Yustinus Gugus Wahyu Endardiyanto

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Original Article

The mutant of rs2075604 in *STK11* improves HDL-c levels among newly diagnosed type 2 diabetes mellitus patients

[El mutante de rs2075604 en *STK11* mejora los niveles de HDL-c entre los pacientes con diabetes mellitus tipo 2 recién diagnosticada]

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Abstract

Context: Type 2 diabetes mellitus (T2DM) patients tend to have lipid abnormalities, thus elevating the risk of complications and mortality. Early detection using a genomic approach could help identify the abnormality of lipid profiles so that it could reduce those burdens. A previous study found a high frequency of mutants in the rs2075604 as the intron area in the *STK11* gene.

Aims: To analyze the effect of rs2075604 related to lipid abnormalities in newly diagnosed T2DM patients.

Methods: This present study conducted a cross-sectional study in the ten public healthcare facilities in Sleman, Yogyakarta. The genetic variants were detected using PCR-RFLP methods. A total of 130 patients who had to consume antidiabetic oral for three months participated in this study.

Results: This study revealed that the mutant variant dominated in this population at 61.5%. Mutant genotype, mutant allele, and dominant model reduce the risk of low HDL (OR = 0.33, 95% CI = 0.11-0.99; OR = 0.46, 95% CI = 0.24-0.90; OR = 0.33, 95% CI = 0.12-0.96; respectively). The improvement of low HDL risk by the mutant allele was confirmed through an adjusted model (OR = 0.47, 95% CI = 0.23-0.98). The mutant allele only influenced high LDL risk in the non-adjusted model (OR = 2.22, 95% CI = 1.02-4.82), but it did not found in other models.

Conclusions: The mutant of rs2075604 has a protective role in low HDL-c risk in Indonesia. However, further study is required to observe the effect on LDL-c.

Keywords: rs2075604; *STK11*; lipid profiles; type 2 diabetes mellitus.

Resumen

Contexto: Los pacientes con diabetes mellitus tipo 2 (DMT2) tienden a presentar anomalías lipídicas, lo que eleva el riesgo de complicaciones y mortalidad. La detección precoz mediante un enfoque genómico podría ayudar a identificar la anormalidad de los perfiles lipídicos, de modo que podría reducir esas cargas. Un estudio anterior halló una alta frecuencia de mutantes en el rs2075604 como zona del intrón en el gen *STK11*.

Objetivos: Analizar el efecto del rs2075604 relacionado con las anomalías lipídicas en pacientes con DMT2 recién diagnosticados.

Métodos: El presente estudio llevó a cabo un estudio transversal en los diez centros sanitarios públicos de Sleman, Yogyakarta. Las variantes genéticas se detectaron mediante métodos PCR-RFLP. Participaron en este estudio 130 pacientes que debían consumir antidiabéticos orales durante tres meses.

Resultados: Este estudio reveló que la variante mutante dominaba en esta población con un 61,5%. El genotipo mutante, el alelo mutante y el modelo dominante reducen el riesgo de HDL bajo (OR = 0,33, IC 95% = 0,11-0,99; OR = 0,46, IC 95% = 0,24-0,90; OR = 0,33, IC 95% = 0,12-0,96; respectivamente). La mejora del riesgo de HDL bajo por el alelo mutante se confirmó mediante un modelo ajustado (OR = 0,47; IC 95% = 0,23-0,98). El alelo mutante sólo influyó en el riesgo de LDL alto en el modelo no ajustado (OR = 2,22; IC 95% = 1,02-4,82), pero no se encontró en otros modelos.

Conclusiones: El mutante del rs2075604 tiene un papel protector en el riesgo de HDL-c bajo en Indonesia. Sin embargo, se requieren más estudios para observar el efecto sobre LDL-c.

Palabras Clave: rs2075604; STK11; perfiles lipídicos; diabetes mellitus tipo 2.

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INTRODUCTION

Indonesia is ranked 5th out of 10 countries with the most diabetic patients (Sun et al., 2022). Diabetes mellitus is the highest cause of death, and the prevalence of DM has increased by 1.6% in Indonesia (Kementerian Kesehatan, 2020). Type 2 diabetes mellitus (T2DM) is the major type of diabetes found in Indonesia, and the Sleman District had the highest number of T2DM in the Province of DI Yogyakarta. Therefore, this present study conducted a study in public health care in the Sleman District (Dinas, 2020).

