPE</th>
<th>Mean HbA1c (mmol/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>7.06±1.83</td>
</tr>
<tr>
<td>CG</td>
<td>7.02±1.79</td>
</tr>
<tr>
<td>GG</td>
<td>6.95±1.75</td>
</tr>
<tr>
<td>T1</td>
<td>7.03±1.93</td>
</tr>
<tr>
<td>T2</td>
<td>7.03±1.93</td>
</tr>
<tr>
<td>T3</td>
<td>6.90±1.80</td>
</tr>
</tbody>
</table>

Figure 1: Mean HbA1c compared across genotypes, in various oral antidiabetic treatment regimes.

CONCLUSION

Carriers of the variant genotypes in TCF7L2 are associated with higher HbA1c, which probably reflects increased T2D severity rather than treatment failure. The observed trend in the combinations utilizing newer antidiabetic agents warrants further detailed investigations.

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Appendix 4: Sample of subject’s Consent Form

(a) English form

CONSENT BY PATIENT FOR CLINICAL RESEARCH

I, ................................................................., MyKAD no.............................................
(Name of the patient)
of ...............................................................
(Address)
hereby agree to take part in the clinical research (clinical study) specified below:

Title: Single Nucleotide Polymorphisms (SNPs) and Pharmacogenomics of Diabetes Mellitus in Malaysia

The nature and purpose has been explained to me by DR MUHAMMAD HUZAIMI BIN HARON
and interpreted by .................................................................
(Name and designation of interpreter)
to the best of his/her ability in ............................................ language/dialect.

I have been told about the nature of the clinical research in terms of methodology, possible adverse effects and complications (as per patient information sheet). After knowing and understanding all the possible advantages and disadvantages of this clinical research, I voluntarily consent of my own free will to participate in the clinical research specified above.

I understand that I can withdraw from this clinical research at any time without assigning any reason whatsoever and in such a situation shall not be denied the benefits of usual treatment by the attending doctors.

Date: ........................................... Signature or thumbprint: ...........................................
(Patient)

IN THE PRESENCE OF

Name: .................................................................
MyKAD no: ................................................................. Signature: .................................................................
(Witness for signature of the patient)
Designation: .................................................................

I confirm that I have explained to the patient the nature and purpose of the above mentioned clinical research.

Date: ........................................... Signature: .................................................................
(Attending doctor)

CONSENT BY PATIENT FOR CLINICAL RESEARCH

RN Name
Sex Age
Unit
Saya, …………………………………………………………………………………………………, No. MyKAD ………………………………………
(Nama pesakit)
beralasam ……………………………………………………………………………………………………………………………
(Fimmat)
dengan ini bersetuju menyertai penyelidikan klinikal (pengajian klinikal) berikut:

Tajuk: Perbezaan Satu Nukleotida dan Farmakogenomik Penyakit Diabetes Mellitus di Malaysia
yang mana sifat dan tujuannya telah diterangkan oleh DR MUHAMMAD HUZAIMI BIN HARON
mengikut terjemahan oleh …………………………………………………………………………………………………………………
yang telah diterjemahkan kepada saya dengan sepenuh kemampuan dan kebolehan dalam bahasa/loghat
………………………………………………………………………………………………………………………………………………
Saya telah diberitahu bahawa dasar penyelidikan klinikal dalam metodologi, risiko dan komplikasi (mengikut kertas maklumat pesakit). Setiap mengetahui dan memahami semua kemungkinan kebaikan dan keburukan penyelidikan klinikal ini, saya merelakan/mengizinkan sendiri menyertai penyelidikan klinikal tersebut di atas.

Saya faham bahawa saya boleh menarik diri dari penyelidikan klinikal ini pada bila-bila masa tanpa memberi sebarang alasan dalam situasi ini dan tidak akan terkecuali dari doktor yang merawat.

Tarikh: ………………… Tandatangan / Cap ibu jari: ……………………………
(Pendekat)

DI HADAPAN

Nama: …………………………………

No. MyKAD: ………………………………… Tandatangan: …………………………………
(Sokai untuk tandatangan pesakit)

Jawatan: ……………………………

Saya sahkan bahawa saya telah menerangkan kepada sifat dan tujuan penyelidikan klinikal tersebut di atas.

