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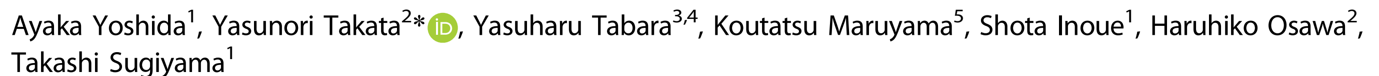
Interaction effect between low birthweight and resistin gene rs1862513 variant on insulin resistance and type 2 diabetes mellitus in adulthood: Toon Genome Study



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Keywords
Low birthweight, Resistin, Type 2 diabetes susceptibility genes

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ABSTRACT

Aims/Introduction: Gene–environment interactions are considered to critically influence type 2 diabetes mellitus development; however, the underlying mechanisms and specific interactions remain unclear. Given the increasing prevalence of low birthweight (LBW) influenced by the intrauterine environment, we sought to investigate genetic factors related to type 2 diabetes development in individuals with LBW.

Materials and Methods: The interaction between 20 reported type 2 diabetes susceptibility genes and the development of type 2 diabetes in LBW (<2,500 g) individuals in a population-based Japanese cohort (n = 1,021) was examined by logistic regression and stratified analyses.

Results: Logistic regression analyses showed that only the *G/G* genotype at the rs1862513 locus of the resistin gene (*RETN*), an established initiator of insulin resistance, was closely related to the prevalence of type 2 diabetes in individuals with LBW. Age, sex and current body mass index-adjusted stratified analyses showed a significant interaction effect of LBW and the *RETN G/G* genotype on fasting insulin, homeostatic model assessment 2-insulin resistance, Matsuda index and the prevalence of type 2 diabetes (all P-values for interaction <0.05). The adjusted odds ratio for type 2 diabetes in the LBW + *G/G* genotype group was 7.33 (95% confidence interval 2.43–22.11; P = 0.002) compared with the non-LBW + non-*G/G* genotype group. Similar results were obtained after excluding the influence of malnutrition due to World War II.

Conclusions: Simultaneous assessment of LBW and the *RETN G/G* genotype can more accurately predict the risk of future type 2 diabetes than assessing each of these factors alone, and provide management strategies, including early lifestyle intervention in LBW population.

INTRODUCTION

Gene–environment interactions have been considered a crucial aspect of type 2 diabetes mellitus development; however, concrete examples are lacking and the underlying mechanisms have not been fully elucidated[1–3]. The lack of clarity regarding these interactions can be attributed to the challenge of quantifying environmental factors on type 2 diabetes.

In 23 of the 36 Organization for Economic Cooperation and Development countries, the proportion of infants with low birthweight (LBW), a well-known phenotype related to the intrauterine environment, has been increasing since 2000[4]. The prevalence of LBW in Japan has also increased substantially

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from 5.1% in 1975 to 9.2% in 2020, and remains high[5]; thus, LBW has become a public health concern. LBW is closely associated with an increased risk of type 2 diabetes in later life[6–9]; however, the underlying mechanisms remain unclear.

The developmental origins of health and disease hypothesis suggests that circumstances during the fetal and developmental periods might increase the risk of developing non-communicable diseases in adulthood[10]. The developmental origins of health and disease hypothesis is based on the thrifty phenotype hypothesis, namely, that in an intrauterine environment characterized by undernutrition, the fetus becomes an LBW infant and acquires an environmentally adapted "thrifty" phenotype[11]. Furthermore, the fetal programming hypothesis suggests adaptation to the environment through metabolic programming, such as epigenetics[12–14]. Specifically, in a prenatal environment of undernutrition, postnatal overnutrition might increase the risk of mismatch with the predictive adaptive response, leading to the development of non-communicable diseases[15]. In a previous population-based cohort study, we found that the prevalence of type 2 diabetes was much higher in individuals with LBW and obesity in adulthood[16]. Alternatively, the fetal insulin hypothesis posits that genetic factors that either reduce insulin secretion from β-cells or increase insulin resistance lead to LBW through the dysfunction of insulin-mediated fetal growth, which in turn leads to the development of type 2 diabetes; however, this hypothesis has not yet been verified[17–19]. Accumulating data from genome-wide association studies have shown that various type 2 diabetes risk alleles were also associated with birthweight[20].

These results suggest that both the intrauterine environment and genetic factors explain an essential part of the close association between LBW and the risk of type 2 diabetes later in life; however, this interaction remains to be verified. Given the increasing prevalence of LBW infants worldwide, clarifying the clinical characteristics and genetic factors related to the onset of type 2 diabetes in the context of LBW could be important for the initiation of early lifestyle interventions targeting disease prevention. Therefore, we carried out a population-based Japanese cohort study to analyze the influence of the interaction between LBW as the quantitative phenotype influenced by the intrauterine environment and the reported risk genotypes of type 2 diabetes susceptibility genes on the emergence of type 2 diabetes in later life.

MATERIALS AND METHODS

Study overview

The Toon Genome Study was carried out as part of the Toon Health Study, a prospective cohort study of the general population in Toon City, Ehime Prefecture, Japan, which was designed to evaluate the pathological mechanism underlying type 2 diabetes[21]. This study has been ongoing since 2009. Interviews, physical examinations and blood testing were carried out on participants aged 30–79 years. Blood tests included the 75-g oral glucose tolerance test, and type 2 diabetes was defined as a fasting blood glucose level ≥7.0 mmol/L, 2-h postprandial glucose level ≥11.1 mmol/L, glycated hemoglobin ≥6.5% (48 mmol/mol) or the current use of hypoglycemic agents, according to American Diabetes Association criteria[22]. Insulin levels were measured using the ECLusys system (Roche Diagnostics, Tokyo, Japan). The homeostatic model assessment 2 for insulin resistance (HOMA2-IR), homeostatic model assessment 2 for β-cell function (HOMA2-B) and Matsuda index were analyzed as previously described[23–25]. Fasting serum resistin levels were measured using a human resistin immunoassay kit (EMD Millipore Corporation, Billerica, MA, USA) according to the manufacturer's instructions. Overweight was defined as a body mass index (BMI) ≥25 kg/m^2.

