



Article

Maternal Age at Menarche Genes Determines Fetal Growth Restriction Risk

Evgeny Reshetnikov ¹, Maria Churnosova ¹ , Yuliya Reshetnikova ¹, Vadim Stepanov ², Anna Bocharova ² , Victoria Serebrova ², Ekaterina Trifonova ² , Irina Ponomarenko ¹, Inna Sorokina ¹, Olga Efremova ¹ , Valentina Orlova ¹, Irina Batlutskaya ¹, Marina Ponomarenko ¹, Vladimir Churnosov ¹, Inna Aristova ¹, Alexey Polonikov ^{1,3} and Mikhail Churnosov ^{1,*}

- ¹ Department of Medical Biological Disciplines, Belgorod State National Research University, 308015 Belgorod, Russia; reshetnikov@bsu.edu.ru (E.R.); churnosovamary@gmail.com (M.C.); 130226@bsu.edu.ru (Y.R.); ponomarenko_i@bsu.edu.ru (I.P.); sorokina@bsu.edu.ru (I.S.); efremova@bsu.edu.ru (O.E.); orlova@bsu.edu.ru (V.O.); bat@bsu.edu.ru (I.B.); 1256888@bsu.edu.ru (M.P.); churnosov_v@bsu.edu.ru (V.C.); aristova@bsu.edu.ru (I.A.); polonikov@rambler.ru (A.P.)
- ² Research Institute for Medical Genetics, Tomsk National Research Medical Center of the Russian Academy of Sciences, 634050 Tomsk, Russia; vadim.stepanov@medgenetics.ru (V.S.); anna.bocharova@medgenetics.ru (A.B.); vika.serebrova@medgenetics.ru (V.S.); ekaterina.trifonova@medgenetics.ru (E.T.)
- ³ Department of Biology, Medical Genetics and Ecology and Research Institute for Genetic and Molecular Epidemiology, Kursk State Medical University, 305041 Kursk, Russia
- * Correspondence: churnosov@bsu.edu.ru

Abstract: We aimed to explore the potential link of maternal age at menarche (mAAM) gene polymorphisms with risk of the fetal growth restriction (FGR). This case (FGR)–control (FGR free) study included 904 women (273 FGR and 631 control) in the third trimester of gestation examined/treated in the Departments of Obstetrics. For single nucleotide polymorphism (SNP) multiplex genotyping, 50 candidate loci of mAAM were chosen. The relationship of mAAM SNPs and FGR was appreciated by regression procedures (logistic/model-based multifactor dimensionality reduction [MB-MDR]) with subsequent in silico assessment of the assumed functionality of FGR-related loci. Three mAAM-appertain loci were FGR-linked to genes such as *KISS1* (rs7538038) (effect allele G-odds ratio (OR)_{allelic} = 0.63/*p*_{perm} = 0.0003; OR_{additive} = 0.61/*p*_{perm} = 0.001; OR_{dominant} = 0.56/*p*_{perm} = 0.001), *NKX2-1* (rs999460) (effect allele A-OR_{allelic} = 1.37/*p*_{perm} = 0.003; OR_{additive} = 1.45/*p*_{perm} = 0.002; OR_{recessive} = 2.41/*p*_{perm} = 0.0002), *GPRC5B* (rs12444979) (effect allele T-OR_{allelic} = 1.67/*p*_{perm} = 0.0003; OR_{dominant} = 1.59/*p*_{perm} = 0.011; OR_{additive} = 1.56/*p*_{perm} = 0.009). The haplotype ACA *FSHB* gene (rs555621*rs11031010*rs1782507) was FRG-correlated (OR = 0.71/*p*_{perm} = 0.05). Ten FGR-implicated interworking models were founded for 13 SNPs (*p*_{perm} ≤ 0.001). The rs999460 *NKX2-1* and rs12444979 *GPRC5B* interplays significantly influenced the FGR risk (these SNPs were present in 50% of models). FGR-related mAAM-appertain 15 polymorphic variants and 350 linked SNPs were functionally momentous in relation to 39 genes participating in the regulation of hormone levels, the ovulation cycle process, male gonad development and vitamin D metabolism. Thus, this study showed, for the first time, that the mAAM-appertain genes determine FGR risk.

Keywords: fetal growth restriction; single nucleotide polymorphism; association; age at menarche



Citation: Reshetnikov, E.; Churnosova, M.; Reshetnikova, Y.; Stepanov, V.; Bocharova, A.; Serebrova, V.; Trifonova, E.; Ponomarenko, I.; Sorokina, I.; Efremova, O.; et al. Maternal Age at Menarche Genes Determines Fetal Growth Restriction Risk. *Int. J. Mol. Sci.* **2024**, *25*, 2647. <https://doi.org/10.3390/ijms25052647>

Academic Editor: Natalia I. Agalakova

Received: 27 December 2023

Revised: 6 February 2024

Accepted: 14 February 2024

Published: 24 February 2024



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1. Introduction

Fetal growth restriction (FGR) is defined as a pathological inhibition of fetal intrauterine growth and the inability of the fetus to reach its growth potential, in which fetal size is below the 10th percentile for a given gestational age [1,2]. FGR is a common complication of pregnancy, the incidence of which reaches up to 10% worldwide [1,3]. FGR is the leading cause of stillbirth (more than 50% of stillborn infants had FGR or were small for gestational age) and neonatal mortality/morbidity [4–7], and the long-term effects of FGR

in adulthood are associated with an increased risk of developing cardiovascular/metabolic disorders (dyslipidemia; insulin resistance; arterial hypertension; obesity; type II diabetes; fatty liver, etc.) [8–10].

The FGR pathogenesis is complex and can be associated with various factors (maternal; placental; fetal), leading to a limited supply of nutrients and oxygen to the fetus [3,11–17]. Maternal risk factors such as advanced age, underweight, hypertension, diabetes, genetics, etc., are essential in the formation of FGR [2,18]. The above violations of the maternal organism can facilitate the evolution of various placental disorders (vascular malperfusion disturbances in the maternal–fetal system (fibrin deposition/infarction/chronic abruption), chronic inflammation of placenta, etc.), leading to change in placental nutrient transport (glucose; amino acids; fatty acids; oxygen intake) which in turn can cause the formation of FGR [2,18,19].

Among the indicators reflecting the state of a woman's reproductive system (hypothalamic–pituitary–ovarian system/axis functioning) and her possible health problems in the future life is the age at menarche (AAM) [20,21]. AAM correlates significantly with hormone-, glucose/insulin-dependent pathways in a woman's body [20,21], and, as a result, can affect the course/complications of pregnancy (e.g., blood pressure, preeclampsia, premature birth, gestational diabetes) [22–27]. Also, such AAM-mediated signs/diseases as body mass index (BMI)/obesity/cardiovascular diseases, etc. [20,28], can have a weighty aftermath for the course/outcomes of pregnancy [18]. Previous studies have shown the association of maternal mAAM (mAAM) with premature birth [24], pregnant blood pressure [25] and preeclampsia [22,23,26], as well as offspring BMI [29,30]. Importantly, all the abovementioned pregnancy course/outcomes directly correlate with FGR [2,18]. AAM gene association with female reproductive organ diseases [31–33], BMI-related phenotypes (height; weight; BMI) of adults [34–39], newborn weight [40], and complications of pregnancy (gestational diabetes) [27] has been demonstrated. Notwithstanding, the relationship of AAM genes with FGR has not been studied to date. We aimed to explore the potential link of mAAM gene polymorphisms with FGR risk.

2. Results

2.1. FGR and FGR Free Group Characteristics

All basic medical/anamnestic/biological characteristics of FGR and FGR free groups from matched/unmatched data are shown in Table 1. According to the information presented in Table 1, such parameters as age ($p = 0.017$), pre-pregnancy maternal BMI (mBMI) parameter distribution ($p = 0.0001$), number of gravidity ($p = 0.004$) and induced abortions ($p = 0.0001$) in the anamnesis, the presence in anamnesis of arterial hypertension ($p = 0.0001$), FGR ($p = 0.00001$) and preeclampsia ($p = 0.001$) between the two cohorts compared were statistically different, and therefore these characteristics were included in the logistic regression models as confounders.

2.2. SNP/Haplotype Association Analysis

All 49 single nucleotide polymorphisms (SNPs) were consistent with Hardy–Weinberg Equilibrium (HWE) (all p -values were ≥ 0.022 at a threshold value for 49 SNPs $p_{\text{bonf}} = 0.05/49 = 0.001$) (Table S1). Three mAAM-appertain loci were FGR-linked, including such genes as *KISS1* (rs7538038) (effect allele G-odds ratio (OR)_{allelic} = 0.63/ $p = 0.0003$ / $p_{\text{perm}} = 0.0003$; OR_{additive} = 0.61/ $p = 0.001$ / $p_{\text{perm}} = 0.001$ /power = 96.00%; OR_{dominant} = 0.56/ $p = 0.001$ / $p_{\text{perm}} = 0.001$ /power = 96.27%, *NKX2-1* (rs999460) (effect allele A-OR_{allelic} = 1.37/ $p = 0.003$ / $p_{\text{perm}} = 0.003$; OR_{additive} = 1.45/ $p = 0.002$ / $p_{\text{perm}} = 0.002$ /power = 93.92%; OR_{recessive} = 2.41/ $p = 0.0002$ / $p_{\text{perm}} = 0.0002$ /power = 99.44%), *GPRC5B* (rs12444979) (effect allele T-OR_{allelic} = 1.67/ $p = 0.0002$ / $p_{\text{perm}} = 0.0003$; OR_{dominant} = 1.59/ $p = 0.011$ / $p_{\text{perm}} = 0.011$ /power = 83.75%; OR_{additive} = 1.56/ $p = 0.005$ / $p_{\text{perm}} = 0.009$ /power = 89.88%) (Table 2). The haplotype ACA *FSHB* gene (rs555621*rs11031010*rs1782507) was FRG-correlated (OR = 0.71/ $p = 0.017$ / $p_{\text{perm}} = 0.05$) (Table 3).

Table 1. Phenotypic characteristics of study participants.

Parameters	FGR Patients $\bar{X} \pm \text{SD}/\%(n)$	Controls $\bar{X} \pm \text{SD}/\%(n)$	<i>p</i> -Value
N	273	631	
Age, years	27.18 $\pm$ 4.84	26.57 $\pm$ 4.94	0.017
Height, m	1.65 $\pm$ 0.06	1.65 $\pm$ 0.06	0.52
Weight, kg	63.53 $\pm$ 11.81	63.50 $\pm$ 11.22	0.78
Pre-pregnancy BMI, kg/m ²	23.40 $\pm$ 4.31	23.40 $\pm$ 3.47	0.23
Underweight (<18.50)	8.69 (24)	5.55 (35)	
Normal weight (18.50–24.99)	66.30 (181)	66.72 (421)	0.0001
Overweight (25.00–29.99)	14.29 (39)	22.19 (140)	
Obesity (>30)	10.62 (29)	5.55 (35)	
Age at menarche and menstrual cycle			
Age at menarche, years	12.80 $\pm$ 1.14	12.83 $\pm$ 1.17	0.51
Early (<12)	3.66 (10)	6.5 (41)	
Average (12–14)	90.11 (246)	86.69 (547)	0.23
Late (>14)	6.23 (17)	6.81 (43)	
Menstrual cycle length, days	28.11 $\pm$ 1.64	28.05 $\pm$ 1.93	0.19
Duration of menstrual bleeding, days	5.02 $\pm$ 0.85	5.04 $\pm$ 1.03	0.93
Reproductive characteristic			
First pregnancy	34.93 (95)	40.41 (255)	0.19
No. of gravidity	1.47 $\pm$ 1.55	1.07 $\pm$ 2.04	0.004
No. of births	0.59 $\pm$ 0.69	0.56 $\pm$ 0.81	0.43
Stillbirth	0.01 $\pm$ 0.10	0.007 $\pm$ 0.08	0.62
No. of spontaneous abortions	0.23 $\pm$ 0.53	0.13 $\pm$ 0.35	0.07
No. of induced abortions	0.64 $\pm$ 0.99	0.37 $\pm$ 0.78	0.0001
Risk factors			
Smoking *	61.54 (168)	63.71 (402)	0.87
Alcohol **	81.68 (223)	79.72 (503)	0.79
History of arterial hypertension	8.79 (24)	1.74 (11)	0.0001
History of sexually transmitted diseases	35.56 (16)	26.62 (168)	0.28
History of preeclampsia	10.99 (30)	3.80 (24)	0.001
History of FGR	19.78 (54)	0.79 (5)	0.00001

Note: BMI, Body mass index; significant *p*-values showed in bold; *—regular and irregular (episodic) smoking at least 1 time or more per week; **—drinking low-alcohol drinks (wine, beer and others) or/and strong alcoholic beverages at least 1 time or more per week; *p* values < 0.05 are shown in bold.

2.3. Association Analysis of SNP Interactions

Ten FGR-risky/protective interworking models were founded for 13 SNPs (out of 49 examined loci) ($p_{\text{perm}} \leq 0.001$) (Table 4). The rs999460 *NKX2-1* and rs12444979 *GPRC5B* interplays significantly influenced FGR risk (these SNPs were present in 50% models [five models each] and their two-SNP interplay was part of three models [30% models] of a three-order interaction). The maximum effect on FGR risk was registered by us for a model that includes such four mAAM polymorphisms as rs1544410 *VDR*-rs1398217 *SKOR2*-rs7579411 *LHCGR*-rs314280 *LIN28B* ($WH = 49.59/p = 1.89 \times 10^{-12}/p_{\text{perm}} < 0.001$) (Table 4). The highest degree of statistical magnitude of associations was registered for such genetic combinations as rs222003 *GG GC* $\times$ rs7538038 *AG KISS1* $\times$ rs999460 *GA NKX2-1* ($\beta(FGR) = -1.07$; $p = 0.00004$), rs3020394 *AA ESR1* $\times$ rs12444979 *CC GPRC5B* ($\beta(FGR) = -0.57$; $p = 0.0003$), rs12444979 *CC GPRC5B* $\times$ rs999460 *GG NKX2-1* $\times$ rs11031010 *CC FSHB* ($\beta(FGR) = -0.64$; $p = 0.0003$) (protective effects) and rs7538038 *AA KISS1* $\times$ rs999460 *AA NKX2-1* ($\beta(FGR) = 0.98$; $p = 0.0004$), rs1544410 *GA VDR* $\times$ rs1398217 *CG SKOR2* $\times$ rs7579411 *CC LHCGR* $\times$ rs314280 *CT LIN28B* ($\beta(FGR) = 1.26$; $p = 0.0004$) (risk effects) (Table S2).

Table 2. Associations of 49 mAAM-involved SNPs with FGR.