On the other hand, several studies revealed that type 2 diabetes mellitus (T2DM) patients tend to have an abnormality of lipid profiles, significantly enhanced triglycerides serum, and reduced HDL-c (Hussain et al., 2017; Rusdiana et al., 2020). Lipid profile abnormalities are the major risk factors to increase complications and mortality due to cardiovascular disease (CVD) among T2DM patients (Ikhsan et al., 2022; Jayakumari et al., 2020; Suhadi et al., 2017). Furthermore, CVD accompanied by T2DM increases mortality risk, and the evidence was reported higher in South East Asia (Ma et al., 2022). Therefore, prevention detection and strategies are required to reduce lipid abnormalities and minimize CVD risk.

Genetic factors have been confirmed involving the susceptibility of T2DM and its complications. The combined analysis of genetic and environmental factors could predict the risk of lipid abnormalities in T2DM patients (Dietrich et al., 2019; Li et al., 2020). Over the past three decades, most studies in pharmacogenomics have increased surprisingly. Genome-wide association study (GWAS) assured that genetic variation in several genes induces lipid abnormalities in T2DM patients, including *APOB, HNF4, LPL, ABCA1, ABCC8, PRKAA2, SCARB1,* and *ADIPOQ* (Cai et al., 2017; Nicchio et al., 2021; Vardarlı et al., 2017). In addition, several studies have performed to detect any association between genetic and CVD risk (Virginia et al., 2021; 2022). Eventually, the non-coding region of single nucleotide polymorphism (SNP) could be a predictor (Witka et al., 2019). Accordingly, the pharmacogenomic approach should be considered a tool for early detection.

One gene which has yet to be explored is *STK11*. *STK11* gene, encoding liver kinase B1 (LKB1), is located on chromosome 19:1218524 (GRCh38). The selection of SNP rs2075604 was due to the high mutant of 46.6% in Vietnamese, a region of South East Asia. However, there has been no publication regarding the frequency of *STK11* rs2075604 mutations in Indonesia. SNP rs2075604 is the intron part of *STK11*. The results of research conducted by Kumari et al. (2022) and Rose (2018) stated that genetic variations in introns could regulate gene expression and affect splicing so that it has a probability of disrupting protein expression. The existence of this SNP can have the potential affected to LKB1 activity. Thus it will also affect abnormality lipid profiles.

Previous studies have confirmed several SNP contributing to enhancing lipid abnormality in T2DM. However, *STK11* rs2075604 has only been observed in the Chinese population related to metformin efficacy (Li et al., 2017). This was the first study reporting the influence of rs2075604 on lipid profile abnormality, especially in Indonesia. Detection of *STK11* rs2075604 mutations could be a part of preventing action for improving ASCVD risk since this recent study was observing newly diagnosed T2DM patients. Therefore, the present study aimed to explore the effect of variant rs2075604 in *STK11* with an abnormality of lipid profiles in T2DM patients.

MATERIAL AND METHODS

The study conducted a cross-sectional study design. The protocol for genetic variant identification has been reviewed and approved by the Ethics Committee of Universitas Respati Yogyakarta (protocol number: 115.3/FIKES/PL/VII/2022). All participants have signed informed consent in the previous study and approved by the Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine, Public Health, and Nursing Universitas Gadjah Mada – Dr. Sardjito General Hospital, Indonesia. The research conducted in ten primary health care in Yogyakarta, Indonesia. This study used a convenience sample of 130 participants based on inclusion and exclusion criteria. The inclusion criteria were newly diagnosed T2DM patients (according to American Diabetes Association (ADA) criteria (American Diabetes Association, 2020), who consumed metformin, sulfonylurea, and/or acarbose at least three months, were 18-70 years old, and had national health insurance. Participants who were prescribed insulin, DPP-IV inhibitor, SGLT-2 inhibitor, and/or GLP-1 receptor agonist were excluded. Patients diagnosed cardiovascular diseases and cancer also excluded.