To exclude the influence of malnutrition during and after World War II in Japan, we carried out a subanalysis with individuals born between 1943 and 1947 excluded.

Genotyping

To evaluate the influence of single-nucleotide polymorphisms (SNPs) on the risk of developing type 2 diabetes in individuals with LBW, we analyzed the risk genotypes of 20 SNPs in type 2 diabetes susceptibility genes identified in prior studies of a Japanese population, and the odds ratio (OR) for type 2 diabetes was ≥1.1[26–31]: rs1862513 (*RETN*), rs8050136 (*FTO*), rs516946 (*ANK1*), rs459193 (*C5orf67*), rs7754840 (*CDKAL1*), rs10811661 (*CDKN2A/2B*), rs780094 (*GCKR*), rs11787792 (*GPSM1*), rs1111875 (*HHEX*), rs7501939 (*HNF1B*), rs1470579 (*IGF2BP2*), rs5219 (*KCNJ11*), rs2237897 (*KCNQ1*), rs6815464 (*MAEA*), rs11257655 (*CAMK1D*), rs7172432 (*C2CD4A*), rs13266634 (*SLC30A8*), rs7612463 (*UBE2E2*), rs12255372 (*TCF7L2*) and rs12571751 (*ZMIZ1*). Genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood (QIAamp DNA blood kit; QIAGEN, Hilden, Germany). SNPs were genotyped by TaqMan analysis using a commercially available primer-probe mix from the Assay-on-Demand system (Applied Biosystems, Waltham, MA, USA). All call rates were greater than 95%.

Birthweight data

To evaluate birthweight, we mailed a self-administered questionnaire to all participants. To reduce recall bias, the data sources were limited to maternal and child health handbooks, family record at birth or information from family members; if there were any unclear or inconsistent answers, we resent a questionnaire or carried out telephone interview. Finally, uncertain data were excluded. We also obtained data on the current use of hypoglycemic agents and the family history of diabetes from the questionnaire. Participants either reported the exact birthweight (in grams), if available, or chose from one of six categories (<2,000; 2,000–2,499; 2,500–2,999; 3,000–3,499; 3,500–3,999; and ≥4,000 g). LBW was defined as a birthweight <2,500 g[32].

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Statistical analysis

Participant characteristics were compared among four groups divided according to the presence or absence of LBW and type 2 diabetes. The Kruskal–Wallis test was used to analyze continuous variables, and the χ^2-test was used for categorical variables. We calculated the ORs and 95% confidence intervals (CIs) for the prevalence of type 2 diabetes among individuals with LBW. The independent variables were risk allele homozygotes of the 20 known type 2 diabetes susceptibility genes. Kruskal–Wallis tests were carried out to compare serum resistin, fasting insulin, HOMA2-IR and Matsuda index levels among the four groups divided according to the presence or absence of LBW and the *G/G* genotype of the human resistin gene (*RETN*) SNP rs1862513 (*RETN G/G* genotype). The Steel test was used in post-hoc analysis for multiple comparisons. To analyze the interaction between LBW and the *RETN G/G* genotype, two-way analysis of variance was carried out. Serum resistin, fasting insulin, HOMA2-IR, Matsuda index and the prevalence of type 2 diabetes were used as dependent variables, whereas age, sex, current BMI, birthweight (non-LBW = 0, LBW = 1), *RETN* genotype at rs1862513 (*C/C* or *C/G* = 0, *G/G* = 1), and a combination of birth weight and genotype (LBW × *RETN G/G* genotype) were used as independent variables. We then calculated the age-, sex- and current BMI-adjusted ORs for the prevalence of type 2 diabetes in all individuals of the cohort using logistic regression analysis. All *P*-values were two-sided, and statistical significance was judged at $P < 0.05$. SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Ethical approval

The study protocol was approved by the Ethics Committee of Ehime University Graduate School of Medicine (Approval No. 29-K3), and conformed to the provisions of the Declaration of Helsinki. Informed consent was obtained from all participants.

Clinical trial registration

This cohort study was registered in the UMIN Clinical Trials Registry (UMIN ID: UMIN000036074).

RESULTS

Clinical characteristics of participants

The eligibility criteria and selection process for inclusion of participants in the present study are shown in Figure 1. Of the 2,505 participants who underwent a medical checkup between August 2009 and June 2022, 1,484 were excluded because of the unavailability of DNA samples (*n* = 21) or unanswered questions/uncertain information about birthweight (*n* = 1,463). Ultimately, 1,021 individuals were included in this study. The characteristics of these participants are summarized in Table 1. In brief, the median age and BMI of the participants were 56 years (interquartile range [IQR] 45–64 years) and 22.4 (IQR 20.5–24.8), respectively, and 32.3% of the participants were men. The prevalence of type 2 diabetes and of LBW were 13.1% and 11.7%, respectively.