Minore Allele (SNP)	Gene	Chr	N	Genetic Models															
				Allelic				Additive				Dominant				Recessive			
				OR	95%CI		<i>p</i>	OR	95%CI		<i>p</i>	OR	95%CI		<i>p</i>	OR	95%CI		<i>p</i>
					L95	U95			L95	U95			L95	U95			L95	U95	
T (rs1514175)	<i>TNNI3K</i>	1	896	1.08	0.88	1.33	0.454	1.04	0.83	1.30	0.759	1.04	0.75	1.44	0.827	1.07	0.69	1.65	0.764
T (rs466639)	<i>RXRG</i>	1	899	0.91	0.66	1.24	0.534	0.89	0.63	1.25	0.505	0.90	0.61	1.33	0.613	0.65	0.20	2.08	0.464
G (rs7538038)	<i>KISS1</i>	1	898	0.63	0.49	0.81	0.0002	0.61	0.46	0.82	0.001	0.56	0.40	0.79	0.001	0.57	0.24	1.37	0.208
C (rs713586)	<i>RBJ</i>	2	899	0.97	0.79	1.19	0.775	0.97	0.78	1.21	0.777	0.97	0.69	1.36	0.838	0.95	0.64	1.40	0.790
A (rs2164808)	<i>POMC</i>	2	898	1.09	0.89	1.34	0.382	1.06	0.84	1.32	0.641	1.14	0.80	1.62	0.475	1.00	0.68	1.48	0.995
A (rs7589318)	<i>POMC</i>	2	900	0.98	0.79	1.22	0.867	0.96	0.75	1.22	0.739	1.16	0.84	1.59	0.364	0.49	0.27	0.91	0.025
C (rs4374421)	<i>LHCGR</i>	2	874	0.93	0.74	1.16	0.504	0.94	0.73	1.21	0.637	0.99	0.71	1.37	0.941	0.76	0.42	1.36	0.356
T (rs7579411)	<i>LHCGR</i>	2	891	0.91	0.74	1.11	0.351	0.98	0.78	1.25	0.890	0.85	0.60	1.20	0.347	1.19	0.80	1.79	0.392
C (rs4953616)	<i>LHCGR</i>	2	892	0.96	0.76	1.20	0.697	0.93	0.72	1.20	0.569	0.89	0.65	1.23	0.478	1.00	0.54	1.84	0.993
G (rs6732220)	<i>FSHR</i>	2	898	0.93	0.74	1.17	0.538	0.87	0.67	1.14	0.321	0.93	0.68	1.28	0.664	0.52	0.23	1.14	0.104
G (rs4953655)	<i>FSHR</i>	2	898	0.87	0.68	1.10	0.248	0.81	0.61	1.06	0.129	0.84	0.60	1.16	0.277	0.50	0.22	1.15	0.104
A (rs12617311)	<i>PLCL1</i>	2	895	0.99	0.80	1.23	0.954	1.05	0.82	1.33	0.714	1.03	0.75	1.43	0.838	1.12	0.68	1.84	0.649
C (rs6438424)	<i>IGSF11</i>	3	888	0.95	0.78	1.17	0.647	0.93	0.74	1.16	0.518	0.96	0.67	1.36	0.800	0.85	0.58	1.25	0.408
A (rs2013573)	<i>UGT2B4</i>	4	899	1.23	0.95	1.60	0.120	1.20	0.88	1.62	0.249	1.22	0.87	1.70	0.252	1.27	0.42	3.83	0.676
A (rs13111134)	<i>UGT2B4</i>	4	896	1.27	1.00	1.62	0.052	1.28	0.96	1.71	0.095	1.35	0.98	1.87	0.068	1.06	0.40	2.81	0.905
C (rs222003)	<i>GC</i>	4	900	1.21	0.80	1.83	0.360	1.07	0.67	1.71	0.765	1.05	0.65	1.72	0.833	2.01	0.18	22.37	0.571
C (rs222020)	<i>GC</i>	4	899	0.96	0.70	1.32	0.806	1.08	0.75	1.55	0.666	1.09	0.75	1.60	0.649	0.98	0.14	7.01	0.985
G (rs3756261)	<i>EGF</i>	4	898	1.00	0.69	1.47	0.983	1.01	0.66	1.56	0.954	1.01	0.64	1.58	0.963	1.11	0.09	14.24	0.935
T (rs757647)	<i>KDM3B</i>	5	889	0.94	0.74	1.19	0.621	0.99	0.75	1.31	0.955	1.08	0.78	1.49	0.658	0.59	0.25	1.41	0.237
G (rs7766109)	<i>F13A1</i>	6	898	1.16	0.95	1.42	0.141	1.06	0.85	1.33	0.619	1.10	0.77	1.58	0.600	1.06	0.73	1.54	0.778
A (rs4946651)	<i>LIN28B</i>	6	900	1.00	0.81	1.22	0.972	1.14	0.90	1.44	0.274	1.20	0.86	1.69	0.288	1.16	0.75	1.77	0.504
C (rs7759938)	<i>LIN28B</i>	6	899	1.04	0.83	1.30	0.718	1.18	0.92	1.52	0.180	1.31	0.95	1.81	0.104	1.05	0.59	1.88	0.861
T (rs314280)	<i>LIN28B</i>	6	888	0.99	0.80	1.22	0.918	1.14	0.89	1.44	0.301	1.18	0.84	1.67	0.334	1.17	0.74	1.83	0.505
A (rs314276)	<i>LIN28B</i>	6	874	0.97	0.78	1.21	0.791	1.10	0.86	1.41	0.445	1.15	0.83	1.59	0.398	1.08	0.63	1.85	0.789
G (rs3020394)	<i>ESR1</i>	6	899	1.24	1.00	1.54	0.049	1.17	0.92	1.49	0.202	1.07	0.78	1.47	0.687	1.74	1.05	2.88	0.033
G (rs1884051)	<i>ESR1</i>	6	900	1.22	0.99	1.52	0.068	1.14	0.89	1.45	0.291	1.04	0.76	1.43	0.812	1.67	1.00	2.80	0.051
C (rs7753051)	<i>IGF2R</i>	6	898	1.01	0.81	1.26	0.910	0.93	0.72	1.20	0.579	1.05	0.76	1.44	0.772	0.53	0.27	1.05	0.068
C (rs1079866)	<i>INHBA</i>	7	899	0.89	0.68	1.16	0.386	0.88	0.65	1.19	0.403	0.91	0.64	1.28	0.579	0.55	0.19	1.60	0.275
T (rs2288696)	<i>FGFR1</i>	8	899	1.12	0.87	1.44	0.367	1.08	0.81	1.44	0.588	1.19	0.85	1.65	0.307	0.59	0.22	1.60	0.298
A (rs10980926)	<i>ZNF483</i>	9	899	0.86	0.69	1.07	0.185	0.85	0.66	1.08	0.186	0.85	0.62	1.18	0.334	0.68	0.38	1.21	0.193
C (rs10441737)	<i>ZNF483</i>	9	880	0.81	0.65	1.02	0.068	0.79	0.61	1.01	0.058	0.79	0.57	1.09	0.144	0.60	0.33	1.07	0.083
C (rs10769908)	<i>STK33</i>	11	885	1.14	0.93	1.40	0.207	1.11	0.89	1.39	0.354	1.35	0.94	1.95	0.106	0.97	0.66	1.42	0.860
G (rs555621)	<i>FSHB</i>	11	896	1.13	0.92	1.39	0.232	1.08	0.85	1.36	0.531	1.16	0.82	1.64	0.395	1.02	0.66	1.57	0.937
A (rs11031010)	<i>FSHB</i>	11	892	1.11	0.82	1.51	0.484	1.12	0.80	1.57	0.498	1.16	0.80	1.69	0.445	0.99	0.29	3.37	0.987
C (rs1782507)	<i>FSHB</i>	11	898	1.08	0.88	1.33	0.476	1.19	0.94	1.51	0.151	1.11	0.80	1.54	0.531	1.59	1.01	2.51	0.047
A (rs6589964)	<i>BSX</i>	11	900	0.87	0.71	1.06	0.165	0.80	0.64	1.01	0.058	0.78	0.55	1.11	0.170	0.70	0.47	1.04	0.080
A (rs1544410)	<i>VDR</i>	12	896	1.18	0.96	1.45	0.121	1.20	0.95	1.53	0.125	1.28	0.92	1.78	0.150	1.26	0.79	1.99	0.332
A (rs999460)	<i>NKX2-1</i>	14	898	1.37	1.11	1.69	0.003	1.45	1.14	1.83	0.002	1.33	0.96	1.83	0.088	2.41	1.53	3.82	0.0002
A (rs4986938)	<i>ESR2</i>	14	898	0.95	0.77	1.18	0.657	0.93	0.73	1.19	0.576	0.90	0.65	1.24	0.510	0.96	0.58	1.59	0.883
A (rs2241423)	<i>MAP2K5</i>	15	895	1.21	0.93	1.57	0.160	1.13	0.83	1.52	0.434	1.13	0.80	1.59	0.480	1.30	0.50	3.38	0.597

Table 2. Cont.

Minore Allele (SNP)	Gene	Chr	N	Genetic Models															
				Allelic				Additive				Dominant				Recessive			
				OR	95%CI		p	OR	95%CI		p	OR	95%CI		p	OR	95%CI		p
					L95	U95			L95	U95			L95	U95			L95	U95	
T (rs12444979)	GPRC5B	16	895	1.67	1.27	2.20	0.0002	1.56	1.14	2.13	0.005	1.59	1.11	2.27	0.011	2.56	0.94	6.92	0.065
A (rs9939609)	FTO	16	898	1.10	0.90	1.35	0.348	1.07	0.85	1.34	0.584	1.06	0.75	1.49	0.748	1.13	0.75	1.70	0.547
A (rs12324955)	FTO	16	898	0.97	0.78	1.22	0.813	0.94	0.74	1.21	0.636	1.05	0.76	1.44	0.786	0.61	0.33	1.14	0.120
G (rs1398217)	SKOR2	18	891	0.97	0.79	1.19	0.778	1.06	0.84	1.34	0.618	0.99	0.70	1.38	0.936	1.26	0.82	1.94	0.296
G (rs2252673)	INSR	19	897	1.04	0.81	1.33	0.787	0.98	0.74	1.30	0.891	1.06	0.76	1.47	0.751	0.56	0.21	1.46	0.233
A (rs1073768)	GHRH	20	899	1.08	0.88	1.32	0.473	1.01	0.81	1.26	0.932	1.17	0.82	1.68	0.397	0.86	0.58	1.27	0.446
C (rs4633)	COMT	22	898	1.08	0.88	1.32	0.442	1.12	0.90	1.40	0.318	1.19	0.83	1.70	0.346	1.14	0.79	1.66	0.488
A (rs5930973)	CD40LG	23	893	1.10	0.73	1.65	0.658	1.10	0.69	1.74	0.690								
T (rs3092921)	CD40LG	23	901	1.13	0.78	1.62	0.524	1.28	0.85	1.92	0.230								

Note: Chr, chromosome; OR, odds ratio; 95%CI, 95% confidence interval of OR; L95, lower limit of 95%CI; U95, upper limit of 95%CI; *p*, significance level, significant *p*-values shown in bold.

Table 3. Associations of haplotypes with FGR.

Haploblocks (Genes) and Included SNPs	Haplotypes	Frequency		OR	<i>p</i>
		FGR (n = 273)	Controls (n = 631)		
H1 (<i>FSHB</i>) rs555621-rs11031010-rs1782507	ACC	0.368	0.349	1.20	0.131
	GAA	0.131	0.120	1.11	0.529
	GCA	0.308	0.290	1.02	0.881
	ACA	0.194	0.242	0.71	0.017
H2 (<i>ZNF483</i>) rs1098092-rs10441737	AC	0.284	0.323	0.80	0.083
	GT	0.716	0.677	1.23	0.104
H3 (<i>ESR1</i>) rs3020394-rs1884051	GG	0.333	0.289	1.15	0.268
	AA	0.667	0.711	0.87	0.235
H4 (<i>LIN28B</i>) rs4946651-rs7759938	AC	0.288	0.280	1.18	0.185
	AT	0.120	0.130	0.96	0.803
	GT	0.592	0.590	0.88	0.283
H5 (<i>UGT2B4</i>) rs2013573-rs13111134	AA	0.191	0.159	1.22	0.202
	GA	0.042	0.033	1.39	0.255
	GG	0.767	0.808	0.77	0.078
H6 (<i>FSHR</i>) rs6732220-rs4953655	GG	0.224	0.246	0.84	0.200
	GA	0.018	0.011	1.60	0.301
	CA	0.757	0.743	1.17	0.243
H7 (<i>LHCGR</i>) rs7579411-rs4953616	TC	0.276	0.286	0.93	0.580
	TT	0.156	0.169	1.10	0.534
	CT	0.568	0.546	1.02	0.896
H8 (<i>POMC</i>) rs7579411-rs4953616	AA	0.297	0.299	0.97	0.785
	AG	0.178	0.153	1.17	0.317
	GG	0.526	0.548	0.95	0.658

Note: significant values shown in bold.

Table 4. SNP × SNP interactions associated with FGR.

N	Models	NH	beta H	WH	NL	beta L	WL	<i>p</i> _{perm}
Two-order interaction ($p < 5 \times 10^{-6}$)								
1	rs3020394 <i>ESR1</i> × rs7538038 <i>KISS1</i>	2	0.494	10.21	3	−0.762	20.93	<0.001
2	rs3020394 <i>ESR1</i> × rs12444979 <i>GPRC5B</i>	3	0.836	22.05	1	−0.571	13.00	<0.001
3	rs7538038 <i>KISS1</i> × rs999460 <i>NKX2-1</i>	3	0.732	23.74	1	−0.773	11.42	<0.001
Three-order interaction ($p < 1 \times 10^{-8}$)								
1	rs222003 <i>GC</i> × rs7538038 <i>KISS1</i> × rs999460 <i>NKX2-1</i>	5	0.871	32.84	1	−1.072	16.80	<0.001
2	rs713586 <i>RB1</i> × rs3020394 <i>ESR1</i> × rs12444979 <i>GPRC5B</i>	5	1.194	33.03	3	−0.794	18.91	<0.001
3	rs3020394 <i>ESR1</i> × rs999460 <i>NKX2-1</i> × rs12444979 <i>GPRC5B</i>	3	0.736	14.48	3	−0.872	32.13	<0.001
4	rs11031010 <i>FSHB</i> × rs999460 <i>NKX2-1</i> × rs12444979 <i>GPRC5B</i>	4	0.801	17.78	3	−0.816	30.32	<0.001
5	rs7538038 <i>KISS1</i> × rs999460 <i>NKX2-1</i> × rs12444979 <i>GPRC5B</i>	6	0.809	29.90	3	−0.809	27.65	<0.001
Four-order interaction ($p < 3 \times 10^{-12}$)								
1	rs1544410 <i>VDR</i> × rs1398217 <i>SKOR2</i> × rs7579411 <i>LHCGR</i> × rs314280 <i>LIN28B</i>	8	1.547	49.59	0	-	-	<0.001
2	rs314280 <i>LIN28B</i> × rs10769908 <i>STK33</i> × rs13111134 <i>UGT2B4</i> × rs7579411 <i>LHCGR</i>	8	1.280	47.32	1	−0.665	2.77	<0.001

Note: The results were obtained using the model-based multifactor dimensionality reduction (MB-MDR) method with adjustment for covariates; NH, number of significant high risk genotypes in the interaction; beta H, regression coefficient for high-risk exposition in Step 2 analysis; WH, Wald statistic for the high-risk category; NL, number of significant low-risk genotypes in the interaction; beta L, regression coefficient for low-risk exposition in Step 2 analysis; WL, Wald statistic for the low-risk category; *p*_{perm}, permutation *p*-value for the interaction model (1000 permutations).

The graph describing the interaction of 15 FGR-associated SNPs (Figure 1) demonstrates the highest indicators (% entropy) of the contribution to the FGR susceptibility of such individual loci as rs12444979 *GPRC5B* (1.14%), rs7538038 *KISS1* (1.06%), and rs999460 *NKX2-1* (0.89%) and such SNP-paired interactions as rs757647 *KDM3B*-rs314280 *LIN28B*

(0.94%), rs999460 *NKX2-1*-rs1544410 *VDR* (−0.65%), rs10769908 *STK33*-rs12444979 *GPRC5B* (−0.77%), and rs3020394 *ESR1*-rs12444979 *GPRC5B* (−0.62%).

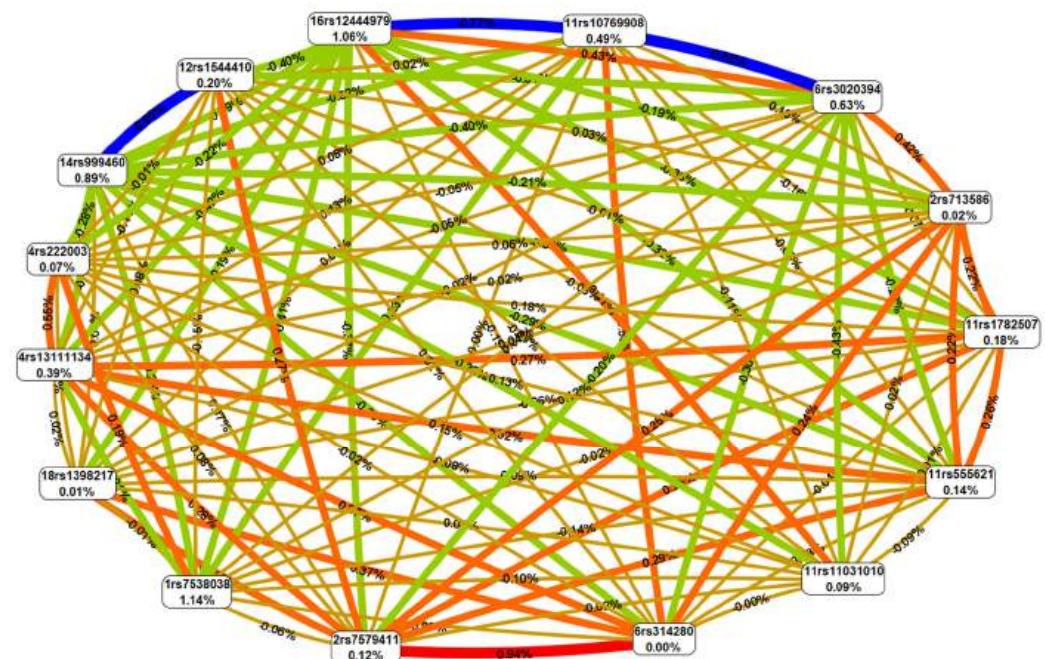


Figure 1. The entropy graph of SNP $\times$ SNP interactions with fetal growth restriction. The figure outlines the SNP $\times$ SNP interactions within the 2-, 3-, and 4-locus models obtained by the MB-MDR method. The polymorphisms are shown by the chromosome number and rs SNP ID. The percentage at the bottom of each SNP represents its entropy, and the percentage on each line represents the percentage of interaction between the 2 SNPs. The red and orange lines indicate a stronger and weaker synergism, respectively, brown—an independent effect of individual SNPs, green—weaker antagonism, blue—stronger antagonism.

2.4. FGR-Significant Locus/Gene Probable Functions

In this section of the work, a detailed analysis of the functional relevance of 15 FGR-causal loci and 430 proxy SNPs was carried out, aimed at assessing the possible connection of the considered loci ($n = 445$) with missense mutations, epigenetic changes, gene expression and splicing regulatory effects and their involvement in FGR-related pathways.