Clinical parameters measurement

The nutritionist measured body weight, height, and waist circumference. A nurse measured blood pressure. Fasting blood glucose (FBG), HbA1c, total cholesterol, HDL-c, LDL-c, and triglycerides were examined after participants fasted during 8-10 hours. FBG was measured using the hexokinase method (Freeman, 2014). HbA1c and lipid profiles (total cho-

lesterol, HDL-c, and triglycerides) were assayed using high-performance liquid chromatography (Cobas D-10 and Cobas C311, respectively) (Kahena et al., 2013; Moustapha et al., 2020). The present study applied Friedewald formulation to calculate the LDL-c level (Friedewald et al., 1972). Data of family history of T2DM and smoking status were collected from the questionnaire.

Isolation of DNA and SNP rs2075604 detection

Peripheral blood samples were collected from participants in an EDTA tube. DNA was isolated according to the kit protocol (Geneaid® Blood DNA Mini K) and stored at -70°C until the genotyping procedure was done (Yamagata et al., 2021). The SNP rs2075604 was identified using the dbSNP database as the National Centre of Biotechnology Information (NCBI, 2022). The primer pair of rs2075604, which was designed for this study, was: forward (5'-GTACGCCACTTCCACAGG-3') and reverse (5'-AAAGGGACTTGACACCCCAC-3') from Macrogen®. The PCR and restriction fragment length polymorphism (RFLP) was done to detect *STK11* rs2075604. The final volume for the PCR reaction is 25 µL. The thermal cycler for a PCR was as follows: denaturation at 95°C, annealing at 57.5°C, and extension at 72°C. BstUI as a restriction enzyme (Thermoscientific®) at CG/CG was used to detect the rs2075604. The results of SNP 2075604 are presented in Fig. 1.

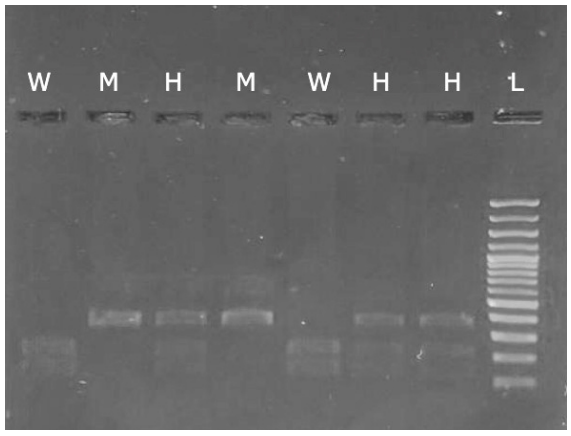

Figure 1. The results of electrophoresis related to SNP 2075604 detection through PCR-RFLP method.

W: wildtype homozygote (GG); M: mutant homozygote (TT); H: heterozygote (GT); L: ladder 100 bp.

Statistical analysis

The profiles of participants' characteristics are presented as n (percentage) for categorical data and mean ± SD for numerical data. The correlation of glycemia indicator and lipid profiles was analyzed using Pearson. Chi-square tests were performed to calculate Odd Ratio (OR) and 95% CI (confidence interval) describing the association between rs2075604 and lipid profile abnormality. For the association analysis, HDL-c below 40 mg/dL, LDL-c over 130 mg/dL, triglycerides below 150 mg/dL, and/or total cholesterol over 200 mg/dL were considered as a high-risk group. An adjustment for those factors was analyzed using logistic regression to reduce confounding factors, including age, gender, BMI, waist circumstances, blood pressure, HbA1c level, fasting plasma glucose level, and smoking status. Significant statistically were defined through $p<0.05$. All statistical analysis using SPSS.

RESULTS

Characteristics of 130 newly diagnosed T2DM patients with regard to all demographic and clinical measurements are shown in Table 1. All participants received diabetes therapy for three months after being diagnosed. Since only newly diagnosed patients were recruited in this study and related to exclusion criteria, there were no patients diagnosed with cardiovascular diseases and cancer. Females, with no family history of T2DM, and passive smokers are dominant among participants. The majority patients tend to be obese according to BMI classification in the Asian population. As descriptive analysis results, the mean of blood pressure, total cholesterol, HDL-c, LDL-c, and triglyceride levels were in the standard criteria, relatively.