Clinical characteristics of individuals with LBW with type 2 diabetes

Logistic regression analyses showed an increased risk of type 2 diabetes in the LBW group compared with the non-LBW group after adjusting for age, sex and current BMI (OR 2.28, 95% CI 1.38–3.78; *P* = 0.001), which is supported by previous reports[6,7]. We then evaluated the clinical characteristics of individuals with type 2 diabetes in the LBW group (Table 1). Stratified analyses according to LBW and type 2 diabetes status showed that the waist-to-hip ratio, family history of diabetes, high-sensitivity C-reactive protein, fasting insulin and HOMA2-IR were substantially higher, whereas high-density lipoprotein cholesterol, $\Delta_{0\text{–}1h}$ immunoreactive insulin/$\Delta_{0\text{–}1h}$ plasma glucose and Matsuda index were lower in the individuals with LBW with type 2 diabetes group. These results suggest that the pathophysiology of type 2 diabetes in individuals with LBW is predominantly attributed to insulin resistance and relative insulin secretion impairment.

Association of the *RETN G/G* genotype with an increased risk of type 2 diabetes in individuals with LBW

Next, we evaluated the influence of the risk genotypes of the 20 reported type 2 diabetes susceptibility genes for the LBW subgroup of the cohort (Table 2). Logistic regression analyses showed that the *RETN G/G* genotype was closely related to an increased risk of type 2 diabetes in individuals with LBW (OR 6.71; 95% CI, 2.13–21.12; *P* = 0.001). However, the risk genotypes of other known type 2 diabetes susceptibility genes were not associated with an increased risk of type 2 diabetes in individuals with LBW. Thus, we subsequently focused on *RETN*, which is known to play a key role in insulin resistance, inflammation, metabolic syndrome and type 2 diabetes[26,33–37].

The proportion of individuals carrying the *RETN G/G* genotype in this Japanese cohort (10.9%) was similar to that previously reported in another Japanese cohort[30]. Also consistent with the previous study, circulating resistin levels were markedly higher in the *RETN G/G* genotype group than in the *C/C* or *C/G* genotype group (median 17.6, IQR 13.4–22.1 vs median 10.0, IQR 7.6–13.7; $P < 0.001$). Furthermore, multivariable regression analyses showed that serum resistin levels were positively associated with current BMI, waist-to-hip ratio, fasting insulin, HOMA2-IR, triglyceride-to-high-density lipoprotein cholesterol ratio and high-sensitivity C-reactive protein levels (Table 3). Conversely, the *RETN G/G* genotype was not associated with the prevalence of LBW (13.5% for the *G/G* genotype vs 11.4% for the *C/C* or *C/G* genotype; *P* = 0.518).

LBW and *RETN G/G* interaction increases the risk of insulin resistance and type 2 diabetes in adulthood

We further investigated the clinical characteristics of individuals with LBW with the *G/G* genotype. Serum resistin levels were

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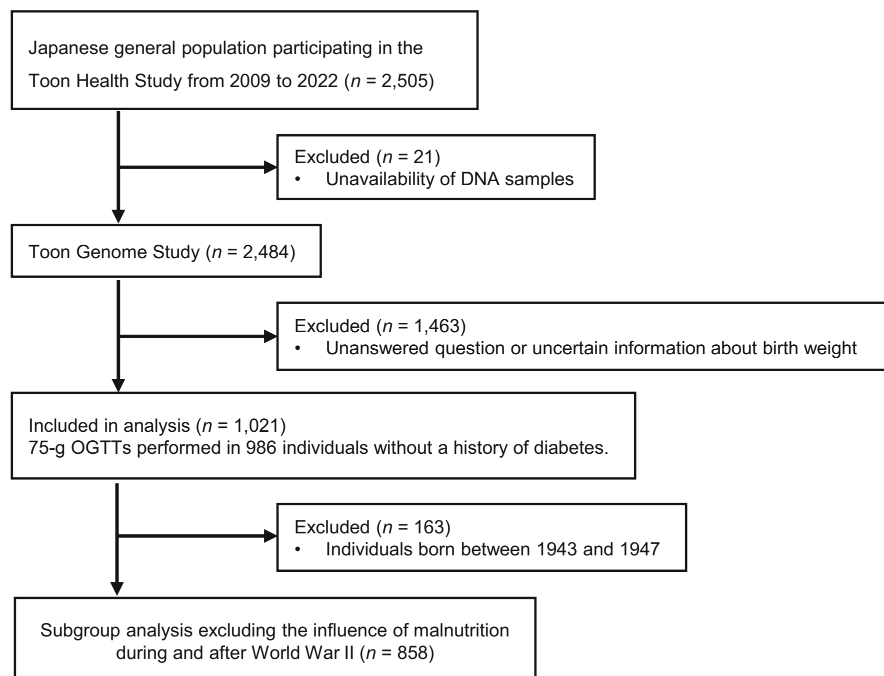

Figure 1 | Flowchart for participant selection. To exclude the influence of malnutrition during and after World War II in Japan, we also carried out a subgroup analysis excluding individuals born between 1943 and 1947. OGTT, oral glucose tolerance test.

significantly increased in individuals with the *G/G* genotype, regardless of birthweight. Furthermore, fasting insulin and HOMA2-IR levels were the highest, and the Matsuda index was the lowest in individuals with both LBW and the *G/G* genotype. The serum resistin, fasting insulin, HOMA2-IR and Matsuda index levels in individuals with LBW and the *C/C* or *C/G* genotype were similar to those in individuals in non-LBW with the *C/C* or *C/G* genotype group (Figure 2a–d).