2.4.1. Missense Mutations and FGR-Linked SNPs

Three loci determining the missense mutations were discovered by us among 430 proxy SNPs such as rs4889 *KISS1* (replacement of proline with arginine in the 81 position of the *KISS1* protein; “deleterious” SIFT grade), rs11676272 *ADCY3* (replacement serine with proline in the 107 position of the *ADCY3* protein; “benign” SIFT grade), rs61742688 *GPRC5B* (replacement of asparagine with lysine in the 268 position of the *GPRC5B* protein; “benign” SIFT grade).

2.4.2. Link FGR-Involved Loci with Deoxyribonucleic Acid (DNA) Epigenetic Changes

It was revealed that all 15 FGR-causal genetic variants and the absolute majority of linkage disequilibrium (LD) SNPs (381 out 430 loci, 88.60%) potentially had different regulatory potential: they were localized in DNA sites (motifs) providing communication with transcription-regulating factors (TrF) (373/445; 83.82%), regulatory-significant gene regions such as enhancers (93/445; 20.90%) and promoters (57/445; 12.81%), potentially functionally active regions of the genome (the so-called open chromatin) (105/445; 23.59%), conservative fragments of human DNA (20/445; 4.49%), and places providing DNA “dialogue” with protein regulators (31/445; 6.97%) (Table S3). The most “outstanding” regulatory

potential has been demonstrated by such proxy loci as rs11865578 (LD with FGR-causal rs12444979 *GPRC5B*) [SNP is in the enhancer/promoter positions and open chromatin in 20/4 and 21 organs, respectively, including FGR-impact cultured cells (derived trophoblast (H1 BMP4 culture), endoderm(CD184+)/ectoderm(CD56+)/mesoderm(CD56+), neuronal progenitor cells(H1,H9) and neuron(H9), etc.), maternal (brain, skeletal muscle, ovary, placenta amnion, etc.) and fetal (brain, muscle, adrenal glands, etc.) organs], rs1222218 and rs58336049 (LD with rs1782507) [loci are in the promoter positions in 24 organs each, open chromatin in 49 and 47 organs, respectively, areas providing gene “dialogue” with 19 and 18 protein regulators, and 11 and 2 TrF, respectively], etc. (Table S3).

Importantly, FGR-causal SNP, rs7538038 *KISS1*, was functionally active (by modulating the activity of enhancers) in FGR-correlated organs: placenta (IDepigenome-E091), a variety of maternal organs such as brain (hippocampus middle [IDepigenome-E071], substantia nigra [IDepigenome-E074], the anterior caudate [IDepigenome-E068], the dorsolateral-prefrontal cortex [IDepigenome-E073], the germinal matrix [IDepigenome-E070]), the female skeletal muscle [IDepigenome-E108], etc., and in a multitude of fetal organs such as the brain, male (IDepigenome-E081) and female (IDepigenome-E082), muscle (IDepigenome-E089/IDepigenome-E090), kidney (IDepigenome-E086), lung (IDepigenome-E088), thymus (IDepigenome-E093), etc. Similarly, another FGR-causal locus, rs999460 *NKX2-1*, also demonstrated high functional potential (by regulating the enhancers or/and promoter activity) in disorder-linked cultured cells such as derived CD184+_endoderm (IDepigenome-E011)/CD56+_ectoderm (IDepigenome-E012)/H1_BMP4_mesendoderm (IDepigenome-E004), etc. (Table S3).

In total, 15 FGR-causal SNPs and 381 variants strongly linked to them possess regulatory influences on the 19 genes (*GPR139*, *REN*, *IQCK*, *ADCY3*, *SKOR2*, *C11orf46*, *TRIM66*, *ESR1*, *LIN28B*, *GC*, *FSHB*, *LHCGR*, *GPRC5B*, *KISS1*, *UGT2B4*, *NKX2-1*, *STK33*, *RBJ*, *VDR*) in the variety of FGR-related maternal/fetal organs/cell cultures (brain, muscle, ovary, placenta, amnion, trophoblast, endoderm, ectoderm, mesoderm, neuronal progenitor cells, neurons, etc.) (Table S3).

2.4.3. Possible Gene Expression Regulatory Effects of FGR-Linked Polymorphisms

Three FGR-involved SNPs had possible regulatory effects on the expression (eQTL) of five genes such as *CENPO*, *ADCY3*, *RBJ* (rs713586), *C11orf46* (rs11031010), *HDHD2* (rs1398217) in peripheral blood (data of the Blood eQTL portal, Table S4). At the same time, 13 loci strongly linked with them (rs713586 and rs1398217) were also eQTL-serious for four genes in blood (*HDHD2*, *ADCY3*, *CENPO*, *RBJ*) (Table S5).

For 12 out of 15 FGR-related loci, we found sizeable effects on the level of transcriptional activity of 22 genes (*GPRC5B*, *ADCY3*, *HDHD2*, *ARL14EP*, *IER3IP1*, *CENPO*, *LIN28B*, *DNAJC27-AS1*, *KNOP1*, *REN*, *STK33*, *RBJ*, *UGT2A3P7*, *STON1-GTF2A1L*, *EFR3B*, *UGT2B4*, *FSHB*, *RP4-710M3.1*, *LINC00577*, *HDAC7*, *POMC*, *TRIM66*), including in organs involved in FGR biology such as subcutaneous (*GPRC5B*, *ADCY3*, *ARL14EP*, *CENPO*, *KNOP1*) and visceral (*KNOP1*, *DNAJC27-AS1*, *ADCY3*, *STK33*) adipose tissue, ovary (*KNOP1*, *ARL14EP*), skeletal muscle (*IER3IP1*, *HDHD2*, *STK33*, *KNOP1*), breast (*STK33*, *GPRC5B*), thyroid (*IER3IP1*, *TRIM66*, *STON1-GTF2A1L*, *KNOP1*, *ARL14EP*), the adrenal gland (*KNOP1*, *ARL14EP*), blood (*KNOP1*, *CENPO*, *DNAJC27-AS1*, *ADCY3*, *ARL14EP*), brain [hypothalamus (*GPRC5B*, *FSHB*), basal ganglia (*GPRC5B*, *ARL14EP*), cortex (*LIN28B*, *FSHB*)], etc. (Table S6). Interestingly, the risk allele for FGR-T rs12444979 *GPRC5B*, was associated ($p_{FDR} \leq 0.05$) with higher *KNOP1* gene mRNA production in subcutaneous ($\beta = 0.64$) and visceral ($\beta = 0.81$) adipose tissue, skeletal muscle ($\beta = 0.73$), breast ($\beta = 0.81$), ovary ($\beta = 1.00$), thyroid (0.58), blood ($\beta = 0.35$), adrenal gland ($\beta = 0.66$), hypothalamus ($\beta = 0.89$) and basal ganglia (nucleus accumbens) ($\beta = 0.82$) of brain and lower *GPRC5B* transcription in the subcutaneous adipose ($\beta = -0.25$) (Table S6).

According to the eQTL data provided in Tables S6 and S7 of the 15 FGR-involved SNPs have 330 proxy SNPs, eQTL-substantial for 23 genes such as *EFR3B*, *ADCY3*, *HDHD2*, *ARL14EP*, *REN*, *CENPO*, *RP11-49K24.8*, *DNAJC27-AS1*, *LINC00577*, *UGT2A3P7*, *RBJ*, *FSHB*,

TRIM66, HACE1, STK33, IER3IP1, NCOA1, LIN28B, SMAD2, POMC, RP4-710M3.1, STON1-GTF2A1L, UGT2B4. The most marked eQTL effects have been demonstrated by loci linked to FGR-associated SNPs *FSHB* (rs5556214; rs11031010; rs1782507-130 LD loci affect the expression of three genes such as *FSHB, RP4-710M3.1, ARL14EP* in the ovary), *STK33* (rs10769908) (130 LD variants are involved in transcriptional activity regulation of two genes [*STK33, TRIM66*] in visceral adipose and breast), *RBJ* (rs713586) (20 proxy SNPs were linked with mRNA levels of seven genes such as *NCOA1, EFR3B, CENPO, POMC, ADCY3, RBJ, DNAJC27-AS1* in blood, visceral/subcutaneous adipose (Table S7).

In total, 12 out of 15 FGR-impact SNPs and 330 LD variants are used essentially for mRNA formation of 27 genes: *RP11-49K24.8, ADCY3, UGT2B4, ARL14EP, UGT2A3P7, C11orf46, TRIM66, CENPO, STON1-GTF2A1L, DNAJC27-AS1, SMAD2, EFR3B, HACE1, FSHB, LIN28B, GPRC5B, LINC00577, HDAC7, RP4-710M3.1, HDHD2, POMC, NCOA1, KNOP1, RBJ, IER3IP1, REN STK33*.

2.4.4. Potential Opportunity of Splicing Regulation of FGR-Related Loci

It was found that 7 out of 15 FGR-associated loci (46.67%) (Table S8) and 250 out of 430 SNPs in LD with them (58.14%) (Table S9) have a potential influence on the formation of alternative splicing variants of immature messenger ribonucleic acid (mRNA) (sQTL) of eight genes such as *SFTA3, ADCY3, LIN28B-AS1, ARL14EP, KNOP1, DNAJC27-AS1, STK33, KATNAL2*. Moreover, these effects were meaningful in such FGR-significant organs of the maternal organism as subcutaneous (*ADCY3, KNOP1, ARL14EP*) and visceral-omentum (*KNOP1, ARL14EP*) adipose, adrenal (*ARL14EP*) and thyroid (*KATNAL2, ARL14EP, KNOP1, SFTA3*) glands, ovary (*KNOP1*), whole blood (*ARL14EP*), skeletal muscle (*KNOP1, ARL14EP*), the brain cortex and pituitary (in both *ARL14EP*), cultured fibroblasts (*ARL14EP*), breast (mammary tissue) (*KNOP1, ARL14EP*) etc. Interestingly, FGR-risky allele T rs12444979 *GPRC5B* was correlated with low sQTL parameters of the *KNOP1* gene in subcutaneous adipose (Intron ID: 19707221:19710509:clu_17456, $\beta = -0.52$, $p = 4.4 \times 10^{-10}$, $p_{FDR} \leq 0.05$), ovary (Intron ID: 19707221:19710509:clu_14053, $\beta = -0.73$, $p = 2.7 \times 10^{-8}$, $p_{FDR} \leq 0.05$), and breast (mammary tissue) (Intron ID: 19707221:19710509:clu_17535, $\beta = -0.49$, $p = 1.6 \times 10^{-6}$, $p_{FDR} \leq 0.05$) (Table S8). The 51 sQTL-impact SNPs in the above organs have been strongly linked to this locus (Table S9). Also, the largest number (116 SNPs) of sQTL-considerable loci for the *ARL14EP* gene in cultured fibroblasts, breast, visceral adipose, and adrenal gland were in disequilibrium with FGR-associated polymorphisms (as part of the haplotype and SNP interaction models) rs555621 and rs1782507 *FSHB* (Table S9). These polymorphisms themselves are also sQTL-serious for the *ARL14EP* gene in the above organs (Table S8).

2.4.5. Probable FGR-Related Pathways

Based on the in silico data obtained at the previous stages of this research, it can be assumed that 39 genes are involved in predisposition to FGR due to the functional effects of 15 FGR-causal SNPs and 430 proxy loci on them (missense alterations in 3 genes [*GPRC5B, ADCY3, KISS1*], epigenetic transformations near 19 genes [*GC, IQCK, REN, ADCY3, C11orf46, ESR1, FSHB, UGT2B4, GPR139, GPRC5B, VDR, STK33, KISS1, LHCGR, LIN28B, NKX2-1, RBJ, SKOR2, TRIM66*], regulation of expression of 27 genes [*UGT2B4, ADCY3, UGT2A3P7, ARL14EP, TRIM66, C11orf46, STON1-GTF2A1L, CENPO, STK33, SMAD2, DNAJC27-AS1, POMC, EFR3B, RP4-710M3.1, FSHB, RP11-49K24.8, REN, GPRC5B, RBJ, HACE1, LINC00577, NCOA1, HDAC7, LIN28B, HDHD2, IER3IP1, KNOP1*] and coordination of splicing of 8 genes [*SFTA3, ADCY3, LIN28B-AS1, ARL14EP, KNOP1, DNAJC27-AS1, STK33, KATNAL2*]). GeneOntology enrichment analysis (released:2023-07-12) allowed us establishment of the involvement of 39 FGR-casual genes in the regulation of hormone levels (GO:0010817; FE-9.21; p_{FDR} -0.029), the ovulation cycle process (GO:0042698; Fold Enrichment (FE)-47.99; p_{FDR} -0.023), male gonad development (GO:0008584; FE-21.51; p_{FDR} -0.020), and vitamin D metabolism (P04396; FE-89.13; p_{FDR} -0.047).

Using the STRING program (released: 12 July 2023), we conducted a detailed and in-depth analysis of protein–protein interplays (PPint) of 39 FGR-causal genes. The results

obtained are shown in Figures 2 and 3. Three substantial KEGG pathways for this 39-gene set such as ovarian steroidogenesis (hsa04913; $p_{\text{FDR}}=0.024$), the estrogen signaling pathway (hsa04915; $p_{\text{FDR}}=0.024$), the cAMP signaling pathway (hsa04024; $p_{\text{FDR}}=0.042$) were detected by the STRING database. PPints were subdivided (clustered) into four groups (Figure 3e). The first cluster, shown in Figure 3a, combining nine proteins (HDAC7, ESR1, FSHB, KISS1, LHCGR, NCOA1, NKX2-1, POMC, SMAD2) has been involved in multiple hormone-mediated signaling and other molecular/reactome pathways such as the ovulation cycle (GO:0042698; $p_{\text{FDR}}=8.71 \times 10^{-7}$), male gonad development (GO:0008584; $p_{\text{FDR}}=8.54 \times 10^{-6}$), ovarian follicle development (GO:0001541; $p_{\text{FDR}}=0.0017$), regulation of hormone levels (GO:0010817; $p_{\text{FDR}}=0.0016$), positive regulation of transcription by RNA polymerase II (GO:0006357; $p_{\text{FDR}}=0.0035$), regulation of cell communication (GO:0010646; $p_{\text{FDR}}=0.0050$), peptide hormone biosynthesis (HSA-209952; $p_{\text{FDR}}=0.0106$), FOXO-mediated transcription of oxidative stress (HSA-9615017; $p_{\text{FDR}}=0.0144$), ADORA2B mediated anti-inflammatory cytokine production (HSA-9660821; $p_{\text{FDR}}=0.0106$), DNA-binding transcription factor binding (GO:0140297; $p_{\text{FDR}}=0.0475$), the phospholipase C-activating G protein-coupled receptor signaling pathway (GO:0007200; $p_{\text{FDR}}=0.0052$), positive regulation of the nitrogen compound metabolic process (GO:0051173; $p_{\text{FDR}}=0.0215$), etc. The second cluster, presented in Figure 3b, consists of twelve proteins (TRIM66, GPRC5B, KNOP1, ADCY3, STON1-GTF2A1L, CENPO, DNAJC27, GPR139, UGT2B4, HACE1, IQCK, STK33) linked with BMI-impact parameters (according to Human Phenotype (Monarch) data) such as waist circumference (EFO:0004342; $p_{\text{FDR}}=0.0034$) and BMI (EFO:0004340; $p_{\text{FDR}}=0.0012$). The third cluster, demonstrated in Figure 3c, incorporates six proteins (GC, VDR, ARL14EP, LIN28B, REN, SFTA3) engaged in vitamin D (calciferol) metabolism (HSA-196791; $p_{\text{FDR}}=0.0132$). The fourth cluster, displayed in Figure 3d, unites five interaction proteins (KATNAL2, EFR3B, HDHD2, IER3IP1, SKOR2) associated with the Yip1 domain and the Yos1-like pathway (STRING local network data; CL:34722; $p_{\text{FDR}}=0.0185$).