A total of mutant genotypes among participants reached 61.9%. In detail, TT = 61.6%, GT = 19.2%, and GG = 19.1%. Fig. 2 summarizes the distribution of high-risk vs. normal lipid profiles in the genotype of rs2075604. All lipid profiles have found a higher percentage as normal criteria in each rs2075604 genotype. Table 2 presents a correlation analysis of clinical data between the hyperglycemia indicator and lipid profile level. The most interesting finding in Table 2 is that increasing the HbA1c level could reduce LDL-c significantly statistically ($r = -0.20$, $p = 0.02$). All lipid profiles appeared to be unaffected by FBG.

The association of rs2075604 and lipid profile abnormalities is presented in Table 3, either in crude/non-adjusted odds ratio or adjusted odds ratio. TT as mutant homozygote genotype, T allele as mutant allele, and dominant model had significant association statistically with low HDL-c level (OR = 0.33, 95% CI = 0.11-0.99, $p = 0.049$; OR = 0.46, 95% CI = 0.24-0.90, $p = 0.02$, respectively). Interestingly, after adjusting by confounding factors, only the T allele was associated with low HDL-c (AOR = 0.47, 95% CI = 0.23-0.98, $p = 0.04$). Furthermore, there was a statistically significant association of rs2075604 with a low-HDLc level in the dominant model without adjust-

ment by confounder. The presence of the TT + GT genotype demonstrated a lower risk of low HDL-c (TT + GT *vs.* GG: OR = 0.33, 95%CI = 0.12-0.96, p = 0.04).

In model 1, this study found that the T allele significantly increased high LDL-c risk statistics (OR = 2.22, 95% CI = 1.02-4.82, p = 0.04). However, after adjusting for the confounder, there was no significant association between rs2075604 and high LDL-c (p>0.05). This research could not find any significant association between rs2075604 and high total cholesterol and triglyceride levels (p>0.05).

DISCUSSION

STK11 is a gene encoding LKB1 that plays a vital role in gluconeogenesis in the liver. LKB1 induces AMPK activation and thus mediates glucose homeostasis in the part of gluconeogenesis processed (Jeon, 2016). LKB1 could suppress amino-acid-driven gluconeogenesis (Just et al., 2020) and affect glucose levels and lipid profiles accordingly. The conformational changes of LKB1 caused by mutation might direct increase blood glucose levels and lipid profiles (Sokolova et al., 2019; Zhang et al., 2019). Recently, several polymorphisms of *STK11* has detected, including rs2075604, rs9282860, and rs8111699. *STK11* genetic variants are related to T2DM risk, metformin effectivity, and cancer (Dawed et al., 2016; Keshavarz et al., 2008; Li et al., 2017).

The previous study on Spanish girls with hyperinsulinemia revealed that *STK11* rs8111899 influences insulin sensitivity and metformin efficacy (López-Bermejo et al., 2010). *STK11* rs2075604 has previously studied metformin efficacy, and it was declared that rs2075604 had a significant association with metformin efficacy. GT carriers could achieve better efficacy compared to wildtype (Li et al., 2017). Thus, the present research investigate the effect of genetic variants in the rs2075604 and lipid profiles. From the literature study discovering, this is the first study that investigated the effect of *STK11* rs2075604 genetic variants and lipid profile abnormalities in Indonesia T2DM patients. In addition, this recent study restricts any confounding factors, especially T2DM duration and therapeutic, because this study only recruited newly diagnosed T2DM in three months.

The participants tend to have normal lipid profiles, which might be backgrounded from new T2DM patients. However, in each genotype, more than 10% of patients had abnormal lipid profiles. Awareness of this condition should be increased because abnormality of lipid profiles tends to be found in T2DM patients. Thus, these lipid abnormalities increase ASCVD risk and mortality (Rusdiana et al., 2020; Suhadi et al., 2017). The pharmacogenetic approach could help to predict the risk of lipid abnormalities among T2DM patients; accordingly, healthcare professionals could give appropriate and personalized therapy.

Table 1. The profiles of participant's characteristics.