Furthermore, we found a significant interaction effect of LBW and the *RETN G/G* genotype with fasting insulin, HOMA2-IR, Matsuda index and the prevalence of type 2 diabetes (*P*-value for interaction = 0.016, 0.049, 0.039 and 0.0003, respectively), but not with serum resistin level (*P*-value for interaction = 0.766), after adjustment for age, sex and current BMI. These results suggest that the interaction between LBW – as a surrogate marker for the influence of the intrauterine environment – and the *RETN G/G* genotype is associated with insulin resistance and type 2 diabetes.

Finally, we evaluated the impact of the interaction effect of LBW and the *RETN G/G* genotype on the development of type 2 diabetes. Multivariate logistic regression analyses showed that the age-, sex- and current BMI- adjusted OR for type 2 diabetes among individuals in the LBW + *G/G* genotype group was 7.33 (95% CI 2.43–22.11; *P* = 0.002) compared with the reference group (Table 4). Furthermore, the OR for type 2 diabetes among individuals in the LBW + *G/G* genotype group was 4.00 (95% CI 1.13–14.10; *P* = 0.031) compared with the LBW + non-*G/G* genotype group.

We obtained reproducible results from the subgroup analysis excluding individuals born between 1943 and 1947 who may have been influenced by intrauterine undernutrition due to the food shortage conditions during and after World War II (Table 5).

Therefore, LBW harboring the *G/G* genotype significantly increases the risk of insulin resistance and the development of type 2 diabetes in adulthood.

DISCUSSION

Information regarding gene–environment interactions in the development of type 2 diabetes might be important for targeting and enabling more effective prevention measures[1,38,39]. Although the role of gene–environment interactions has been partially indicated in obesity, their association with the development of type 2 diabetes has remained unclear[3]. One reason for this uncertainty is the challenge in quantifying environmental factors.

Genetic factors and the intrauterine environment related to reduced insulin secretion or insulin resistance are considered to contribute significantly to the link between LBW and developing type 2 diabetes in later life[11,18,19]; however, there has been no evidence of the specific interaction between LBW and type 2 diabetes susceptibility genes to date. In the present study,

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Table 1 | Characteristics of participants in four groups divided by birthweight and incidence of diabetes

Characteristic	Overall	Non-LBW† and non-diabetes‡	Non-LBW and diabetes	LBW and non-diabetes	LBW and diabetes	*P*-value
n	1,021	796	106	91	28	
Sex (male/female)	330/691	242/554	48/58	24/67	16/12	<0.001
Age (years), median (IQR)	56 (45–64)	54 (43–63)	63 (57–70)**	56 (44–65)	64 (61–70)**	<0.001
BMI (kg/m^2), median (IQR)	22.4 (20.5–24.8)	22.3 (20.3–24.7)	24.2 (21.6–26.6)**	21.6 (20.4–23.7)	24.3 (22.0–25.9)*	<0.001
Waist (cm), median (IQR)	81.5 (75.0–89.0)	81.0 (74.5–88.0)	87.0 (79.0–93.0)**	79.0 (73.5–86.0)	86.0 (83.8–94.3)**	<0.001
WHR, median (IQR)	0.88 (0.84–0.93)	0.88 (0.84–0.93)	0.91 (0.86–0.96)**	0.88 (0.83–0.93)	0.94 (0.89–0.96)**	<0.001
Family history of diabetes, *n* (%)	276 (27.0)	190 (23.9)	47 (44.3)	21 (23.1)	18 (64.3)	<0.001
Overweight, *n* (%)	237 (23.2)	174 (21.9)	44 (41.5)	10 (11.0)	9 (32.1)	<0.001
MetS, *n* (%)	197 (19.3)	120 (15.1)	52 (49.1)	12 (13.2)	13 (46.4)	<0.001
SBP (mmHg), median (IQR)	121 (108–136)	119 (107–133)	138 (125–148)**	117 (105–133)	129 (120–139)*	<0.001
DBP (mmHg), median (IQR)	75 (66–83)	74 (65–82)	81 (75–88)**	71 (65–80)	79 (73–83)	<0.001
Total cholesterol (mmoL/L), median (IQR)	5.3 (4.8–5.9)	5.3 (4.8–5.9)	5.3 (4.8–5.8)	5.2 (4.6–5.7)	5.1 (4.6–5.5)	0.234
HDL cholesterol (mmoL/L), median (IQR)	1.6 (1.4–1.9)	1.3 (1.4–1.9)	1.5 (1.2–1.8)**	1.6 (1.4–1.8)	1.2 (1.1–1.5)**	<0.001
Triglyceride (mmoL/L), median (IQR)	1.0 (0.7–1.4)	1.0 (0.7–1.3)	1.3 (0.9–1.8)**	0.9 (0.7–1.4)	1.3 (0.8–1.9)	<0.001
Triglyceride-to-HDL cholesterol ratio, median (IQR)	1.4 (0.9–2.2)	1.4 (0.9–2.1)	2.0 (1.2–3.2)**	1.3 (0.9–2.1)	2.0 (1.5–3.6)*	<0.001
hs-CRP (mg/dL), median (IQR)	0.04 (0.02–0.07)	0.03 (0.02–0.07)	0.05 (0.03–0.10)**	0.04 (0.02–0.07)	0.07 (0.04–0.10)*	<0.001
HbA1c (%), median (IQR)	5.5 (5.2–5.7)	5.4 (5.1–5.6)	6.0 (5.7–6.4)**	5.4 (5.2–5.6)	6.0 (5.7–6.3)**	<0.001
HbA1c (mmol/mol), median (IQR)	37 (33–39)	36 (32–38)	42 (39–46)	36 (33–38)	42 (39–45)	
Fasting PG (mmol/L), median (IQR)	5.1 (4.8–5.4)	5.0 (4.7–5.3)	5.9 (5.4–6.7)**	4.9 (4.7–5.2)	5.8 (5.3–6.1)**	<0.001
Fasting IRI (pmol/L), median (IQR)	34.0 (23.6–48.6)	33.3 (22.9–47.9)	42.4 (25.0–75.7)**	31.3 (22.9–44.5)	47.9 (34.0–60.4)*	<0.001
HOMA2-IR, median (IQR)	0.64 (0.44–0.93)	0.62 (0.43–0.89)	0.87 (0.53–1.48)**	0.59 (0.43–0.81)	0.94 (0.66–1.20)*	<0.001
HOMA2-B (%), median (IQR)	68.3 (54.7–85.0)	69.1 (56.3–85.0)	60.6 (40.3–82.7)*	68.3 (54.9–87.9)	69.0 (57.1–85.3)	0.004
75-g OGTT§, median (IQR)						
Fasting PG (mmol/L)	5.0 (4.7–5.3)	5.0 (4.7–5.3)	5.8 (5.4–6.2)**	4.9 (4.7–5.2)	5.7 (5.2–6.1)**	<0.001
1-h PG (mmol/L)	7.8 (6.1–9.7)	7.4 (5.9–9.3)	12.3 (10.8–13.9)**	7.4 (6.0–8.9)	12.2 (11.0–14.2)**	<0.001
2-h PG (mmol/L)	6.4 (5.4–7.7)	6.2 (5.3–7.3)	11.2 (8.5–12.9)**	6.2 (5.3–7.1)	11.2 (9.8–11.8)**	<0.001
Fasting IRI (pmol/L)	33.3 (23.6–47.9)	33.3 (22.9–47.2)	41.7 (22.2–72.2)*	31.3 (22.9–44.5)	50.0 (41.0–60.4)**	<0.001
1-h IRI (pmol/L)	322.3 (218.8–477.1)	327.8 (219.5–477.1)	315.3 (220.2–497.3)	273.6 (216.7–433.4)	354.2 (203.5–518.8)	0.669
2-h IRI (pmol/L)	288.9 (204.2–420.2)	280.6 (197.2–400.0)	395.9 (263.2–693.8)**	258.4 (206.3–369.5)	477.8 (261.8–686.2)*	<0.001
Δ_{0-1h}IRI/Δ_{0-1h}PG	0.9 (0.5–1.6)	1.0 (0.6–1.8)	0.3 (0.2–0.6)**	1.0 (0.6–1.6)	0.5 (0.2–0.5)**	<0.001
Matsuda index	7.4 (4.9–10.5)	7.6 (5.3–10.7)	4.6 (2.9–7.7)**	7.9 (6.0–11.0)	4.1 (3.4–5.1)**	<0.001