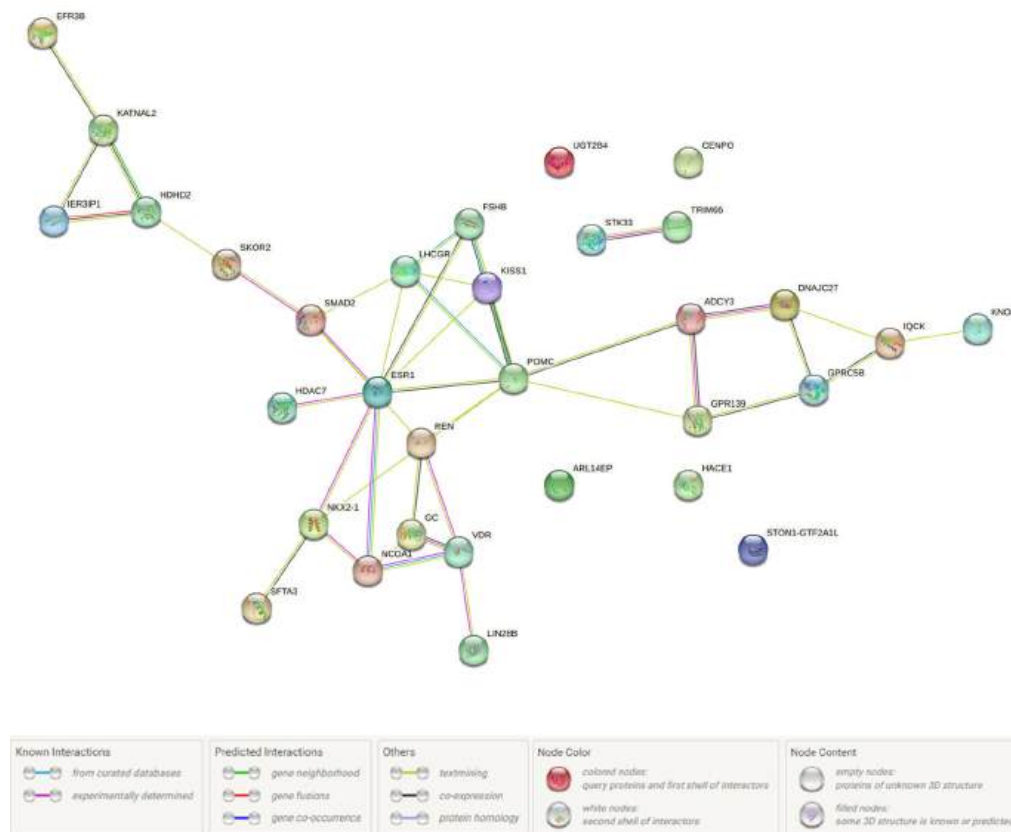


Figure 2. FGR-related protein–protein interaction networks inferred using the STRING resource.

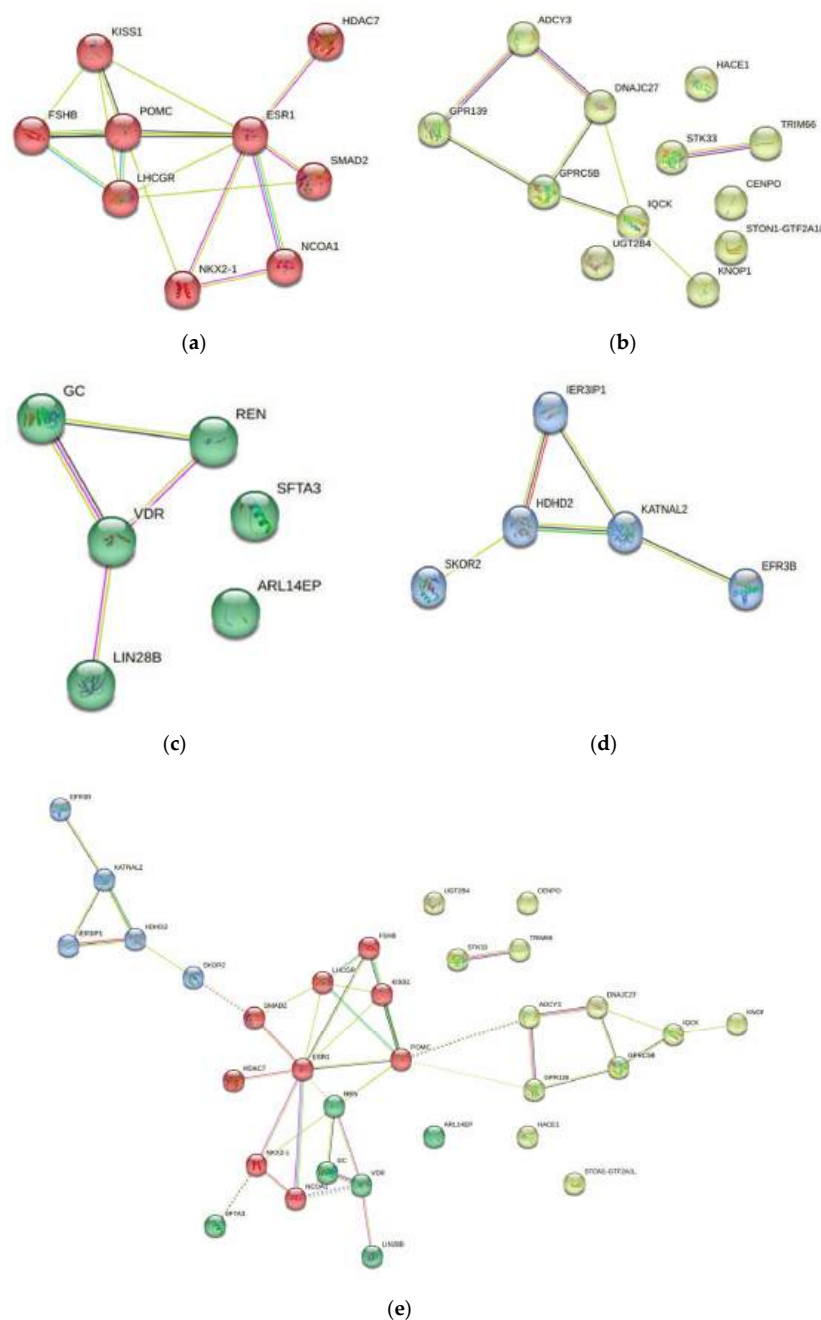


Figure 3. FGR-related protein–protein interaction clusters inferred using the STRING resource (four groups of PPint clusters are highlighted in color: Cluster 1, red (a); Cluster 2, yellow (b); Cluster 3, green (c); Cluster 4, blue (d); summary of four clusters (e)).

The result outline of this study is presented in Figure 4.

2.5. Syntropic Effects of mAAM-Involved Genes in FGR, mAAM, Pre-Pregnancy mBMI and Offspring BW

We conducted a comparative analysis of the data obtained in this paper with the results of our previous studies devoted to the study of associations of the same list of mAAM-related loci in the same population (women of the Russian ethnic group from Central Russia) with maternal AAM and BMI (mBMI) [36], BW [40], and uterus benign proliferative diseases (uterine leiomyoma (UL) [33]; endometrial hyperplasia (EH) [31]; endometriosis [32]) in order to identify common genetic factors underlying these reproductively significant phenotypes. As a result of this comparative analysis (Table S10),

FGR-related polymorphisms associated with mAAM, mBMI and BW in this population were established (Table S10, [31–33,36,40]): out of 15 FGR-associated loci, 11 variants were associated with mBMI/BW (73.33%), including 5 SNPs with BW (33.33%), 2 SNPs-mBMI (13.33%) and 4 SNPs with both BW and mBMI (26.67%); only 2 FGR-associated loci were mAAM-associated (13.33%).

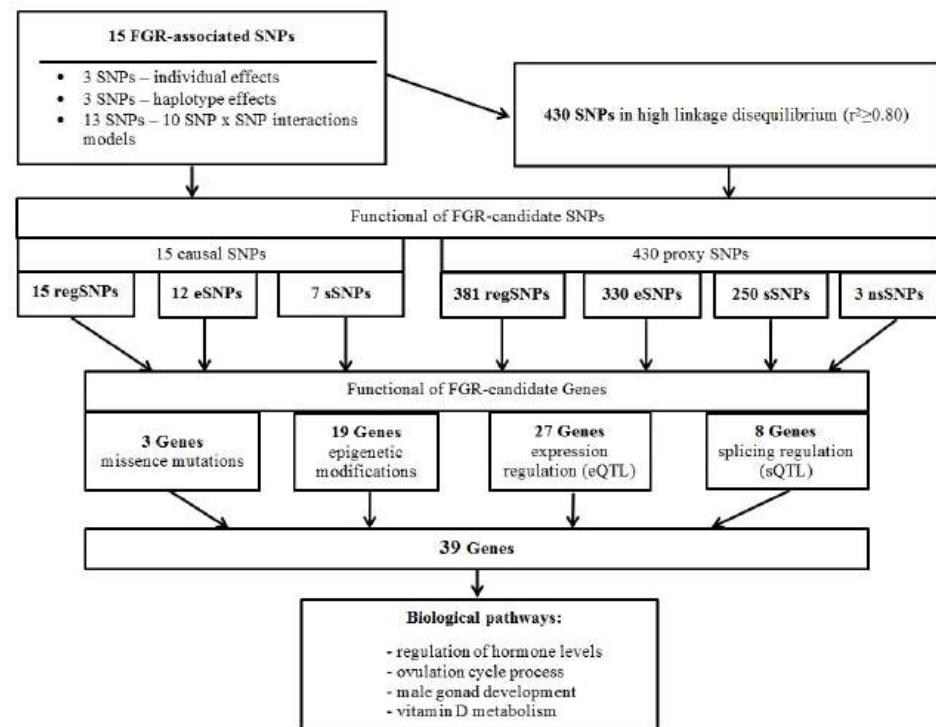


Figure 4. Study result outline.

Common genetic determinants for the three phenotypes—FGR, BW and mBMI—were four loci including rs314280 *LIN28B*, rs3020394 *ESR1*, rs555621 *FSHB* and rs999460 *NKX2-1* (Table S10). Along with this, ten out of fifteen FGR-associated mAAM-significant polymorphisms (66.67%) also determined susceptibility to uterus benign proliferative diseases: seven SNPs were UL-linked (46.67%) and six SNPs were EH- and endometriosis- associated (40.00% each). Interestingly, three loci including rs4374421 *LHCGR*, rs12324955 *FTO*, rs1782507 *FSHB* (13.63%) have been associated simultaneously with FGR and two different proliferative uterine diseases mentioned above, and three *FSHB* gene polymorphisms (rs11031010; rs555621; rs1782507) were correlated with FGR and all three uterine diseases under consideration (Table S10). These data convincingly demonstrate significant similarity in genetic determinants (mAAM-related loci) FGR and BW/mBMI (73.33%) on the one hand, and FGR and uterus benign proliferative diseases (66.67%) on the other hand.

Amid FGR-correlated genes, a large majority—60.00%—were mBMI-linked and only 31.43% were mAAM-associated; meanwhile, interestingly, 25.71% of genes (*LIN28B*; *HACE1*; *ADCY3*; *LIN28B-AS1*; *EFR3B3*; *RBJ*; *LHCGR*; *STON1-GTF2A1L*; *POMC*) were enabled in the genetic determination of all three examined phenotypic sings (FGR, mAAM, mBMI) [Figure 5a, genes functionally affected by mAAM-involved loci such as 15 SNPs (FGR; the data of this research), 22 SNPs (BW [40]), 13 SNPs (AAM [36]), 14 SNPs (BMI [36]) and proxy loci]. Meanwhile, 67.74% of mBMI-linked genes and 47.83% of mAAM-associated genes were FGR-correlated genes (Figure 5a). Among the FGR-associated genes, 65.71% were BW-influential, and amid the BW-linked genes, 51.11% were FGR-affecting (Figure 5b). The common FGR- and BW-relating genes were *LIN28B*; *SFTA3*; *GC*; *ADCY3*; *LIN28B-AS1*; *LHCGR*; *ARL14EP*; *IQCK*; *GPRC5B*; *CENPO*; *ESR1*; *DNAJC27-AS1*; *EFR3B*; *FSHB*; *KNOP1*; *GPR139*; *HACE1*; *RBJ*; *KISS1*; *NKX2-1*; *REN*; *POMC*; *UGT2B4*.

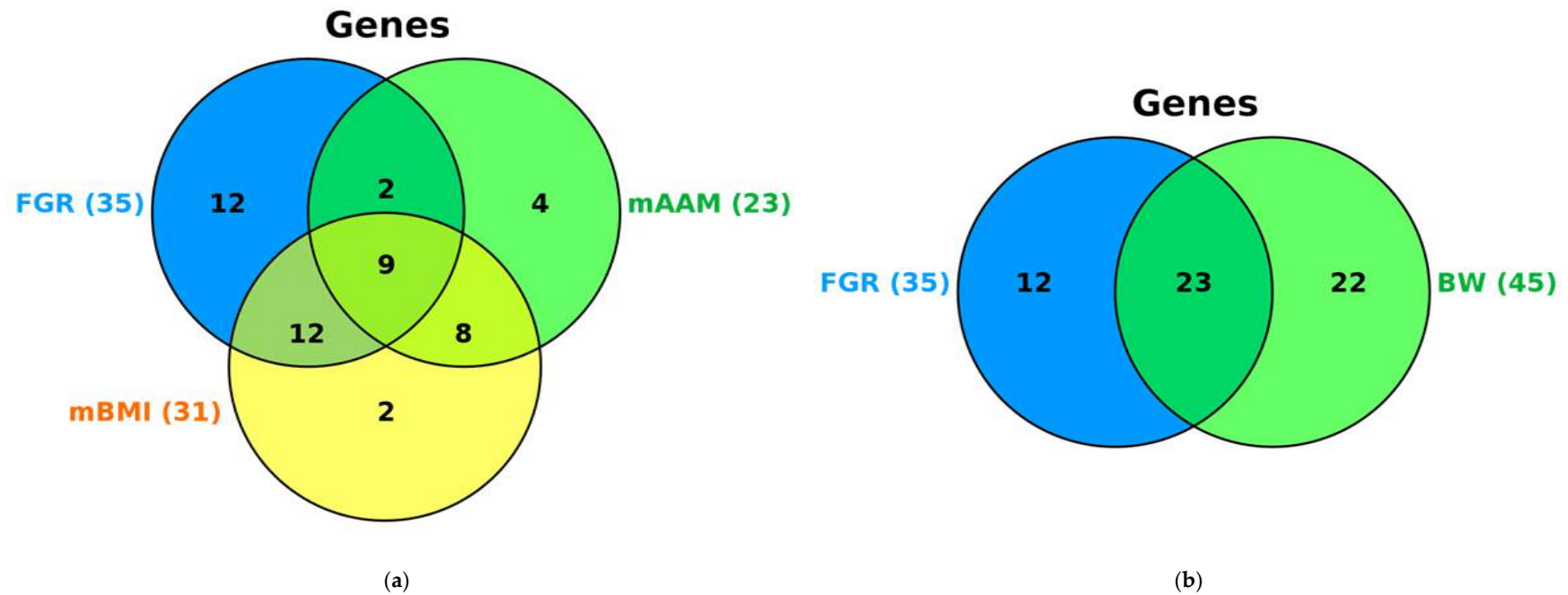


Figure 5. Venn diagram characterizing the syntropic effects of mAAM-involved genes in FGR and maternal AAM (mAAM) and pre-pregnancy BMI (mBMI) (a), FGR and offspring BW (b) (due to the functionality of FGR-,BW-,AAM- and BMI-associated mAAM-involved loci (15 SNPs [the data of this work], 13 SNPs (mAAM) and 14 SNPs (mBMI) [36] and 22 SNPs (offspring BW) [40], respectively) and proxy variants).

3. Discussion

This is the first study to find the association of mAAM-involved gene polymorphisms and FGR susceptibility risk. Three SNPs independently (rs999460 *NKX2-1*; rs7538038 *KISS1*; rs12444979 *GPRC5B*), one haplotype *FSHB* gene (rs555621*rs11031010*rs1782507) and ten SNPs-interworking models of 13 loci were FGR-implicated. FGR-correlated mAAM-related 15 polymorphisms with 430 proxy variants were functionally meaningful to 39 genes participating in the regulation of hormone levels, the ovulation cycle process, male gonad development and vitamin D metabolism.

The present study revealed associations of rs12444979 *GPRC5B* with FGR both independently (the T allele of this SNPs was risky for FGR, OR = 1.56–1.67) and as part of SNP interactions models (50% of FGR risk models included this SNPs). Also, in our previously performed genetic study in this population (Russian women of Central Russia), the relationship of maternal rs12444979 *GPRC5B* (as part of interloci “dialogue” models) with offspring birth weight (BW) [40] was shown. rs12444979 *GPRC5B* was AAM-bounded [41,42] and BMI-involved [43–46], wherein the T allele of this SNP correlated with a later AAM [41], and an alternative genetic variant for it, the C allele, was associated with increased BMI [43,44,46]. Hence, the maternal AAM-boosting/BMI-lowering allele rs12444979 *GPRC5B* was an FGR risk factor. It is believed that low pre-pregnancy weight and low weight gain during pregnancy in a woman are linked to an increased FGR risk [11,15,17].