Tarikh: ………………………………… Tandatangan: …………………………………
(Doktor yang merawat)

KEIZINAN OLEH PESAKIT UNTUK
KAJIAN KLINIKAL

RN
Nama
Jantina
Umur
Unit
Appendix 5: Subject Data Form

(a) Page 1

SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs) and PHARMACOGENOMICS OF DIABETES MELLITUS IN MALAYSIA

Research by Department of Pharmacology, Faculty of Medicine UM F5122/2008A

PERSONAL & CONTACT INFORMATION

Name

MyKAD no. Ethnicity Sex

Address

Phone no. Home Handphone

FAMILY HISTORY

Familial Ethnicity

Father Paternal Grandfather Paternal Grandmother

Mother Maternal Grandfather Maternal Grandmother

Father Paternal grandparents Paternal siblings

Mother Maternal grandparents Maternal siblings

DIABETES MELLITUS HISTORY

Duration (years) and/or Year diagnosed

Diabetic Medications

Retinopathy Cardiovascular

Neuropathy Peripheral vascular

Nephropathy
### Social History

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Alcohol Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td>Current drinker</td>
</tr>
<tr>
<td>Amount per day</td>
<td>Unit per week</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>Duration (years)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>Ex-drinker</td>
</tr>
<tr>
<td>Duration (years)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exercise Status</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency per week (days)</td>
<td>Duration per day (hours)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of exercise (tick where appropriate, and state amount in minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking</td>
</tr>
<tr>
<td>Swimming</td>
</tr>
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</table>

### Anthropometric Information

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>BMI</th>
<th>Waist (cm)</th>
<th>Hip (cm)</th>
<th>WHR</th>
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<td></td>
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</table>

<table>
<thead>
<tr>
<th>Blood pressure / mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

### Biochemical Information

<table>
<thead>
<tr>
<th>FBG</th>
<th>HbA1c</th>
<th>*2H PP Glu</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TC</th>
<th>HDL</th>
<th>LDL</th>
<th>TG</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sulfonylurea concentration(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
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<table>
<thead>
<tr>
<th>Allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Appendix 6: Subject Information Sheet

(a) English, page 1

**SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs) and THE PHARMACOGENOMICS OF DIABETES MELLITUS IN MALAYSIA**

**INTRODUCTION**

Diabetes mellitus (aka diabetes, kencing manis) is a global burden. Diabetes have shortened life-span due to multiple unpleasant and dangerous complications (coronary heart disease, kidney disease and blindness), ultimately leading to premature death from these problems. To date, there is no way of knowing who will develop diabetes, even though there are various factors related to it, i.e. a diet that is high in sugar coupled with a sedentary lifestyle.

Thousands of people in Malaysia are suffering from diabetes. Besides modifying their lifestyle to include a reduction in sugar intake from foods and exercising regularly, sufferers are also given antidiabetic medications to help the body use sugar more efficiently or by reducing the level of sugar in the diabetic’s blood. There are various types of antidiabetic medications available today that are capable of achieving the objective, but it has been shown that not all diabetics respond to treatment as well as it is hoped. Others will develop serious side effects even with the small doses given to them.

With the recent completion of the Human Genome Project in 2003, in which the genetic make-up of the human species were mapped thoroughly, it is now possible to look at the genetic cause(s) of 2 problems: 1) the genes predisposing an individual to diabetes, and 2) the genes responsible for treatment failure with antidiabetic medications. Currently there are a number of genes already identified in various countries and ethnic groups that could lead to the development of diabetes, as well as treatment failure with antidiabetic medications. In our research project, we want to examine the genes responsible for these problems in our multicultural Malaysian population. This is called ‘pharmacogenomics’, a branch of science dealing with the effects of genetic variance on how the human body interacts with medications.

**PURPOSE OF STUDY**

To examine the genetic make-up of the Malaysian population, specifically looking for:

1. Variants in common genes that could predispose to development of diabetes, and
2. Variants in common genes involved in the ‘processing’ of medications as it passes through our body, linking certain variants to failure to respond to antidiabetic medications.

**WHO SHOULD NOT ENTER THIS STUDY?**

Participation in this study is open to all individual, whether they are diabetic or not. However, to limit certain types of error in our analysis, certain factors (if present) could jeopardize the validity of our study. Therefore, these individuals could not be considered as participants:

1. Those diagnosed of having the type of diabetes which requires insulin injections rather than taking antidiabetic medications alone,
2. Those already having signs or symptoms of coronary heart disease or kidney disease,
3. Those that have abnormalities in the levels of liver enzymes,
4. Healthy individuals that have a history of diabetes in their family, or
5. Healthy individuals that has a fasting level of glucose of more a certain level (>6.1 mmol/L).