†Low birthweight was defined as <2,500 g. ‡Diabetes mellitus was defined as a fasting blood glucose level ≥7.0 mmol/L, 2-h postprandial glucose level ≥11.1 mmol/L, glycated hemoglobin ≥6.5% (48 mmol/mol) or current use of antihyperglycemic agents according to American Diabetes Association criteria. §The 75-g oral glucose tolerance test was carried out on 986 individuals without a history of diabetes. *P*-values were calculated using the Kruskal–Wallis test or χ^2-test among the four groups. The Steel test was used in post-hoc analysis. *$P < 0.05$, **$P < 0.001$ versus non- low birthweight and non-diabetes group. Δ_{0-1h} IRI/Δ_{0-1h} PG, (1-h insulin – fasting insulin)/(1-h plasma glucose – fasting plasma glucose); BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA2-B, homeostatic model assessment 2 for β-cell function; HOMA2-IR, homeostatic model assessment 2 for insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; IRI, immunoreactive insulin; LBW, low birthweight; MetS, metabolic syndrome; OGTT, oral glucose tolerance test; PG, plasma glucose; SBP, systolic blood pressure; WHR, waist-to-hip ratio.

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Table 2 | Influence of homozygosity for risk alleles of type 2 diabetes mellitus susceptibility genes on the incidence of type 2 diabetes in individuals with low birthweight

SNP	Gene	OR[†]	95% CI	*P*-value
rs1862513	*RETN*	6.71	2.13–21.12	0.001
rs516946	*ANK1*	0.62	0.22–1.79	0.380
rs459193	*C5orf67*	0.80	0.26–2.48	0.702
rs7754840	*CDKAL1*	2.00	0.74–5.38	0.170
rs10811661	*CDKN2A/2B*	1.47	0.60–3.61	0.404
rs8050136	*FTO*	3.42	0.46–25.50	0.230
rs780094	*GCKR*	0.83	0.24–2.82	0.762
rs11787792	*GPSM1*	1.10	0.38–3.21	0.863
rs1111875	*HHEX*	5.10	0.80–32.67	0.086
rs7501939	*HNF1B*	2.21	0.56–8.66	0.255
rs1470579	*IGF2BP2*	1.50	0.50–4.53	0.472
rs5219	*KCNJ11*	0.93	0.23–3.74	0.920
rs2237897	*KCNQ1*	1.22	0.48–3.15	0.677
rs6815464	*MAEA*	2.04	0.86–4.81	0.104
rs7172432	*C2CD4A*	2.39	0.88–6.54	0.089
rs11257655	*CAMK1D*	1.64	0.50–5.42	0.418
rs13266634	*SLC30A8*	1.60	0.67–3.82	0.287
rs7612463	*UBE2E2*	1.14	0.39–3.33	0.807
rs12571751	*ZMIZ1*	1.89	0.71–5.00	0.202
rs12255372	*TCF7L2*	N/A	N/A	N/A