Our in silico materials pointed to significant SNP-eQTL and SNP-sQTL correlations: the FGR risk allele T rs12444979 *GPRC5B* was associated with higher *KNOP1* gene mRNA production in multiple FGR-impact organs such as adipose (subcutaneous; visceral), skeletal muscle, ovary, thyroid, blood, adrenal gland, brain (hypothalamus, basal ganglia), lower *GPRC5B* transcription in subcutaneous adipose and low *KNOP1* gene splicing level (together with 51 proxy SNPs) in adipose (subcutaneous), ovary, breast. The *GPRC5B* gene (it is placed on 12p13.1) encodes a receptor protein coupled with G proteins [47], playing an essential role in many different FGR-significant factors (insulin resistance, inflammation, cell growth/differentiation/apoptosis, etc.) due to intracellular signaling via pathways such as mitogen-activated protein kinase (MAPK)-c-Jun NH2-terminal kinase (JNK), transforming growth factor *beta* (TGF- β), interferon *gamma* (IFN γ), cyclic adenosine monophosphate (cAMP), nuclear factor κ B (NF- κ B), signal transducer and activator of transcription (STAT3), focal adhesion kinase (FAK)/Src family kinases (SRC), and signaling cascades [48–50]. There are experimental data (obtained using transfected cell line models) on the key role of *GPRC5B* in metabolic stress processes (due to the modulation of interaction with phosphorylated sphingomyelin synthase 2) underlying lipid-generated insulin resistance [49]. The fundamental value of *GPRC5B* in the development of a chronic inflammatory process and the formation of insulin resistance in adipose as a result has been proven on a *GPRC5B*-deficient mice model [51], which indicated the critical role of this gene in the regulation of insulin-susceptible organ (muscles, adipose, central nervous system) metabolism. These processes are essential in the pathophysiology of FGR [7]. The *KNOP1* gene (for which SNP rs12444979 *GPRC5B* was sQTL-significant) encoded a nuclear protein such as lysine-rich nucleolar protein 1 interacting with a zinc finger 106 protein [51]. This protein has been involved in the regulation of particular developmental genes (e.g., *TSG118*, *TSPYL*) by chromatin rebuilding [52].

As a result of this study, correlation between rs7538038 *KISS1* and FGR was shown (allele G, OR = 0.56–0.61). This SNP was functionally active (due to the *KISS1* gene enhancers activity modulating) in FGR-correlated organs such as placenta, maternal brain (hippocampus, substantia nigra, cortex, etc.) and skeletal muscle, a multitude of fetal organs (brain male/female, muscle, kidney, lung, etc.) (our in silico materials). In previous studies, rs7538038 *KISS1* was linked with AAM (the G allele was a genetic factor of early AAM) [53], central precocious puberty in girls (allele G was risky for central precocious puberty) [54], BW and endometrial hyperplasia (as part of inter-genic interworkings, [31,40],

respectively). So, we can generalize that the AAM-reducing allele G rs7538038 *KISS1*, also associated with central precocious puberty of girls, is an FGR-protective factor.

The *KISS1* gene encodes the kisspeptin protein (KP), which is cleaved into shorter, biologically active molecules—kisspeptins (KP-54, KP-14, KP-13; KP-10), which have a biological effect by activating the G-protein-coupled receptor 54 (GPR54), also known as the KISS receptor-1 [55]. The KP/GPR54 system plays an important physiological role in neuroendocrine regulation of reproduction by influencing the hypothalamic–pituitary–gonadal axis. In addition, it affects fertility, implantation processes, and stages of the menstrual cycle [56,57]. In placental tissues, *KISS1* mRNAs and KPs are found in the syncytiotrophoblast and, to a lesser extent, in the cytotrophoblast, whereas *KISS1R* is expressed in the syncytiotrophoblast and villous and invasive extracellular trophoblast [58]. There are data on the implication of KPs in placentation regulation. In particular, KP-10 produced by trophoblast cells in the first trimester inhibits cell migration [58]. It is assumed that a decrease in the expression of *KISS1* and *KISS1R* may be correlated with a violation of placentation and FGR development: a number of studies have recorded a decrease in the level of KPs in pregnant women with FGR compared with women with physiological pregnancy [59–61]. In addition, pregnant women with FGR are characterized by a weaker increase in the level of KPs throughout pregnancy and a lower level of KPs at the end of the first and third trimester of gestation [59].

The FGR-causal locus of rs999460 *NKX2-1* increases this pregnancy complication risk (allele A, OR = 1.37–2.41) and determines susceptibility to FGR in various intergenic interactions. This SNP has a high functional potential: it was involved in the enhancer or/and promoter activity regulating disorder-linked cultured cells such as the derived CD184+_endoderm, the CD56+_ectoderm, the H1_BMP4_mesendoderm, etc., determining the nucleic acids binding with such 5TrFs as STAT, AIRE, Foxa, Arid5a, Pax-45 and controlling *SFTA3* gene splicing in the thyroid (FGR-risk allele A was linked with high *SFTA3* sQTL). Previously, associations of rs999460 *NKX2-1* with AAM [53], female BMI [36], endometrial hyperplasia [31], and offspring BW [40] were presented. Interestingly, the AAM-boosting A allele rs999460 *NKX2-1* [53] determined a high risk of FGR (OR = 1.37–2.41, our data) and was associated with a low BW [40].

NKX2-1 encodes a protein—factor transcription regulation (called TTF1 [thyroid transcription factor 1]) that communicates and “enables” (activates) promoters of the several thyroid-related hormone/protein genes such as thyroperoxidase, thyroglobulin, and the thyroid-stimulating hormone receptor [<https://www.genecards.org/> (accessed on 21 September 2023)]. Besides this, the above hormones/proteins suppress TrF NR1D1 production and inhibit, due to this, the activity of genes important for processes of gluconeogenesis and adipogenesis, bile acid/lipid metabolism, and inflammatory cell responses [62]. According to literature materials, transcription factor TTF1 (protein product of the *NKX2-1* gene) is intensively synthesized in the process intrauterine development in several embryonic organs such as brain (hypothalamus, diencephalon, ventral forebrain, etc.), lungs, thyroid, etc. [63]. Thyroid-implicated TTF1 production is vital for both the early stages of thyroid formation and embryonic development/growth overall [63]. TTF1 with other several thyroid-associated TrFs (FOXE1/HHEX/PAX8) is collectively expressed in the process of thyroid formation in progenitor/mature follicular cells of this gland, providing thyroid formation/growth/differentiation/function/homeostasis at a necessary level [63]. In TTF1 absence cases, thyroid progenitor cells may undergo apoptosis leading to their disappearance in the early stages of embryonic growth, resulting in a significant decrease in the number/mass of thyroid follicular cells; its formation is disrupted, and degradation occurs [64]. The structural–functional disturbances of the thyroid may underlie various pregnancy complications such as premature childbirth, birth of preterm newborns and infants with low BW [63], which correlate with FGR outright [7]. Epidemiological data indicate the presence of hypothyroxinemia at the 30th week of the gestation period in more than half of all infants with low BW [64].

Importantly, there is a unified result obtained for all three genes (*KISS1*, *NKX2-1*, *GPRC5B*) strongly associated with FGR: allelic variants of these genes are associated with an increased risk of FGR (the A allele, rs999460 *NKX2-1* [OR = 1.37–2.41], and the T allele, rs12444979 *GPRC5B* [1.56–1.67]), which in previous studies showed a link with late menarche [41,53] and low BW (rs999460 *NKX2-1* [40]) and adult BMI (rs12444979 *GPRC5B* [43,44]); and vice versa, the G allelic variant of the *KISS1* gene (rs7538038) is correlated with a low risk of FGR (OR = 0.56–0.63), according to earlier studies, associated with the early menarche [53]. It should be noted that the association of low maternal BMI with an increased risk of FGR is now believed to be proven and is not in doubt [2,11,15]. There is also no doubt about the connection between genetic determinants of late/early AAM and low/high BMI, which has been repeatedly proven in previous research [34,35,37–39]. In accordance with the above scientific facts, the relationship we establish between the genetic factors of late/early mAAM and low/high FGR risk corresponds to the generally accepted ideas in this field at the present time: later menarche→low BMI→high FGR risk.

In this work, we convincingly demonstrate a significant similarity in genetic determinants (mAAM-related loci) FGR and BW/mBMI (73.33%) on the one hand and FGR and uterus benign proliferative diseases (66.67%) on the other hand. In our earlier study, the proportion of “common” polymorphisms for BW and mBMI (36.36%) and proliferative uterine diseases (UL (40.90%), EH (45.45%), endometriosis (36.36%) [40]) in general corresponded to the data of this study. Nevertheless, if the common genetic determinants for BW/mAAM/mBMI were four loci (rs1073768 *GHRH*; rs4374421 *LHCGR*; rs4633 *COMT*; rs4946651 *LIN28B* [62]), then in this study, no such “common” genetic factors were identified for FGR/BW/mAAM/mBMI, but “common” genetic variants for FGR/BW/mBMI were completely different from the above list of SNPs (4 SNPs-rs314280 *LIN28B*; rs3020394 *ESR1*; rs555621 *FSHB*; rs999460 *NKX2-1*). There are also significant differences in the list of “common” genetic determinants for FGR and three benign uterine diseases (3 SNPs *FSHB*-rs11031010; rs555621; rs1782507; materials of this study) and for BW and the same three uterine diseases (3 SNPs-rs12324955 *FTO*; rs4374421 *LHCGR*; rs1782507 *FSHB*; materials of the previous study [40]). These data show that despite the presence of “common” heredity (due to mAAM-related factors) between FGR and BW/mBMI/UL/EH/endometriosis and BW and mBMI/UL/EH/endometriosis, the specific genetic determinants (polymorphisms) underlying this differ significantly, despite the significant similarity of FGR and BW in the mAAM-linked polymorphisms that define them (60.00%).

The significant similarity in the genetic “architecture” of FGR and BW shown in our study (a high percentage, more than 50%, of common genes such as *LIN28B*; *SFTA3*; *GC*; *ADCY3*; *LIN28B-AS1*; *LHCGR*; *ARL14EP*; *IQCK*; *GPRC5B*; *CENPO*; *ESR1*; *DNAJC27-AS1*; *EFR3B*; *FSHB*; *KNOP1*; *GPR139*; *HACE1*; *RBJ*; *KISS1*; *NKX2-1*; *REN*; *POMC*; *UGT2B4*) is consistent with the biomedical logic (as a rule, a fetus/newborn with a low body weight is the “basis” of the FGR group) and the literature data on this topic [7,29]. For example, the *LIN28B* gene (according to our data, this gene is essential for both FGR and BW) controls the formation of powerful specific regulators of the cell cycle (the let-7 family of miRNA) [65] and involved in the pubertal growth/development timing in girls/boys [66]. There is persuasive experimental evidence that *LIN28B*-let7 regulating the insulin/phosphoinositide 3-kinases (PI3Ks)/mammalian target of the rapamycin (mTOR) pathway (by modulating the insulin receptor (INSR), insulin-like growth factor1 receptor (IGF1R), insulin receptor substrate 2 (IRS2) effects) is a midland controller of glucose metabolism (changing insulin resistance and glucose tolerance) in mammals [67]. Several let-7 targets such as *Hmga2*, *Myc*, *Igf2bp1*, *Kras* are well-known controllers of glucose/insulin metabolism and mammalian size of body [68]. The polymorphisms of this gene, according to the results of multiple investigations, have been associated with adult height/weight/BMI [69–72]. Thus, our materials and literature data indicate that *LIN28B* may be one of the potentially relevant causal genes for both BW and FGR.

4. Materials and Methods

4.1. Study Design/Subjects

The outline of study design is shown in Figure 6. This case (FGR)–control (FGR-free) study included 904 women (273 FGR and 631 control) in the third trimester of gestation examined/treated in the Departments of Obstetrics (Belgorod Regional Clinical Hospital, Russia) during 2008–2017. All participants provided informed consent (form signed in person) prior to the start of this study. The medical ethics commission of both the Belgorod State University and the Belgorod Regional Clinical Hospital approved protocol/design of this study.

When forming the sample (FGR/FGR free), we used (a) a 24–41-week single pregnancy ending in a live birth, (b) Russian nationality (self-reported), (c) birthplace inside of Russia (Central region) [73,74] as inclusion parameters (criteria). Such parameters as age of <16 years, multifetal pregnancy, fetal/newborn congenital defects, maternal uterine congenital disturbance, and delivery at <24 weeks were used as exclusion criteria.

Clinical information, newborn growth/weight values, fetal ultrasound study (fetometry) results (analysis carried out using device TOSHIBA XARIO SSA-660A) were used for FGR diagnosis [75,76]. The degrees of FGR were determined by comparing nomograms with photometry data [77]. In the studied FGR group ($n = 273$), the first degree was diagnosed in 48.72% ($n = 133$) of participants, the second degree in 42.49% ($n = 116$), the third degree in 8.79% ($n = 24$). The pregnancy control group ($n = 631$) did not have FGR.

The participants of present research have previously been involved in other genetic studies of disorders/outcomes of pregnancy (newborn weight, preeclampsia, FGR) (detailed data on the results of these studies are contained in previous publications [40,75,76,78–82]). Table 1 presents the biological/medical characteristics of the FGR/FGR free cohorts formed.

4.2. Genetic Laboratory Analysis

To identify associations of mAAM genes with FGR, we specifically selected SNPs in these genes considering the ensuing four criteria [31–33,36,40]: (a) a previously acknowledged link with mAAM (generalizing literature data are given in Table S11, [34–36,41,42,44,45,53,66,70,83–127]); (b) a previously demonstrated correlation with mAAM-related traits such as anthropometric phenotypes (height; weight; BMI; obesity), vit.D metabolic traits, etc. (Table S11); (c) functionality validity such as epigenetic alterations, connection with transcription of genes, etc. (this assessment was carried out in silico using Haploreg data [128], the obtained estimates of SNPs functionality are presented in Table S12); (d) effective (minor) allele frequency of $\geq 5\%$ (among Europeans). As a result, the application of the above criteria made it possible to include 50 functionally significant SNPs that we previously used in the study of genetic factors of AAM [36], newborn weight [40], and female reproductive system pathology [31–33]. In total, 40 loci among 50 selected for this research were mAAM-appertain (13 SNPs in genome-wide association studies (GWAS) and 27 SNPs in associative studies) and 10 SNPs (rs222003/rs222020 GC; rs1884051/rs3020394 *ESR1*; rs4633 *COMT*; rs12324955 *FTO*; rs1544410 *VDR*; rs3756261 *EGF*; rs7766109 *F13A1*; rs2252673 *INSR*); although they were not mAAM-significant, they were involved in mAAM-important pathways such as hormone/vitamin D traits (disorder), etc. (Table S11), and had potential functional capabilities (Table S12). Additionally, 15 out of 50 SNPs have been linked with several anthropometric phenotypes (Table S11).

To collect 4–5 mL of peripheral (venous) blood, vacuum tubes (containing ethylene diamine tetra acetic acid (EDTA)) were used, from which genomic DNA was subsequently extracted (the “classical” method of isolation based on stepwise phenol–chloroform–ethanol procedures was used [129]). The resulting DNA was stored in kelvinator (temperature $-80\text{ }^{\circ}\text{C}$). For multiplex genotyping on the Sequenom device (experimental genotyping procedures were carried out at the “Medical Genomics” Core Facility of Tomsk National Research Medical Center of the Russian Academy of Sciences (Tomsk, Russia), “working” samples with a DNA level (concentration) of 5–10 ng in one microliter were prepared (the Nanodrop-2000 measuring device (spectrophotometer) was used). To estimate the

experimental data obtained, such indicators of SNP genotyping quality control were used as the call rate of at least 90% and the duplicate (blank) check success rate of at least 99% (90%) [33,130]. One SNP, rs11724758 *FABP2*, did not meet the above quality requirements (call rate = 86.13%) and was excluded from further statistical genetic analysis. Overall, 49 SNPs corresponded to all of the abovementioned quality requirements.

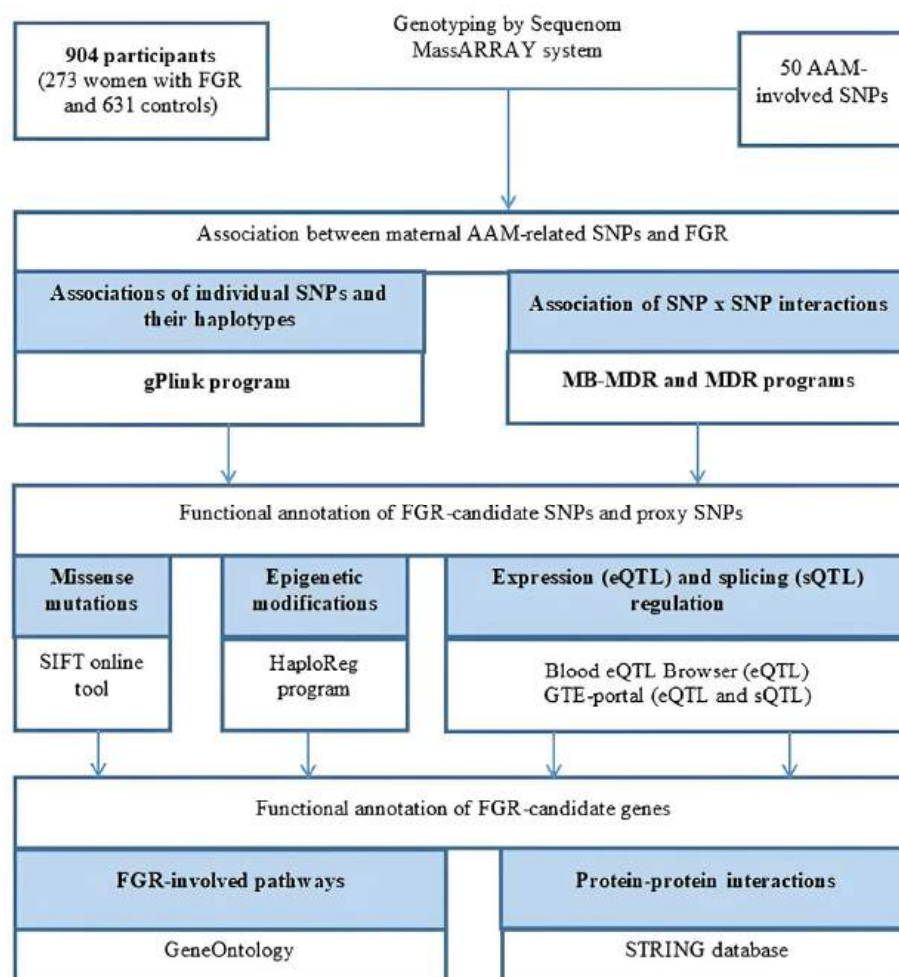


Figure 6. Study design.