Characteristics	n (%) / mean ± SD
Gender (male)	36 (27.7)
Age (years old)	56.31 ± 44.68
BMI (kg/m^2)	25.22 ± 3.82
Waist circumstances (cm)	88.05 ± 9.44
Blood pressure (mmHg) (systolic/diastolic)	125.52 ± 11.57 / 79.65 ± 6.47
Total cholesterol (mg/dL)	185.90 ± 33.93
HDL-c (mg/dL)	47.35 ± 8.48
LDL-c (mg/dL)	110.65 ± 31.58
Triglycerides (mg/dL)	139.28 ± 83.58
HbA1c (%)	8.12 ± 1.31
FBG (mg/dL)	143.98 ± 39.05
Family history (yes)	16 (12.3)
Smoking status (active smoker)	20 (15.4)
Antidiabetic treatment	
Monotherapy metformin	94 (72.3)
Metformin+glimepiride	36 (27.7)

BMI: body mass index, HDL-c: high density lipoprotein cholesterol, LDL-c: low density lipoprotein cholesterol; FBG: fasting blood glucose.

Table 2. The correlation of glycemia indicators (HbA1c and fasting blood glucose) and lipid profiles.

Glycemia indicators	Total cholesterol		HDL-c		LDL-c		Triglycerides	
	r	p	r	p	r	p	r	p
HbA1c	-0.15	0.09	-0.03	0.75	-0.20	0.02*	0.08	0.35
FBG	-0.04	0.66	-0.11	0.21	-0.10	0.24	0.17	0.05

FBG: fasting blood glucose. *p<0.05

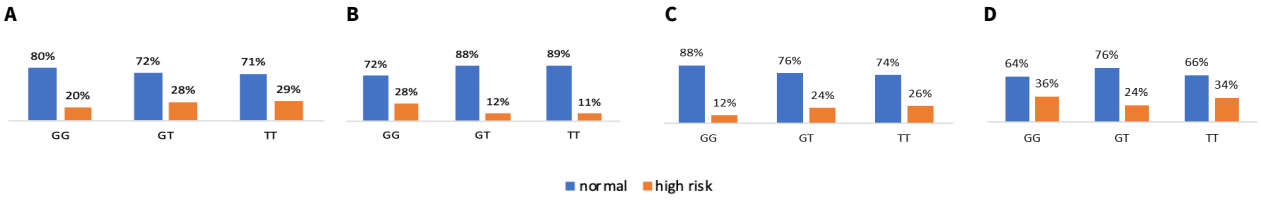

Figure 2. The distribution of lipid profiles according to *STK11* rs2075604 genotype.

Distribution of STK11 rs2075604 related to normal *vs.* high risk of **(A)** Total cholesterol; **(B)** HDL-c; **(C)** LDL-c; and **(D)** Triglycerides. GG: wildtype homozygote; GT: heterozygote;TT: mutant homozygote.

Table 3. The association between rs2075604 with the abnormality of lipid profiles.

Groups	High total cholesterol level		Low HDL-c level		High LDL-c level		High triglycerides level	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Model 1								
TT	1.61 (0.54-4.82)	0.39	0.33 (0.11-0.99)	0.049*	2.61 (0.71-9.63)	0.15	0.91 (0.35-2.32)	0.84
GT	1.56 (0.42-5.78)	0.51	0.35 (0.08-1.55)	0.17	2.32 (0.51-10.54)	0.28	0.56 (0.16-1.92)	0.36
GG	1.00 (reference)							
T	1.37 (0.73-2.57)	0.33	0.46 (0.24-0.90)	0.02*	2.22 (1.02-4.82)	0.04*	1.02 (0.57-1.81)	0.95
G	1.00 (reference)							
Dominant model								
TT + GT	1.60 (0.55-4.65)	0.39	0.33 (0.12-0.96)	0.04*	2.54 (0.70-9.16)	0.16	0.82 (0.33-2.03)	0.66
GG	1.00 (reference)							
Recessive model								
GG + GT	0.78 (0.35-1.76)	0.55	1.97 (0.74-5.26)	0.18	0.62 (0.26-1.48)	0.28	0.84 (0.39-1.80)	0.66
TT	1.00 (reference)							
Model 2								
TT	1.62 (0.49-5.34)	0.43	0.35 (0.10-1.22)	0.10	3.04 (0.77-12.06)	0.11	1.06 (0.39-2.87)	0.91
GT	1.46 (0.35-6.16)	0.61	0.29 (0.06-1.44)	0.13	2.64 (0.54-13.02)	0.23	0.49 (0.14-1.79)	0.28
GG	1.00 (reference)							
T	1.25 (0.63-2.52)	0.52	0.47 (0.23-0.98)	0.04*	2.25 (0.98-5.17)	0.06	1.16 (0.63-2.13)	0.63
G	1.00 (reference)							
Dominant model								
TT + GT	1.58 (0.49-5.04)	0.44	0.33 (0.10-1.08)	0.07	2.94 (0.76-11.34)	0.12	0.88 (0.34-2.29)	0.79
GG	1.00 (reference)							
Recessive model								
GG + GT	0.75 (0.30-1.86)	0.54	1.64 (0.56-4.80)	0.37	0.57 (0.22-1.45)	0.24	0.68 (0.30-1.54)	0.35
TT	1.00 (reference)							