[†]Odds ratios of the incidence of type 2 diabetes in individuals with low birthweight were estimated using logistic regression analyses, which included homozygosity for risk alleles of 19 known type 2 diabetes susceptibility genes as independent variables and a type 2 diabetes diagnosis as the dependent variable (n = 119). All call rates were >95%. As there was only one individual homozygous for the *TCF7L2* (rs12255372) risk allele (*T/T*), the OR and 95% confidence interval could not be calculated. CI, confidence interval; N/A, not available; OR, odds ratio; SNP, single-nucleotide polymorphism.

we present evidence of significant gene–environment interaction effects on the development of type 2 diabetes. This population-based cohort study showed that the pathology of type 2 diabetes in individuals with LBW was associated with insulin resistance and relative insulin secretion impairment (Table 1). Furthermore, we found a significant interaction effect between LBW and the *RETN* rs1862513 *G/G* genotype on insulin resistance and the prevalence of type 2 diabetes.

RETN is located on chromosome 19p13, and the *G/G* genotype at *RETN* rs1862513 is closely linked to an increase of resistin levels and insulin resistance[26,34–37]. The present findings suggest that overlapping of the *RETN G/G* genotype and the predictive adaptive response to the intrauterine environment might facilitate insulin resistance, and that this response continues after birth. Furthermore, the *RETN G/G* genotype and increasing resistin levels are associated not only with insulin resistance, but also with other type 2 diabetes-related factors[33–37]. Therefore, when an individual with LBW carrying the *RETN G/G* genotype is subsequently exposed to overnutrition after birth, the risk of type 2 diabetes will be increased due to the drastic mismatch with the fetal environment.

Notably, previous studies and the present study claimed that LBW is associated with an increased risk of type 2 diabetes[6–9]. Furthermore, the OR for type 2 diabetes among individuals in the LBW + *G/G* genotype group was 4.00 compared with the LBW + non-*G/G* genotype group. Therefore, together with previous reports[38,39], the present results support the importance of the simultaneous assessment of both birthweight as a surrogate marker for the intrauterine environment and *RETN* rs1862513 variant to predict the risk of future diabetes more accurately than assessing each of these factors alone.

Genetic factors and epigenetic changes, such as those caused by intrauterine undernutrition, are known to persist across generations[40,41]. Appropriate exercise and nutritional therapy might change the DNA methylation status of the human skeletal muscle and adipose tissue, and lifestyle interventions might also modify epigenetics during fetal life[42,43]. We propose a novel concept whereby individuals at high risk of type 2 diabetes can be identified through assessment of the *RETN G/G* genotype in the LBW population, which might lead to early lifestyle interventions and offer a precision medicine approach in the prevention of type 2 diabetes.

There are some reports regarding an association between serum resistin levels and birthweight; however, this link remains

Table 3 | Association between serum resistin levels and diabetes-related factors in the study population (n = 1,021) based on multivariate regression analysis

	Dependent variables											
	Current BMI		WHR		Fasting IRI		HOMA2-IR		TG/HDL-C		hs-CRP	
Independent variables	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value
Age	0.166	<0.001	0.394	< 0.001	–0.004	0.881	0.022	0.419	0.120	<0.001	–0.003	0.936
Sex	–0.199	<0.001	–0.146	< 0.001	–0.028	0.288	–0.026	0.330	–0.216	<0.001	0.020	0.539
Current BMI	N/A		N/A		0.554	<0.001	0.524	<0.001	0.257	<0.001	0.150	<0.001
Resistin	0.118	<0.001	0.063	0.026	0.099	<0.001	0.107	<0.001	0.123	<0.001	0.088	0.005

BMI, body mass index; HOMA2-IR, homeostatic model assessment 2-insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IRI, immunoreactive insulin; N/A, not applicable; TG/HDL-C, triglyceride-to-high-density lipoprotein cholesterol ratio; WHR, waist-to-hip ratio; β, standardized coefficient.