4.3. Statistical Genetic Analysis

Analysis of the HWE for every polymorphism in FGR/FGR free cohorts was performed [131,132]. Association between FGR risk and mAAM-connected SNPs was detected by logistic regression with the help of such software tools as gPlink (version 1.07) [133] (for individual loci [four genetic models such as allelic, recessive, additive, dominant [134] were tested] and SNP haplotypes), MB-MDR (version 2.6) [135,136] and multifactor dimensionality reduction (MDR) [137,138] (for SNP interworking) taking into account multi-test calibration (permutation was performed) [139,140] and covariates (such as age, BMI before the current pregnancy, number of gravidity and induced abortions in the anamnesis, the presence in anamnesis of arterial hypertension, FGR and preeclampsia according to the information granted in Table 1). The following parameters, p_{perm} , were declared as statistically meaningful: for individual SNPs, $p_{\text{perm}} \leq 0.0125$ (multi-test calibration based on Bonferroni correction [0.05/4 according to the quantity of examined genetic models] was performed); for SNPs haplotypes, $p_{\text{perm}} \leq 0.050$; for models of SNPs interactions, $p_{\text{perm}} < 0.001$. It seems important that when choosing FGR-related SNP interworking models for permutation testing in order to obtain more reliable results, we used additional Bonferroni corrections

(the potential quantity of 49-locus feasible recombination taken into account). As a result, significance level parameters p for models of different multi-locus levels were derived (used as “threshold indicators” for choosing FGR-related SNP interworking models for permutation testing) such as 2 SNP interworking $-<0.05/1176 = 4 \times 10^{-5}$; 3 SNP interworking $-<0.05/18,424 = 3 \times 10^{-6}$; 4 SNP interworking $-<0.05/211,876 = 2 \times 10^{-7}$ [40]. The subjects amounted to $n = 904$ (case = 273/control = 631), with a scheduled study power of $\geq 80\%$ allowing identification of differences at the level of $OR_{additive}$ 1.33–1.56, $OR_{dominant}$ 1.59–1.63, $OR_{recessive}$ 1.61–4.71. Power indicators for FGR-linked loci were computed by the Quanto tool [141].

FGR-significant locus/gene probable functions. We explored FGR-correlated loci and LD SNPs (r^2 was not less than 0.80 [142,143]) from the standpoint of their possible functionality [144–146]. For the purpose of in-depth/comprehensive analysis of materials on this issue, based on the positively proven in extensive (including GWAS) genetic research with an in silico approach [147–150], six different contemporary bioinformatic programs/resources were utilized, such as (a) GTE Consortium data [151], (b) HaploReg [128], (c) GeneOntology knowledge base [152], (d) STRING [153], (e) Blood eQTL resource [154], and (f) SIFT [155].

5. Conclusions

The present study proves the link between mAAM-involved gene polymorphisms with FGR mediated by functional effects of FGR-associated SNPs. The data obtained expand the understanding of the medico-biological significance of maternal age at menarche genes in the formation of pregnancy complications.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/ijms25052647/s1>.

Author Contributions: Conceptualization, Y.R., I.P. and A.P.; Methodology, A.B., V.S. (Victoria Serebrova) and E.T.; Data curation, I.S., O.E., V.O. and I.B.; Formal analysis, E.R., I.A. and I.P.; Project administration, V.S. (Vadim Stepanov) and M.C. (Mikhail Churnosov); Writing—original draft, E.R., M.C. (Maria Churnosova) and M.P.; Writing—review and editing, V.C., Y.R., I.A. and M.C. (Mikhail Churnosov). All authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Local Ethical Committee of the Belgorod State University (28 January 2008, No. 1).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The data generated in the present study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Society for Maternal-Fetal Medicine (SMFM). Electronic address: Pubs@smfm.org; Martins, J.G.; Biggio, J.R.; Abuhamad, A. Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction: (Replaces Clinical Guideline Number 3, April 2012). *Am. J. Obstet. Gynecol.* **2020**, *223*, B2–B17. [CrossRef]
2. Melamed, N.; Baschat, A.; Yinon, Y.; Athanasiadis, A.; Mecacci, F.; Figueras, F.; Berghella, V.; Nazareth, A.; Tahlak, M.; McIntyre, H.D.; et al. FIGO (international Federation of Gynecology and obstetrics) initiative on fetal growth: Best practice advice for screening, diagnosis, and management of fetal growth restriction. *Int. J. Gynaecol. Obstet.* **2021**, *152* (Suppl. S1), 3–57. [CrossRef] [PubMed]
3. Bamfo, J.E.; Odibo, A.O. Diagnosis and management of fetal growth restriction. *J. Pregnancy* **2011**, *2011*, 640715. [CrossRef] [PubMed]
4. Crispi, F.; Miranda, J.; Gratacós, E. Long-term cardiovascular consequences of fetal growth restriction: Biology, clinical implications, and opportunities for prevention of adult disease. *Am. J. Obstet. Gynecol.* **2018**, *218*, S869–S879. [CrossRef] [PubMed]

5. Pels, A.; Beune, I.M.; van Wassenaer-Leemhuis, A.G.; Limpens, J.; Ganzevoort, W. Early-onset fetal growth restriction: A systematic review on mortality and morbidity. *Acta Obstet. Gynecol. Scand.* **2020**, *99*, 153–166. [[CrossRef](#)] [[PubMed](#)]
6. Mierzynski, R.; Dluski, D.; Darmochwal-Kolarz, D.; Poniedziałek-Czajkowska, E.; Leszczynska-Gorzela, B.; Kimber-Trojnar, Z.; Agnieszka-Wankowicz; Oleszczuk, J. Intra-uterine Growth Retardation as a Risk Factor of Postnatal Metabolic Disorders. *Curr. Pharm. Biotechnol.* **2016**, *17*, 587–596. [[CrossRef](#)] [[PubMed](#)]
7. Malhotra, A.; Allison, B.J.; Castillo-Melendez, M.; Jenkin, G.; Polglase, G.R.; Miller, S.L. Neonatal Morbidities of Fetal Growth Restriction: Pathophysiology and Impact. *Front. Endocrinol.* **2019**, *10*, 55. [[CrossRef](#)] [[PubMed](#)]
8. Barker, D.J.; Osmond, C.; Forsén, T.J.; Kajantie, E.; Eriksson, J.G. Trajectories of growth among children who have coronary events as adults. *N. Engl. J. Med.* **2005**, *353*, 1802–1809. [[CrossRef](#)]
9. Simeoni, U.; Armengaud, J.B.; Siddeek, B.; Tolsa, J.F. Perinatal Origins of Adult Disease. *Neonatology* **2018**, *113*, 393–399. [[CrossRef](#)]
10. D’Agostin, M.; Di Sipio Morgia, C.; Vento, G.; Nobile, S. Long-term implications of fetal growth restriction. *World J. Clin. Cases* **2023**, *11*, 2855–2863. [[CrossRef](#)]
11. Sawant, L.D.; Venkat, S. Comparative Analysis of Normal versus Fetal Growth Restriction in Pregnancy: The Significance of Maternal Body Mass Index, Nutritional Status, Anemia, and Ultrasonography Screening. *Int. J. Reprod. Med.* **2013**, *2013*, 671954. [[CrossRef](#)]
12. Voskamp, B.J.; Kazemier, B.M.; Ravelli, A.C.; Schaaf, J.; Mol, B.W.; Pajkrt, E. Recurrence of small-for-gestational-age pregnancy: Analysis of first and subsequent singleton pregnancies in The Netherlands. *Am. J. Obstet. Gynecol.* **2013**, *208*, 374.e1–374.e6. [[CrossRef](#)]
13. Albu, A.R.; Anca, A.F.; Horhoianu, V.V.; Horhoianu, I.A. Predictive factors for intrauterine growth restriction. *J. Med. Life* **2014**, *7*, 165–171. [[PubMed](#)]
14. Nardozza, L.M.; Caetano, A.C.; Zamarian, A.C.; Mazzola, J.B.; Silva, C.P.; Marçal, V.M.; Lobo, T.F.; Peixoto, A.B.; Araujo Júnior, E. Fetal growth restriction: Current knowledge. *Arch. Gynecol. Obstet.* **2017**, *295*, 1061–1077. [[CrossRef](#)] [[PubMed](#)]
15. Shi, M.Y.; Wang, Y.F.; Huang, K.; Yan, S.Q.; Ge, X.; Chen, M.L.; Hao, J.H.; Tong, S.L.; Tao, F.B. [The effect of pre-pregnancy weight and the increase of gestational weight on fetal growth restriction: A cohort study]. *Zhonghua Yu Fang Yi Xue Za Zhi* **2017**, *51*, 1074–1078. (In Chinese) [[CrossRef](#)] [[PubMed](#)]
16. Beune, I.M.; Bloomfield, F.H.; Ganzevoort, W.; Embleton, N.D.; Rozance, P.J.; van Wassenaer-Leemhuis, A.G.; Wynia, K.; Gordijn, S.J. Consensus Based Definition of Growth Restriction in the Newborn. *J. Pediatr.* **2018**, *196*, 71–76.e1. [[CrossRef](#)] [[PubMed](#)]
17. Tamura, N.; Hanaoka, T.; Ito, K.; Araki, A.; Miyashita, C.; Ito, S.; Minakami, H.; Cho, K.; Endo, T.; Sengoku, K.; et al. Different Risk Factors for Very Low Birth Weight, Term-Small-for-Gestational-Age, or Preterm Birth in Japan. *Int. J. Environ. Res. Public Health* **2018**, *15*, 369. [[CrossRef](#)]
18. Ortega, M.A.; Fraile-Martínez, O.; García-Montero, C.; Sáez, M.A.; Álvarez-Mon, M.A.; Torres-Carranza, D.; Álvarez-Mon, M.; Bujan, J.; García-Hondurilla, N.; Bravo, C.; et al. The Pivotal Role of the Placenta in Normal and Pathological Pregnancies: A Focus on Preeclampsia, Fetal Growth Restriction, and Maternal Chronic Venous Disease. *Cells* **2022**, *11*, 568. [[CrossRef](#)] [[PubMed](#)]
19. Gaccioli, F.; Lager, S. Placental Nutrient Transport and Intrauterine Growth Restriction. *Front. Physiol.* **2016**, *7*, 40. [[CrossRef](#)]
20. Yermachenko, A.; Dvornyk, V. Nongenetic determinants of age at menarche: A systematic review. *Biomed. Res. Int.* **2014**, *2014*, 371583. [[CrossRef](#)]
21. Plant, T.M. The hypothalamo–pituitary–gonadal axis. *J. Endocrinol.* **2015**, *226*, 41–54. [[CrossRef](#)]
22. Rudra, C.L.; Williams, M.A. BMI as a modifying factor in the relations between age at menarche, menstrual cycle characteristics, and risk of preeclampsia. *Gynecol. Endocrinol.* **2005**, *21*, 200–205. [[CrossRef](#)] [[PubMed](#)]
23. Abetew, D.F.; Enquobahrie, D.A.; Dishy, M.; Rudra, C.B.; Miller, R.S.; Williams, M.A. Age at menarche, menstrual characteristics, and risk of preeclampsia. *ISRN Obstet. Gynecol.* **2011**, *2011*, 472083. [[CrossRef](#)]
24. Li, H.; Song, L.; Shen, L.; Liu, B.; Zheng, X.; Zhang, L.; Li, Y.; Xia, W.; Lu, B.; Zhang, B.; et al. Age at menarche and prevalence of preterm birth: Results from the Healthy Baby Cohort study. *Sci. Rep.* **2017**, *7*, 12594. [[CrossRef](#)]
25. Petry, C.J.; Ong, K.K.; Hughes, I.A.; Acerini, C.L.; Dunger, D.B. Age at Menarche and Blood Pressure in Pregnancy. *Pregnancy Hypertens.* **2019**, *15*, 134–140. [[CrossRef](#)] [[PubMed](#)]
26. Deng, P.; Yu, Q.; Tang, H.; Lu, Y.; He, Y. Age at Menarche Mediating Visceral Adipose Tissue’s Influence on Pre-eclampsia: A Mendelian Randomization Study. *J. Clin. Endocrinol. Metab.* **2023**, *108*, 405–413. [[CrossRef](#)] [[PubMed](#)]
27. Lu, L.; Wan, B.; Sun, M. Mendelian randomization identifies age at menarche as an independent causal effect factor for gestational diabetes mellitus. *Diabetes Obes. Metab.* **2023**, *25*, 248–260. [[CrossRef](#)]
28. D’Aloisio, A.A.; DeRoo, L.A.; Baird, D.D.; Weinberg, C.R.; Sandler, D.P. Prenatal and infant exposures and age at menarche. *Epidemiology* **2013**, *24*, 277–284. [[CrossRef](#)]
29. Wang, H.; Zhang, Y.; Tian, Y.; Li, F.; Yan, C.; Wang, H.; Luo, Z.; Jiang, F.; Zhang, J. Maternal age at menarche and offspring body mass index in childhood. *BMC Pediatr.* **2019**, *19*, 312. [[CrossRef](#)]
30. Coall, D.A.; Chisholm, J.S. Evolutionary perspectives on pregnancy: Maternal age at menarche and infant birth weight. *Soc. Sci. Med.* **2003**, *57*, 1771–1781. [[CrossRef](#)]
31. Ponomarenko, I.; Reshetnikov, E.; Polonikov, A.; Sorokina, I.; Yermachenko, A.; Dvornyk, V.; Churnosov, M. Candidate genes for age at menarche are associated with endometrial hyperplasia. *Gene* **2020**, *757*, 4933. [[CrossRef](#)]