**WHAT WILL BE THE BENEFITS OF THE STUDY:**

[Signatures and dates]
a) **TO YOU AS THE SUBJECT?**

To the healthy volunteers, you will have the chance to know whether you have the genes that can predispose to the development of diabetes.

To those with diabetes, you will know why certain antidiabetic medications fail to lower your blood sugar levels and whether you are more suited to certain types of antidiabetic medication.

b) **TO THE INVESTIGATOR?**

We will have the chance to document the frequency of certain types of genetic variants that can predispose to diabetes in the Malaysian population, and thus suggest an appropriate screening programme to detect those with these genetic variants and give proper advice in terms of prevention of diabetes to them. With detection of genetic variants of people who would respond differently to common antidiabetic medication, we can then develop an antidiabetic medication regime tailor-made just for them, i.e. “personalised medication”.

**PROCEDURES TO FOLLOW**

Upon agreement of participation signed by you, your bodily parameters (blood pressure, weight, height, waist circumference and hip circumference) will be measured. After that, a small amount of blood (10mls) will be withdrawn from your arm after an overnight fast and sent for various metabolic testing (level of sugar and level of insulin; the hormone responsible for controlling sugar in the blood) as well as DNA and genetic testing. Certain groups of individuals will also undergo an oral glucose tolerance test (OGTT) – where the body’s response to a sudden increase in the level of glucose (sugar) in the blood is determined.

**WHAT ARE THE POSSIBLE DRAWBACKS?**

Besides the time spent and some discomfort from the blood-taking procedure, there are absolutely no drawbacks as there are no medications involved that would lead to unpleasant side effects.

**CAN I REFUSE TO TAKE PART IN THIS STUDY?**

Absolutely, as participation is voluntary and subject to you signing a consent/agreement form. Even after signing the agreement, you can still withdraw from participating if you feel uncomfortable with any aspect of the study. However, as the findings will benefit not just you, but the whole Malaysian population, and the discomfort is minimal, why would you want to withdraw?

**WHO CAN I CONTACT IF I HAVE ADDITIONAL QUESTIONS DURING THE COURSE OF THIS STUDY?**

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PERBEZAAN SATU NUKLEOTIDA dan FARMAKOGENOMIK DIABETES MELLITUS DI MALAYSIA

PENGENALAN

Penyakit kencing manis (juga dikenali sebagai diabetes mellitus atau diabetes) membebanakan seluruh masyarakat dunia. Sejauh yang kita tahu, penyakit ini amat cepat meningkat dan menyebabkan pelbagai keselamatan daripada penyakit tersebut (penyakit jantung koroner, penyakit buah pinggang dan kebutaan) yang akhirnya akan membawa kepada maut pada usia yang agak muda. Pada masa kini, walaupun terdapat beberapa faktor yang diikatkan dengan risiko mendapat kencing manis seperti perubahan gaya hidup dan kecenderungan aktiviti fizikal, tiada cara mutlak untuk mengetahui siapa yang mempunyai risiko yang lebih tinggi untuk mendapat kencing manis dikalangan kita.

Beliau-ribu pesakit yang menghidapi penyakit kencing manis di Malaysia diberi ubat antidiabetik untuk membantu badan mereka mengatur gula di dalam darah dengan lebih berkesan dan untuk mengurangkan paras gula di dalam darah. Diapting itu, mereka juga disarankan untuk mengurangkan pengambilan gula di dalam makanan dan bersenam selalu. Terdapat pelbagai jenis ubat antidiabetik, namun begitu kesan ubat-ubatan tersebut tidaklah berbeza-beza dikalangan para pesakit kencing manis. Ada yang memerlukan penanganan yang teruk walaupun diberb os yang kecil, ada pula yang tidak dapat menggantikan paras gula mereka walaupun dos yang diberi sudah melebihi tahap yang memerlukan.


TUJUAN MELAKUKAN KAJIAN

Untuk mengkaji baka/gen penduduk Malaysia, melihat secara spesifik pada:
1. Perbezaan baka/gen yang menyebabkan seseorang lebih mudah mendapat kencing manis, dan
2. Perbezaan baka/gen yang terlibat dalam 'pemprosesan' ubat-ubatan di dalam tubuh, dan mengetahui perbezaan tertentu kepada kegagalan rawatan dan unik anti-diabetik.