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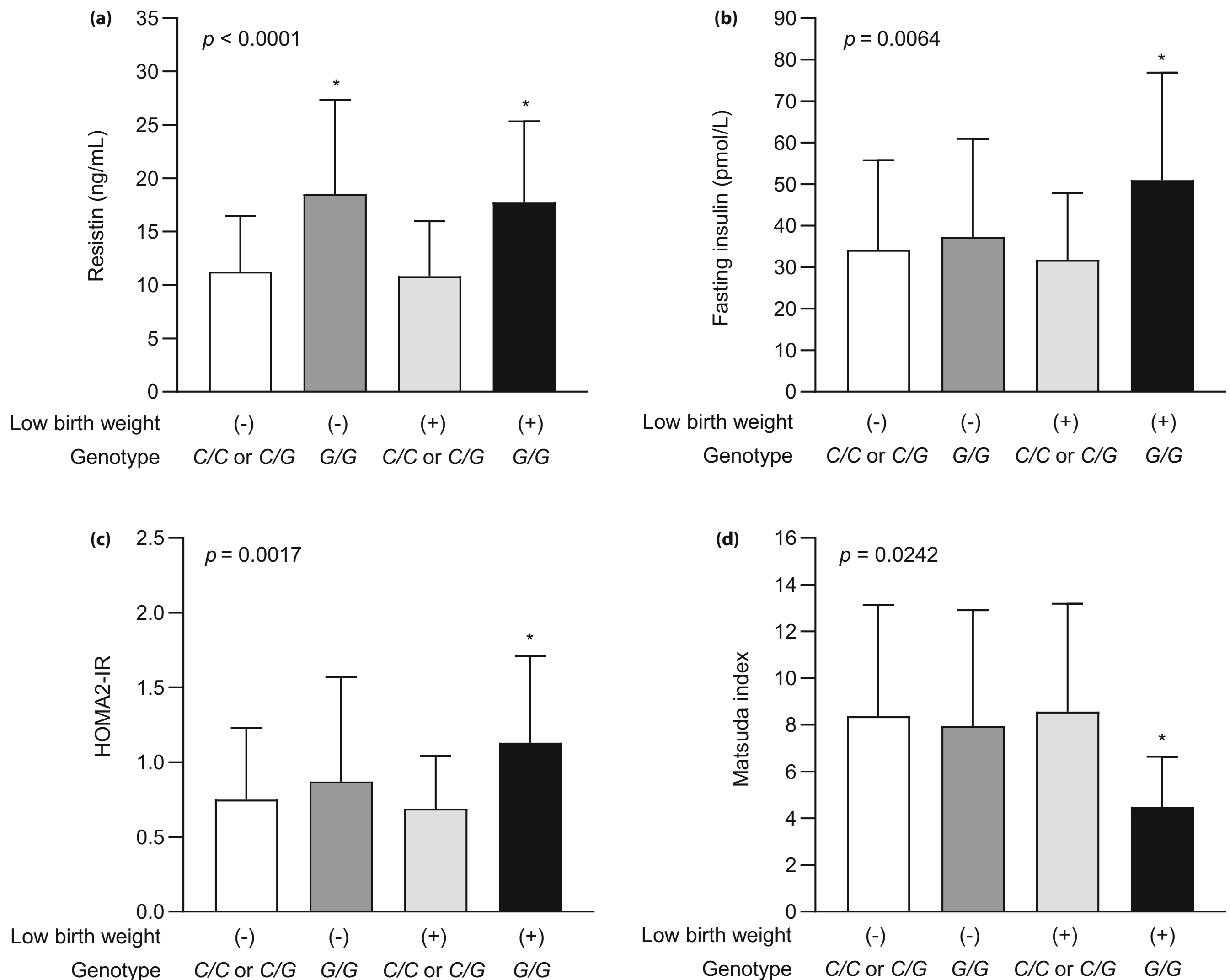

Figure 2 | Serum resistin levels and insulin resistance according to birthweight and the *RETN* SNP rs1862513 genotype. The Kruskal–Wallis test was used to compare (a) serum resistin, (b) fasting insulin, (c) homeostatic model assessment 2 for insulin resistance (HOMA2-IR), and (d) Matsuda index levels in the four groups based on birthweight and the *G/G* genotype of the *RETN* rs1862513 variant, and the Steel test was used in post-hoc analysis. *P < 0.05 versus non-low birthweight and non-*G/G* groups. Data are expressed as the mean ± standard deviation.

controversial[44,45]. In the present study, the *RETN G/G* genotype was not associated with the prevalence of LBW. A key limitation of this study is that we were unable to obtain information about the mothers' *RETN* rs1862513 variant status. Nevertheless, in the case of an individual with the *RETN G/G* genotype, their mother carries the risk variant *G*. Previous studies have reported that the *RETN* rs1862513 *C/G* or *G/G* genotype was associated with higher resistin levels and insulin resistance than those of *C/C* genotype group[26,34–37]. It has been reported that serum resistin levels in pregnant women were negatively correlated with birthweight[45]. Furthermore, resistin is secreted from the placenta, resistin levels are more concentrated in the cord blood than in maternal blood and resistin levels in the fetus increase with gestational age[46–48]. The developmental origins of health and disease hypothesis and related studies suggest that insulin resistance is induced as the predictive adaptive response to an intrauterine environment of poor nutrition[10,11]. Therefore, the predictive adaptive response, including increased maternal insulin resistance related to the *RETN G* allele, might be beneficial for adapting to a poor intrauterine environment[12–14]. A prospective cohort study is desirable to confirm the influence of the mother's *RETN* risk variant on intrauterine environment and birthweight of offspring.

The strengths of the present study are as follows. This is the first study to report a substantial interaction effect between LBW as a quantitative surrogate marker for the intrauterine

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Table 4 | Risk of developing type 2 diabetes mellitus according to birthweight status and genotype of the *RETN* single-nucleotide polymorphism rs1862513[†] (overall)

Variable	Non-LBW and non-*G/G*	Non-LBW and *G/G*	LBW and non-*G/G*	LBW and *G/G*	*P*-value
Cases of T2DM, *n* (%)	93/806 (11.5)	13/96 (13.5)	19/104 (18.3)	9/15 (60.0)	<0.001
Unadjusted OR (95% CI)	1.00 (Ref)	1.20 (0.64–2.24)	1.71 (0.99–2.95)	11.50 (4.00–33.03)******	<0.001
Adjusted OR (95% CI)					
Age	1.00 (Ref)	1.02 (0.54–1.95)	1.56 (0.88–2.74)	7.67 (2.57–22.88)******	0.002
Age and sex	1.00 (Ref)	1.07 (0.56–2.05)	1.59 (0.90–2.81)	7.33 (2.44–22.00)******	0.002
Age, sex and current BMI	1.00 (Ref)	1.02 (0.53–1.98)	1.75 (0.98–3.11)	7.33 (2.43–22.11)******	0.002

**P* < 0.01 versus reference. ***P* < 0.01 versus non-low birthweight and *G/G* group. ****P* < 0.05 versus low birthweight and non-*G/G* group. [†]Odds ratios were calculated using multivariate logistic regression analysis involving age, sex and current body mass index as independent variables, and the onset of type 2 diabetes in adulthood as the dependent variable. The reference group (Ref) comprised individuals with non-low birthweight and the *C/C* or *C/G* (non-*G/G*) genotype of the human resistin gene (*RETN*) single-nucleotide polymorphism rs1862513. BMI, body mass index; CI, confidence interval; LBW, low birthweight; OR, odds ratio; SNP, single-nucleotide polymorphism; T2DM, type 2 diabetes.