32. Ponomarenko, I.; Reshetnikov, E.; Polonikov, A.; Verzilina, I.; Sorokina, I.; Elgaeva, E.E.; Tsepilov, Y.A.; Yermachenko, A.; Dvornyk, V.; Churnosov, M. Candidate genes for age at menarche are associated with endometriosis. *Reprod. Biomed. Online* **2020**, *41*, 943–956. [\[CrossRef\]](#)
33. Ponomarenko, I.; Reshetnikov, E.; Polonikov, A.; Verzilina, I.; Sorokina, I.; Yermachenko, A.; Dvornyk, V.; Churnosov, M. Candidate genes for age at menarche are associated with uterine leiomyoma. *Front. Genet.* **2021**, *11*, 512940. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Elks, C.E.; Perry, J.R.B.; Sulem, P.; Chasman, D.I.; Franceschini, N.; He, C.; Lunetta, K.L.; Visser, J.A.; Byrne, E.M.; Cousminer, D.L.; et al. Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. *Nat. Genet.* **2010**, *42*, 1077–1085. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Perry, J.R.; Day, F.; Elks, C.E.; Sulem, P.; Thompson, D.J.; Ferreira, T.; He, C.; Chasman, D.I.; Esko, T.; Thorleifsson, G.; et al. Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche. *Nature* **2014**, *514*, 92–97. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Ponomarenko, I.; Reshetnikov, E.; Altuchova, O.; Polonikov, A.; Sorokina, I.; Yermachenko, A.; Dvornyk, V.; Golovchenko, O.; Churnosov, M. Association of genetic polymorphisms with age at menarche in Russian women. *Gene* **2019**, *686*, 228–236. [\[CrossRef\]](#)
37. Gill, D.; Brewer, C.F.; Del Greco, M.F.; Sivakumaran, P.; Bowden, J.; Sheehan, N.A.; Minelli, C. Age at menarche and adult body mass index: A Mendelian randomization study. *Int. J. Obes.* **2018**, *42*, 1574–1581. [\[CrossRef\]](#) [\[PubMed\]](#)
38. Bell, J.A.; Carslake, D.; Wade, K.H.; Richmond, R.C.; Langdon, R.J.; Vincent, E.E.; Holmes, M.V.; Timpson, N.J.; Davey Smith, G. Influence of puberty timing on adiposity and cardiometabolic traits: A Mendelian randomisation study. *PLoS Med.* **2018**, *15*, e1002641. [\[CrossRef\]](#) [\[PubMed\]](#)
39. Jo, E.J.; Han, S.; Wang, K. Estimation of Causal Effect of Age at Menarche on Pubertal Height Growth Using Mendelian Randomization. *Genes* **2022**, *13*, 710. [\[CrossRef\]](#) [\[PubMed\]](#)
40. Reshetnikova, Y.; Churnosova, M.; Stepanov, V.; Bocharova, A.; Serebrova, V.; Trifonova, E.; Ponomarenko, I.; Sorokina, I.; Efremova, O.; Orlova, V.; et al. Maternal Age at Menarche Gene Polymorphisms Are Associated with Offspring Birth Weight. *Life* **2023**, *13*, 1525. [\[CrossRef\]](#)
41. Fernandez-Rhodes, L.; Demerath, E.W.; Cousminer, D.L.; Tao, R.; Dreyfus, J.G.; Esko, T.; Smith, A.V.; Gudnason, V.; Harris, T.B.; Launer, L.; et al. Association of adiposity genetic variants with menarche timing in 92,105 women of European descent. *Am. J. Epidemiol.* **2013**, *178*, 451–460. [\[CrossRef\]](#)
42. Yermachenko, A.; Dvornyk, V. UGT2B4 previously implicated in the risk of breast cancer is associated with menarche timing in Ukrainian females. *Gene* **2016**, *1*, 85–89. [\[CrossRef\]](#)
43. Huang, J.; Huffman, J.E.; Huang, Y.; Do Valle, Í.; Assimes, T.L.; Raghavan, S.; Voight, B.F.; Liu, C.; Barabási, A.L.; Huang, R.D.L.; et al. Genomics and phenomics of body mass index reveals a complex disease network. *Nat. Commun.* **2022**, *13*, 7973. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Speliotes, E.K.; Willer, C.J.; Berndt, S.I.; Monda, K.L.; Thorleifsson, G.; Jackson, A.U.; Allen, H.L.; Lindgren, C.M.; Luan, J.; Mägi, R.; et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat. Genet.* **2010**, *42*, 937–948. [\[CrossRef\]](#)
45. Yang, T.L.; Guo, Y.; Li, S.M.; Li, S.K.; Tian, Q.; Liu, Y.J.; Deng, H.W. Ethnic differentiation of copy number variation on chromosome 16p12.3 for association with obesity phenotypes in European and Chinese populations. *Int. J. Obes.* **2013**, *37*, 188–1890. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Abadi, A.; Peralta-Romero, J.; Suarez, F.; Gomez-Zamudio, J.; Burguete-Garcia, A.I.; Cruz, M.; Meyre, D. Assessing the effects of 35 European-derived BMI-associated SNPs in Mexican children. *Obesity* **2016**, *24*, 1989–1995. [\[CrossRef\]](#)
47. GeneCards: The Human Gene Database. Available online: <https://www.genecards.org/> (accessed on 22 February 2023).
48. Jiang, X.; Xu, X.; Wu, M.; Guan, Z.; Su, X.; Chen, S.; Wang, H.; Teng, L. GPRC5A: An Emerging Biomarker in Human Cancer. *Biomed Res. Int.* **2018**, *2018*, 1823726. [\[CrossRef\]](#)
49. Kim, Y.J.; Greimel, P.; Hirabayashi, Y. GPRC5B-Mediated Sphingomyelin Synthase 2 Phosphorylation Plays a Critical Role in Insulin Resistance. *iScience* **2018**, *8*, 250–266. [\[CrossRef\]](#) [\[PubMed\]](#)
50. Atanes, P.; Ruz-Maldonado, I.; Hawkes, R.; Liu, B.; Persaud, S.J.; Amisten, S. Identifying Signalling Pathways Regulated by GPRC5B in β -Cells by CRISPR-Cas9-Mediated Genome Editing. *Cell Physiol. Biochem.* **2018**, *45*, 656–666. [\[CrossRef\]](#)
51. Kim, Y.J.; Sano, T.; Nabetani, T.; Asano, Y.; Hirabayashi, Y. GPRC5B activates obesity-associated inflammatory signaling in adipocytes. *Sci. Signal* **2012**, *5*, ra85. [\[CrossRef\]](#)
52. Grasberger, H.; Bell, G.I. Subcellular recruitment by TSG118 and TSPYL implicates a role for zinc finger protein 106 in a novel developmental pathway. *Int. J. Biochem. Cell Biol.* **2005**, *37*, 1421–1437. [\[CrossRef\]](#)
53. He, C.; Kraft, P.; Chasman, D.I.; Buring, J.E.; Chen, C.; Hankinson, S.E.; Paré, G.; Chanock, S.; Ridker, P.M.; Hunter, D.J. A large-scale candidate gene association study of age at menarche and age at natural menopause. *Hum. Genet.* **2010**, *128*, 515–527. [\[CrossRef\]](#)
54. Li, Y.; Tao, N.; Chen, M.; Chu, J.; Huang, X.; Kong, X. Gene Polymorphisms Associated with Central Precocious Puberty and Hormone Levels in Chinese Girls. *Int. J. Endocrinol.* **2022**, *2022*, 9450663. [\[CrossRef\]](#)
55. de Roux, N.; Genin, E.; Carel, J.C.; Matsuda, F.; Chaussain, J.L.; Milgrom, E. Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 10972–10976. [\[CrossRef\]](#) [\[PubMed\]](#)
56. Hameed, S.; Jayasena, C.N.; Dhillon, W.S. Kisspeptin and fertility. *J. Endocrinol.* **2011**, *208*, 97–105. [\[CrossRef\]](#) [\[PubMed\]](#)

57. Clarke, H.; Dhillon, W.S.; Jayasena, C.N. Comprehensive Review on Kisspeptin and Its Role in Reproductive Disorders. *Endocrinol. Metab.* **2015**, *30*, 124–141. [[CrossRef](#)] [[PubMed](#)]
58. Hu, K.L.; Chang, H.M.; Zhao, H.C.; Yu, Y.; Li, R.; Qiao, J. Potential roles for the kisspeptin/kisspeptin receptor system in implantation and placentation. *Hum. Reprod. Update* **2019**, *25*, 326–343. [[CrossRef](#)] [[PubMed](#)]
59. Armstrong, R.A.; Reynolds, R.M.; Leask, R.; Shearing, C.H.; Calder, A.A.; Riley, S.C. Decreased serum levels of kisspeptin in early pregnancy are associated with intra-uterine growth restriction and pre-eclampsia. *Prenat. Diagn.* **2009**, *29*, 982–985. [[CrossRef](#)] [[PubMed](#)]
60. Cetković, A.; Miljic, D.; Ljubić, A.; Patterson, M.; Ghatei, M.; Stamenković, J.; Nikolic-Djurovic, M.; Pekic, S.; Doknic, M.; Glišić, A.; et al. Plasma kisspeptin levels in pregnancies with diabetes and hypertensive disease as a potential marker of placental dysfunction and adverse perinatal outcome. *Endocr. Res.* **2012**, *37*, 78–88. [[CrossRef](#)] [[PubMed](#)]
61. Abbara, A.; Al-Memar, M.; Phylactou, M.; Daniels, E.; Patel, B.; Eng, P.C.; Nadir, R.; Izzi-Engbeaya, C.; Clarke, S.A.; Mills, E.G.; et al. Changes in Circulating Kisspeptin Levels During Each Trimester in Women with Antenatal Complications. *J. Clin. Endocrinol. Metab.* **2022**, *107*, e71–e83. [[CrossRef](#)] [[PubMed](#)]
62. Liu, Z.; Chen, X.; Zhou, S.; Liao, L.; Jiang, R.; Xu, J. The histone H3K9 demethylase Kdm3b is required for somatic growth and female reproductive function. *Int. J. Biol. Sci.* **2015**, *11*, 494–507. [[CrossRef](#)]
63. Guan, L.; Zhao, X.; Tang, L.; Chen, J.; Zhao, J.; Guo, M.; Chen, C.; Zhou, Y.; Xu, L. Thyroid Transcription Factor-1: Structure, Expression, Function and Its Relationship with Disease. *Biomed. Res. Int.* **2021**, *2021*, 9957209. [[CrossRef](#)]
64. Kusakabe, T.; Kawaguchi, A.; Hoshi, N.; Kawaguchi, R.; Hoshi, S.; Kimura, S. Thyroid-specific enhancer-binding protein/NKX2.1 is required for the maintenance of ordered architecture and function of the differentiated thyroid. *Mol. Endocrinol.* **2006**, *20*, 1796–1809. [[CrossRef](#)]
65. Tsalikas, J.; Romer-Seibert, J. LIN28: Roles and regulation in development and beyond. *Development* **2015**, *14*, 2397–2404. [[CrossRef](#)]
66. Ong, K.K.; Elks, C.E.; Li, S.; Zhao, J.H.; Luan, J.A.; Andersen, L.B.; Bingham, S.A.; Brage, S.; Smith, G.D.; Ekelund, U.; et al. Genetic variation in LIN28B is associated with the timing of puberty. *Nat. Genet.* **2009**, *41*, 729–733. [[CrossRef](#)]
67. Zhu, H.; Shyh-Chang, N.; Segrè, A.V.; Shinoda, G.; Shah, S.P.; Einhorn, W.S.; Takeuchi, A.; Engreitz, J.M.; Hagan, J.P.; Kharas, M.G.; et al. The Lin28/let-7 axis regulates glucose metabolism. *Cell* **2011**, *147*, 81–94. [[CrossRef](#)]
68. Zhu, H.; Shah, S.; Shyh-Chang, N.; Shinoda, G.; Einhorn, W.S.; Viswanathan, S.R.; Takeuchi, A.; Grasemann, C.; Rinn, J.L.; Lopez, M.F.; et al. Lin28a transgenic mice manifest size and puberty phenotypes identified in human genetic association studies. *Nat. Genet.* **2010**, *42*, 626–630. [[CrossRef](#)]
69. Ong, K.K.; Elks, C.E.; Wills, A.K.; Wong, A.; Wareham, N.J.; Loos, R.J.; Kuh, D.; Hardy, R. Associations between the pubertal timing-related variant in LIN28B and BMI vary across the life course. *J. Clin. Endocrinol. Metab.* **2011**, *96*, E125–E129. [[CrossRef](#)] [[PubMed](#)]
70. Cousminer, D.L.; Stergiakouli, E.; Berry, D.J.; Ang, W.; Groen-Blokhuis, M.M.; Körner, A.; Siitonen, N.; Ntalla, I.; Marinelli, M.; Perry, J.R.; et al. Genome-wide association study of sexual maturation in males and females highlights a role for body mass and menarche loci in male puberty. *Hum. Mol. Genet.* **2014**, *23*, 4452–4464. [[CrossRef](#)] [[PubMed](#)]
71. Berndt, S.I.; Gustafsson, S.; Mägi, R.; Ganna, A.; Wheeler, E.; Feitosa, M.F.; Justice, A.E.; Monda, K.L.; Croteau-Chonka, D.C.; Day, F.R.; et al. Genome-wide meta-analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture. *Nat. Genet.* **2013**, *45*, 501–512. [[CrossRef](#)] [[PubMed](#)]
72. Wood, A.R.; Esko, T.; Yang, J.; Vedantam, S.; Pers, T.H.; Gustafsson, S.; Chu, A.Y.; Estrada, K.; Luan, J.; Kutalik, Z.; et al. Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat. Genet.* **2014**, *46*, 1173–1186. [[CrossRef](#)] [[PubMed](#)]
73. Rashina, O.V. Associations of polymorphic variants of candidate genes with the development of H. pylori-negative duodenal ulcer in residents of the Central Chernozem region of Russia. *Res. Results Biomed.* **2023**, *9*, 333–346. [[CrossRef](#)]
74. Pasenov, K.N. Features of associations of SHBG-related genes with breast cancer in women, depending on the presence of hereditary burden and mutations in the BRCA1/CHEK2 genes. *Res. Results Biomed.* **2024**, *10*, 69–88. [[CrossRef](#)]
75. Reshetnikov, E.; Zarudskaya, O.; Polonikov, A.; Bushueva, O.; Orlova, V.; Krikun, E.; Dvornyk, V.; Churnosov, M. Genetic markers for inherited thrombophilia are associated with fetal growth retardation in the population of Central Russia. *J. Obstet. Gynaecol. Res.* **2017**, *43*, 1139–1144. [[CrossRef](#)] [[PubMed](#)]
76. Golovchenko, O.; Abramova, M.; Ponomarenko, I.; Reshetnikov, E.; Aristova, I.; Polonikov, A.; Dvornyk, V.; Churnosov, M. Functionally significant polymorphisms of ESR1 and PGR and risk of intrauterine growth restriction in population of Central Russia. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2020**, *253*, 52–57. [[CrossRef](#)]
77. Hadlock, F.P.; Deter, R.L.; Harrist, R.B. Sonographic detection of abnormal fetal growth patterns. *Clin. Obstet. Gynecol.* **1984**, *27*, 342–351. [[CrossRef](#)]
78. Golovchenko, O.V. Molecular genetic determinants of pre-eclampsia. *Res. Results Biomed.* **2019**, *5*, 139–149. [[CrossRef](#)]
79. Abramova, M.; Churnosova, M.; Efremova, O.; Aristova, I.; Reshetnikov, E.; Polonikov, A.; Churnosov, M.; Ponomarenko, I. Effects of pre-pregnancy over-weight/obesity on the pattern of association of hypertension susceptibility genes with preeclampsia. *Life* **2022**, *12*, 2018. [[CrossRef](#)]