SIAPAKAH YANG TIDAK PATUT MENYERTAI KAJIAN INI?

Semua individu, tidak kira penghidap kencing manis atau tidak, adalah dijempit menyerai kajian ini. Walau bagaimanapun, untuk mengurangkan masalah semasa pengamalan data nanti, terdapat beberapa faktor yang mungkin akan mengurangkan keselamatan kajian ini. Oleh yang demikian, golongan di bawah tidak disaibkan sebagai peserta:
1. Yang menghidapi jenis kencing manis yang memerlukan cuci-cuci insulin,
2. Yang sudah ada gejala atau tanda-tanda penyakit jantung koroner atau penyakit buah pinggang,
3. Yang mempunyai masalah / kehamilan pada fungsi hati,
4. Sihat tetapi ada sebarang kencing manis di dalam keluarga mereka, atau
5. Sihat tetapi paras gula dalam darah semasa berpuasa melebihi tahap tertentu (>6.1 mmol/L)

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APAKAH KEBAJikan MENYERTAI KAJIAN INI KEPADA:

1. ANDA SEBAGAI SUBJEK KAJIAN?
Sukarelawan yang sihat akan dapat mengetahui risiko mereka untuk mendapat penyakit kencing manis berdasarkan analisa baka/gen tertentu.
Para penghidap kencing manis akan dapat memahami kenapa ada jenis ubat antidiabetik yang tidak dapat mengurangkan paras gula mereka, dan ubat jenis mana yang sesuai dengan baka/gen mereka.

2. KAMI SEBAGAI PENYIASAT?
Kami akan dapat melihat kekesalan perbezaan baka/gen yang memudahkan seseorang itu mendapat kencing manis dalam populasi penduduk Malaysia, dan seterusnya mencadangkan langkah-langkah untuk mengesahkan individu yang membaun baka/gen tersebut untuk kaunseling cara hidup sihat, untuk mengelakkan kencing manis. Disamping itu, apabila perbezaan baka/gen yang menentukan kesan rawatan dengan ubat antidiabetik sudah diketahui, kami dapat mencipta struktur rawatan yang lebih efektif, yang sesuai dengan baka/gen individu masing-masing, iaitu "ubatan individu atau personalized medication".

LANGKAH-LANGKAH YANG PERLU DIKUTI
Apabila anda telah menandatangani surat perjanjian untuk menyertai kajian ini, ukuran badan (berat, tinggi, ukuralit pinggang, ukuralit pinggul) dan tekanan darah akan diambil. Selepas itu, sedikit darah akan diambil (10ml) daripada lengan anda setelah berpuasa semalam untuk kajian metabolik (paras gula dan paras insulin, iaitu hormon yang menang paras gula dalam darah) dan kajian DNA dan genetik. Beberapa kumpulan individu juga akan diminta menjalani ujian kekenaan gula perukakan (oral glucose tolerance test, OGTT) – mengkaji tindakbalas badan kepada kenaikan paras gula dalam darah secara mendadak.

ADAKAH TERDAPAT SEBARANG KEBURUKAN JIKA MENYERTAI KAJIAN INI?
Oleh kerana kajian ini tidak melibatkan pemberian ubat-ubatan yang boleh mendatangkan kesan sampingan, keburukan yang ada hanya keluangan masa anda dan sedikit ketidakselesaan semasa pengambilan darah.

BOLEHKAH Saya Menolak Untuk Menyertai KAJIAN INI?
Sudah tentu boleh, kerana penyerapan dalam kajian ini adalah secara sukarela dan setelah anda menandatangani surat kebenaran/perjanjian. Walaupun setelah menandatangani, anda masih terasa ragu-ragu atau tidak selesa dengan kajian ini, kami tidak akan menghalang anda untuk memutus diri. Akan tetapi, penemuan yang baik diperolehi dari pada kajian ini bukan sahaja akan menguntungkan anda, malah sebahagian rakyat Malaysia, sudah tentu anda tidak mahu menarik diri boleh?

SIAPA YANG SAYA BOLEH HUBUNGI UNTUK MAKLUMAT LANJUT SEMASA KAJIAN INI DIJALANKAN?

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