Table 5 | Risk of developing type 2 diabetes mellitus according to birthweight status and genotype of *RETN* single-nucleotide polymorphism rs1862513[†] (a subgroup analysis excluding subjects born between 1943 and 1947[‡])

Variable	Non-LBW and non-*G/G*	Non-LBW and *G/G*	LBW and non-*G/G*	LBW and *G/G*	*P*-value
Cases of T2DM, *n* (%)	78/732 (10.7)	10/78 (12.8)	11/87 (12.6)	8/13 (61.5)	<0.001
Unadjusted OR (95% CI)	1.00 (Ref)	1.23 (0.61–2.49)	1.21 (0.62–2.38)	13.42 (4.28–42.02)******	<0.001
Adjusted OR (95% CI)					
Age	1.00 (Ref)	1.11 (0.54–2.32)	1.10 (0.54–2.22)	8.79 (2.69–28.77)******	0.005
Age and sex	1.00 (Ref)	1.17 (0.56–2.45)	1.12 (0.55–2.27)	8.01 (2.42–26.52)******	0.009
Age, sex and current BMI	1.00 (Ref)	1.13 (0.53–2.38)	1.29 (0.63–2.62)	7.93 (2.39–26.37)******	0.009

**P* < 0.01 versus reference. ***P* < 0.01 versus non-low birthweight and G/G group. ****P* < 0.05 versus low birthweight and non-G/G group. [†]Odds ratios were calculated using multivariate logistic regression analysis involving age, sex and current body mass index as independent variables, and the onset of type 2 diabetes in adulthood as the dependent variable. The reference group comprised individuals with non-low birthweight and the C/C or C/G (non-G/G) genotype of the human resistin gene (RETN) single-nucleotide polymorphism rs1862513. [‡]To exclude the influence of malnutrition during and after World War II in Japan, we conducted a subgroup analysis excluding subjects born between 1943 and 1947. BMI, body mass index; CI, confidence interval; LBW, low birthweight; OR, odds ratio; SNP, single-nucleotide polymorphism.

environment and the *RETN* genotype on the development of type 2 diabetes in adulthood. Although *RETN* is a well-known insulin resistance-related gene, the involvement of the rs1862513 genotype in fetal risk loci related to birthweight and/or type 2 diabetes has not been clarified to date, possibly because this locus cannot be directly genotyped using commercially available genotyping arrays. Furthermore, there are ethnic differences in the distribution and associations of the rs1862513 genotype. For example, no significant association between the rs1862513 genotype and plasma resistin levels has been observed in white people of European descent[49,50]. Wibaek *et al.*[8] recently reported that LBW was associated with an increased risk of developing type 2 diabetes independent of a known genetic risk of type 2 diabetes. Conversely, the association between LBW and an increased risk of developing type 2 diabetes was not significant in individuals with the *RETN C/C* or *C/G* genotype in the present study. This difference might be related to the fact that the previous genome-wide association study was only based on individuals of European ethnicity. Furthermore, the OR of future type 2 diabetes calculated using the combination of LBW and the *RETN G/G* genotype was much higher than that obtained using the single assessment of birthweight status or the *RETN* genotype. These results further support the importance of the simultaneous assessment of gene and environment factors in predicting the development of type 2 diabetes.

The present study also had several limitations. First, it is preferable to obtain birthweight information only from maternal and child health handbooks; however, this can prove difficult in retrospective studies. As a previous study showed an excellent correlation between self-reported and actual birthweights[51], we also accepted data based on family records at birth or information from family members, whereas uncertain data were excluded. Second, it was not possible to assess gestational age. Information regarding gestational age was obtained for only 601 of the 1,021 individuals with available birthweight data. Therefore, it was difficult to differentiate among premature, growth-restricted and growth-stunted infants in this study[52]. Third, we were unable to assess maternal, umbilical and fetal serum resistin levels or insulin resistance.

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Fourth, we could not assess the status of paternal or maternal diabetes; however, previous studies have reported a difference between paternal and maternal diabetes status in birthweight and insulin resistance[53,54]. Fifth, owing to a lack of detailed data regarding the fetal environment, it was not possible to clarify whether the cause of LBW was attributable only to intrauterine undernutrition. Sixth, we could not assess catch-up growth, which might contribute to increased risks of abdominal obesity and type 2 diabetes later in life[55]. Seventh, we carried out a population-based study with 1,021 individuals; as a result, the number of individuals with LBW with type 2 diabetes was 28, with 15 of these individuals carrying the *RETN G/G* genotype. The number of cases of type 2 diabetes was thus too small to carry out further analyses adjusted by generation. Therefore, further studies with larger populations are desirable to confirm these associations.

In conclusion, this population-based study shows that the interaction of LBW influenced by the intrauterine environment and the *RETN G/G* genotype can more accurately predict the risk of type 2 diabetes in adulthood than assessing each of these factors alone. As LBW represents a public health challenge with an increasing global incidence, assessment of the *RETN rs1862513* genotype might provide appropriate management strategies, including early lifestyle intervention, in the population with LBW.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The Committee of Ehime University Graduate School of Medicine approved this study on 4 March 2019 (approval number 29-K3). The study was carried out under the principles of the Declaration of Helsinki.

Informed consent: All participants provided informed consent prior to study enrollment.

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Animal studies: N/A.

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