*p<0.05. Model 1: crude odds ratio; model 2: adjusted odds ratio for age, gender, BMI, waist circumstances, blood pressure, HbA1c level, fasting plasma glucose level, and smoking status. GG: wildtype homozygote; GT: heterozygote;TT: mutant homozygote.

The most exciting finding was that the mutant allele of rs2075604 (T allele) had a protective factor against low HDL-c. This intron variant may have a beneficial effect related to HDL-c. It was confirmed that low HDL-c levels could increase ASCVD risk (Kjeldsen et al., 2022; Li et al., 2020). Therefore, this result indicated that ASCVD risk was reduced among patients with a mutant allele of rs2075604.

In addition, this study found an abnormal correlation related to HbA1c and LDL-c. It was obvious that uncontrolled HbA1c could worsen LDL-c in theoretically from clinical data (Hussain et al., 2017; Nair et al., 2020). Previous studies also could not detect HbA1c as an LDL-c predictor (Alzahrani et al., 2019). The irrelevant result might be caused by the high variance factors contributing to the lipid profile abnormality, not only controlled HbA1c. However, the irrelevant correlation between HbA1c and LDL-c did not affect the association of *STK11* rs2075604. After considering the HbA1c level, there is no significant association between *STK11* rs2075604 and high LDL-c.

Interestingly, the T allele, mutant without adjusting with any confounding factors, increases the risk of high LDL-c. The significant association was deleted in model 2. It could be meant that high LDL-c was more affected by other clinical data compared to *STK11* rs2075604. Previous studies confirmed that uncontrolled blood glucose and smoking highly affected LDL-c (Jain and Ducatman, 2018; Panjeta et al., 2018). Notably, diet is another factor contributing to lipid profiles (Schoeneck and Iggman, 2021).

The major limitations of this study are (1) cross-sectional study design; therefore, the causation could not be determined between exposure of mutant and lipid profiles abnormality, (2) confounding factors, including diet, physical activities, and adherence, could not be identified, thus contributing bias in these finding, (3) sample size is acceptable, and this research recruited from 10 primary health cares; however it remains not representative in Indonesian race.

CONCLUSION

This recent study indicated that *STK11* rs2075604 is a new perspective related to one of the protectant factors for low HDL-c among newly diagnosed T2DM. T allele as a mutant of rs2075604 has the protective role to low HDL-c risk among newly diagnosed T2DM patients in Indonesia. *STK11* rs2075604 could be a better strategy to emphasize poor HDL-c level management. A healthcare professional could utilize this finding to prioritize patients to reduce ASCVD. Due to the mutant allele only affecting LDL-c in the non-adjusted model, further study is recommended to confirm and validate the effect of rs2075604 on LDL-c.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Contribution	Virginia DM,	Patramurti C	Hendra P	Lorenza PNFP	Ngai FE	Anastasia N	Defi MN	Wahyuningsih MSH	Nugrahaningsih DAA
Concepts or ideas	x	x	x				x	x	
Design	x	x	x				x		
Definition of intellectual content	x	x							
Literature search	x	x	x						
Experimental studies	x			x	x	x	x		
Data acquisition	x			x	x	x	x		
Data analysis			x	x	x	x	x		
Statistical analysis	x							x	x
Manuscript preparation	x			x	x	x	x		
Manuscript editing		x	x					x	x
Manuscript review	x	x	x	x	x	x	x	x	x

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