80. Reshetnikov, E.; Ponomarenko, I.; Golovchenko, O.; Sorokina, I.; Batlutskaya, I.; Yakunchenko, T.; Dvornyk, V.; Polonikov, A.; Churnosov, M. The VNTR polymorphism of the endothelial nitric oxide synthase gene and blood pressure in women at the end of pregnancy. *Taiwan J. Obstet. Gynecol.* **2019**, *58*, 390–395. [\[CrossRef\]](#)
81. Abramova, M.Y. Genetic markers of severe preeclampsia. *Res. Results Biomed.* **2022**, *8*, 305–316. (In Russian) [\[CrossRef\]](#)
82. Churnosov, M.; Abramova, M.; Reshetnikov, E.; Lyashenko, I.V.; Efremova, O.; Churnosova, M.; Ponomarenko, I. Polymorphisms of hypertension susceptibility genes as a risk factors of preeclampsia in the Caucasian population of central Russia. *Placenta* **2022**, *129*, 51–61. [\[CrossRef\]](#) [\[PubMed\]](#)
83. Graff, M.; Ngwa, J.S.; Workalemahu, T.; Homuth, G.; Schipf, S.; Teumer, A.; Völzke, H.; Wallaschofski, H.; Abecasis, G.R.; Edward, L.; et al. Genome-wide analysis of BMI in adolescents and young adults reveals additional insight into the effects of genetic loci over the life course. *Hum. Mol. Genet.* **2013**, *22*, 3597–3607. [\[CrossRef\]](#)
84. Hong, K.W.; Oh, B. Recapitulation of genome-wide association studies on body mass index in the Korean population. *Int. J. Obes.* **2012**, *36*, 1127–1130. [\[CrossRef\]](#) [\[PubMed\]](#)
85. Delahanty, R.J.; Beeghly-Fadiel, A.; Long, J.R.; Gao, Y.T.; Lu, W.; Xiang, Y.B.; Zheng, Y.; Ji, B.T.; Wen, W.Q.; Cai, Q.Y.; et al. Evaluation of GWAS-identified genetic variants for age at menarche among Chinese women. *Hum. Reprod.* **2013**, *28*, 1135–1143. [\[CrossRef\]](#) [\[PubMed\]](#)
86. Pyun, J.A.; Kim, S.; Cho, N.H.; Koh, I.; Lee, J.Y.; Shin, C.; Kwack, K. Genome-wide association studies and epistasis analyses of candidate genes related to age at menarche and age at natural menopause in a Korean population. *Menopause* **2014**, *21*, 522–529. [\[CrossRef\]](#)
87. Engelman, C.D.; Fingerlin, T.E.; Langefeld, C.D.; Hicks, P.J.; Rich, S.S.; Wagenknecht, L.E.; Bowden, D.W.; Norris, J.M. Genetic and environmental determinants of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels in Hispanic and African Americans. *J. Clin. Endocrinol. Metab.* **2008**, *93*, 3381–3388. [\[CrossRef\]](#)
88. Xu, X.H.; Xiong, D.H.; Liu, X.G.; Guo, Y.; Chen, Y.; Zhao, J.; Recker, R.R.; Deng, H.W. Association analyses of vitamin D-binding protein gene with compression strength index variation in Caucasian nuclear families. *Osteoporos. Int.* **2010**, *21*, 99–107. [\[CrossRef\]](#)
89. Zhang, Y.; Wang, X.; Liu, Y.; Qu, H.; Qu, S.; Wang, W.; Ren, L. The GC, CYP2R1 and DHCR7 genes are associated with vitamin D levels in northeastern Han Chinese children. *Swiss Med. Wkly.* **2012**, *142*, w13636. [\[CrossRef\]](#)
90. Wang, H.J.; Hinney, A.; Song, J.Y.; Scherag, A.; Meng, X.R.; Grallert, H.; Illig, T.; Hebebrand, J.; Wang, Y.; Ma, J. Association of common variants identified by recent genome-wide association studies with obesity in Chinese children: A case-control study. *BMC Med. Genet.* **2016**, *17*, 7. [\[CrossRef\]](#) [\[PubMed\]](#)
91. Chenthuran, T.; Galhenage, G.H.; Jayasekara, R.W.; Dissanayake, V.H. Polymorphism in the epidermal growth factor gene is associated with pre-eclampsia and low birthweight. *J. Obstet. Gynaecol. Res.* **2014**, *5*, 1235–1242. [\[CrossRef\]](#) [\[PubMed\]](#)
92. Schweighofer, N.; Lerchbaum, E.; Trummer, O.; Schwetz, V.; Pilz, S.; Pieber, T.R.; Obermayer-Pietsch, B. Androgen levels and metabolic parameters are associated with a genetic variant of F13A1 in women with polycystic ovary syndrome. *Gene* **2012**, *504*, 133–139. [\[CrossRef\]](#) [\[PubMed\]](#)
93. He, C.; Kraft, P.; Chen, C.; Buring, J.E.; Paré, G.; Hankinson, S.E.; Chanock, S.J.; Ridker, P.M.; David, J.; Chasman, D.I. Genome-wide association studies identify novel loci associated with age at menarche and age at natural menopause. *Nat. Genet.* **2009**, *41*, 724–728. [\[CrossRef\]](#) [\[PubMed\]](#)
94. Perry, J.R.; Stolk, L.; Franceschini, N.; Lunetta, K.L.; Zhai, G.; McArdle, P.F.; Smith, A.V.; Aspelund, T.; Bandinelli, S.; Boerwinkle, E.; et al. Meta-analysis of genome-wide association data identifies two loci influencing age at menarche. *Nat. Genet.* **2009**, *41*, 648–650. [\[CrossRef\]](#) [\[PubMed\]](#)
95. Lango Allen, H.; Estrada, K.; Lettre, G.; Berndt, S.I.; Weedon, M.N.; Rivadeneira, F.; Willer, C.J.; Jackson, A.U.; Vedantam, S.; Raychaudhuri, S.; et al. Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* **2010**, *7317*, 832–838. [\[CrossRef\]](#)
96. Cousminer, D.L.; Berry, D.J.; Timpson, N.J.; Ang, W.; Thiering, E.; Byrne, E.M.; Taal, H.R.; Huikari, V.; Bradfield, J.P.; Kerkhof, M.; et al. Genome-wide association and longitudinal analyses reveal genetic loci linking pubertal height growth, pubertal timing and childhood adiposity. *Hum. Mol. Genet.* **2013**, *13*, 2735–2747. [\[CrossRef\]](#)
97. Leinonen, J.T.; Surakka, I.; Havulinna, A.S.; Kettunen, J.; Luoto, R.; Salomaa, V.; Widen, E. Association of LIN28B with Adult Adiposity-Related Traits in Females. *PLoS ONE* **2012**, *11*, e48785. [\[CrossRef\]](#)
98. Widén, E.; Ripatti, S.; Cousminer, D.L.; Surakka, I.; Lappalainen, T.; Järvelin, M.R.; Eriksson, J.G.; Raitakari, O.; Salomaa, V.; Sovio, U.; et al. Distinct variants at LIN28B influence growth in height from birth to adulthood. *Am. J. Hum. Genet.* **2010**, *86*, 773–782. [\[CrossRef\]](#)
99. Carroll, J.; Saxena, R.; Welt, C.K. Environmental and genetic factors influence age at menarche in women with polycystic ovary syndrome. *J. Pediatr. Endocrinol. Metab.* **2012**, *25*, 459–466. [\[CrossRef\]](#)
100. Sulem, P.; Gudbjartsson, D.F.; Rafnar, T.; Holm, H.; Olafsdottir, E.J.; Olafsdottir, G.H.; Jonsson, T.; Alexandersen, P.; Feenstra, B.; Boyd, H.A.; et al. Genome-wide association study identifies sequence variants on 6q21 associated with age at menarche. *Nat. Genet.* **2009**, *41*, 734–738. [\[CrossRef\]](#)
101. Carty, C.L.; Spencer, K.L.; Setiawan, V.W.; Fernandez-Rhodes, L.; Malinowski, J.; Buyske, S.; Young, A.; Jorgensen, N.W.; Cheng, I.; Carlson, C.S.; et al. Replication of genetic loci for ages at menarche and menopause in the multi-ethnic Population Architecture using Genomics and Epidemiology (PAGE) study. *Hum. Reprod.* **2013**, *28*, 1695–1706. [\[CrossRef\]](#)

102. Wang, J.T.; Guo, Y.; Yang, T.L.; Xu, X.H.; Dong, S.S.; Li, M.; Li, T.Q.; Chen, Y.; Deng, H.W. Polymorphisms in the estrogen receptor genes are associated with hip fractures in Chinese. *Bone* **2008**, *43*, 910–914. [[CrossRef](#)] [[PubMed](#)]
103. Doo, M.; Kim, Y. Association between ESR1 rs1884051 polymorphism and dietary total energy and plant protein intake on obesity in Korean men. *Nutr. Res. Pract.* **2011**, *5*, 527–532. [[CrossRef](#)] [[PubMed](#)]
104. Dahlman, I.; Vaxillaire, M.; Nilsson, M.; Lecoeur, C.; Gu, H.F.; Cavalcanti-Proença, C.; Efendic, S.; Ostenson, C.G.; Brismar, K.; Charpentier, G.; et al. Estrogen receptor alpha gene variants associate with type 2 diabetes and fasting plasma glucose. *Pharmacogenetics Genom.* **2008**, *18*, 967–975. [[CrossRef](#)] [[PubMed](#)]
105. Chen, C.T.; Fernández-Rhodes, L.; Brzyski, R.G.; Carlson, C.S.; Chen, Z.; Heiss, G.; North, K.E.; Woods, N.F.; Rajkovic, A.; Kooperberg, C.; et al. Replication of loci influencing ages at menarche and menopause in Hispanic women: The Women's Health Initiative SHARe Study. *Hum. Mol. Genet.* **2012**, *21*, 1419–1432. [[CrossRef](#)] [[PubMed](#)]
106. Demerath, E.W.; Liu, C.T.; Franceschini, N.; Chen, G.; Palmer, J.R.; Smith, E.N.; Chen, C.T.; Ambrosone, C.B.; Arnold, A.M.; Bandera, E.V.; et al. Genome-wide association study of age at menarche in African-American women. *Hum. Mol. Genet.* **2013**, *22*, 3329–3346. [[CrossRef](#)] [[PubMed](#)]
107. Tian, Y.; Zhao, H.; Chen, H.; Peng, Y.; Cui, L.; Du, Y.; Wang, Z.; Xu, J.; Chen, Z.-J. Variants in FSHB are associated with polycystic ovary syndrome and luteinizing hormone level in han chinese women. *J. Clin. Endocrinol. Metab.* **2016**, *101*, 2178–2184. [[CrossRef](#)] [[PubMed](#)]
108. Kitanaka, S.; Isojima, T.; Takaki, M.; Numakura, C.; Hayasaka, K.; Igarashi, T. Association of vitamin D-related gene polymorphisms with manifestation of vitamin D deficiency in children. *Endocr. J.* **2012**, *59*, 1007–1014. [[CrossRef](#)]
109. Laczmanski, L.; Lwow, F.; Mossakowska, M.; Puzianowska-Kuznicka, M.; Szwed, M.; Kolackov, K.; Krzyzanowska-Swiniarska, B.; Bar-Andziak, E.; Chudek, J.; Sloka, N.; et al. Association between vitamin D concentration and levels of sex hormones in an elderly Polish population with different genotypes of VDR polymorphisms (rs10735810, rs1544410, rs7975232, rs731236). *Gene* **2015**, *559*, 73–76. [[CrossRef](#)]
110. Cobayashi, F.; Lourenço, B.H.; Cardoso, M.A. 25-Hydroxyvitamin D3 levels, BsmI polymorphism and insulin resistance in Brazilian Amazonian children. *Int. J. Mol. Sci.* **2015**, *16*, 12531–12546. [[CrossRef](#)]
111. Jia, F.; Sun, R.F.; Li, Q.H.; Wang, D.X.; Zhao, F.; Li, J.M.; Pu, Q.; Zhang, Z.Z.; Jin, Y.; Liu, B.L.; et al. Vitamin D receptor BsmI polymorphism and osteoporosis risk: A meta-analysis from 26 studies. *Genet. Test. Mol. Biomark.* **2013**, *1*, 30–34. [[CrossRef](#)]
112. Suh, K.T.; Eun, I.S.; Lee, J.S. Polymorphism in vitamin D receptor is associated with bone mineral density in patients with adolescent idiopathic scoliosis. *Eur. Spine J.* **2010**, *19*, 1545–1550. [[CrossRef](#)] [[PubMed](#)]
113. Stavrou, I.; Zois, C.; Chatzikyriakidou, A.; Georgiou, I.; Tsatsoulis, A. Combined estrogen receptor α and estrogen receptor β genotypes influence the age of menarche. *Hum. Reprod.* **2006**, *21*, 554–557. [[CrossRef](#)] [[PubMed](#)]
114. Rask-Andersen, M.; Jacobsson, J.A.; Moschonis, G.; Ek, A.E.; Chrousos, G.P.; Marcus, C.; Manios, Y.; Fredriksson, R.; Schiöth, H.B. The MAP2K5-linked SNP rs2241423 is associated with BMI and obesity in two cohorts of Swedish and Greek children. *BMC Med. Genet.* **2012**, *13*, 36. [[CrossRef](#)] [[PubMed](#)]
115. Lv, D.; Zhang, D.D.; Wang, H.; Zhang, Y.; Liang, L.; Fu, J.F.; Xiong, F.; Liu, G.L.; Gong, C.X.; Luo, F.H.; et al. Genetic variations in SEC16B, MC4R, MAP2K5 and KCTD15 were associated with childhood obesity and interacted with dietary behaviors in Chinese school-age population. *Gene* **2015**, *560*, 149–155. [[CrossRef](#)] [[PubMed](#)]
116. Mei, H.; Chen, W.; Jiang, F.; He, J.; Srinivasan, S.; Smith, E.N.; Schork, N.; Murray, S.; Berenson, G.S. Longitudinal replication studies of GWAS risk SNPs influencing body mass index over the course of childhood and adulthood. *PLoS ONE* **2012**, *7*, e31470. [[CrossRef](#)] [[PubMed](#)]
117. Willer, C.J.; Schmidt, E.M.; Sengupta, S.; Peloso, G.M.; Gustafsson, S.; Kanoni, S.; Ganna, A.; Chen, J.; Buchkovich, M.L.; Mora, S.; et al. Discovery and refinement of loci associated with lipid levels. *Nat. Genet.* **2013**, *45*, 1274–1283.
118. Frayling, T.M.; Timpson, N.J.; Weedon, M.N.; Zeggini, E.; Freathy, R.M.; Lindgren, C.M.; Perry, J.R.; Elliott, K.S.; Lango, H.; Rayner, N.W.; et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* **2007**, *316*, 889–894. [[CrossRef](#)] [[PubMed](#)]
119. Perry, J.R.; Voight, B.F.; Yengo, L.; Amin, N.; Dupuis, J.; Ganser, M.; Grallert, H.; Navarro, P.; Li, M.; Qi, L.; et al. Stratifying type 2 diabetes cases by BMI identifies genetic risk variants in LAMA1 and enrichment for risk variants in lean compared to obese cases. *PLoS Genet.* **2012**, *8*, e1002741. [[CrossRef](#)]
120. Hsiao, T.J.; Lin, E. Association of a common rs9939609 variant in the fat mass and obesity-associated (FTO) gene with obesity and metabolic phenotypes in a Taiwanese population: A replication study. *J. Genet.* **2016**, *95*, 595–601. [[CrossRef](#)]
121. Duicu, C.; Mărginean, C.O.; Voidăzan, S.; Tripon, F.; Bănescu, C. FTO rs9939609 SNP is associated with adiponectin and leptin levels and the risk of obesity in a cohort of Romanian children population. *Medicine* **2016**, *20*, e3709. [[CrossRef](#)]
122. Petkeviciene, J.; Smalinskiene, A.; Klumbiene, J.; Petkevicius, V.; Kriaucioniene, V.; Lesauskaite, V. Physical activity, but not dietary intake, attenuates the effect of the FTO rs9939609 polymorphism on obesity and metabolic syndrome in Lithuanian adult population. *Public Health* **2016**, *135*, 23–29. [[CrossRef](#)] [[PubMed](#)]
123. Quan, L.L.; Wang, H.; Tian, Y.; Mu, X.; Zhang, Y.; Tao, K. Association of fat-mass and obesity-associated gene FTO rs9939609 polymorphism with the risk of obesity among children and adolescents: A meta-analysis. *Eur. Rev. Med. Pharmacol. Sci.* **2015**, *19*, 614–623. [[PubMed](#)]
124. Tu, W.; Wagner, E.K.; Eckert, G.J.; Yu, Z.; Hannon, T.; Pratt, J.H.; He, C. Associations between menarche-related genetic variants and pubertal growth in male and female adolescents. *J. Adolesc. Health* **2015**, *56*, 66–72. [[CrossRef](#)] [[PubMed](#)]

125. Cotsapas, C.; Speliotes, E.K.; Hatoum, I.J.; Greenawalt, D.M.; Dobrin, R.; Lum, P.Y.; Suver, C.; Chudin, E.; Kemp, D.; Reitman, M.; et al. Common body mass index-associated variants confer risk of extreme obesity. *Hum. Mol. Genet.* **2009**, *18*, 3502–3507. [CrossRef] [PubMed]
126. Goodarzi, M.O.; Louwers, Y.V.; Taylor, K.D.; Jones, M.R.; Cui, J.; Kwon, S.; Chen, Y.D.; Guo, X.; Stolk, L.; Uitterlinden, A.G.; et al. Replication of association of a novel insulin receptor gene polymorphism with polycystic ovary syndrome. *Fertil. Steril.* **2011**, *95*, 1736–1741.e11. [CrossRef]
127. Du, J.; Wang, Z.; Zhang, J.; Jia, L.; Zhang, F.; Shi, Y.; Chen, Z. Association between single nucleotide polymorphism of rs2252673 of INSR gene and polycystic ovarian syndrome. *Zhonghua Fu Chan Ke Za Zhi* **2014**, *12*, 919–924.
128. Ward, L.D.; Kellis, M. HaploReg v4: Systematic mining of putative causal variants, cell types, regulators and target genes for human complex traits and disease. *Nucleic Acids Res.* **2016**, *44*, D877–D881. [CrossRef]
129. Mathew, C.G. The isolation of high molecular weight eukaryotic DNA. *Methods Mol. Biol.* **1985**, *2*, 31–34. [CrossRef]
130. Pavlova, N.; Demin, S.; Churnosov, M.; Reshetnikov, E.; Aristova, I.; Churnosova, M.; Ponomarenko, I. The Modifying Effect of Obesity on the Association of Matrix Metalloproteinase Gene Polymorphisms with Breast Cancer Risk. *Biomedicines* **2022**, *10*, 2617. [CrossRef]
131. Ivanova, T.A. Sex-specific features of interlocus interactions determining susceptibility to hypertension. *Res. Results Biomed.* **2024**, *10*, 53–68. [CrossRef]
132. Nielsen, D.M.; Ehm, M.G.; Weir, B.S. Detecting marker-disease association by testing for Hardy-Weinberg disequilibrium at a marker locus. *Am. J. Hum. Genet.* **1998**, *63*, 1531–1540. [CrossRef] [PubMed]
133. Purcell, S.; Neale, B.; Todd-Brown, K.; Thomas, L.; Ferreira, M.A.; Bender, D.; Maller, J.; Sklar, P.; de Bakker, P.I.; Daly, M.J.; et al. PLINK: A tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* **2007**, *81*, 559–575. [CrossRef] [PubMed]
134. Novakov, V.; Novakova, O.; Churnosova, M.; Sorokina, I.; Aristova, I.; Polonikov, A.; Reshetnikov, E.; Churnosov, M. Intergenic Interactions of SBNO1, NFAT5 and GLT8D1 Determine the Susceptibility to Knee Osteoarthritis among Europeans of Russia. *Life* **2023**, *13*, 405. [CrossRef] [PubMed]
135. Calle, M.L.; Urrea, V.; Malats, N.; Van Steen, K. Mbmdr: An R package for exploring gene-gene interactions associated with binary or quantitative traits. *Bioinformatics* **2010**, *26*, 2198–2199. [CrossRef]
136. Calle, M.L.; Urrea, V.; Vellalta, G.; Malats, N.; Steen, K.V. Improving strategies for detecting genetic patterns of disease susceptibility in association studies. *Stat. Med.* **2008**, *27*, 6532–6546. [CrossRef]
137. Moore, J.H.; Gilbert, J.C.; Tsai, C.T.; Chiang, F.T.; Holden, T.; Barney, N.; White, B.C. A flexible computational framework for detecting, characterizing, and interpreting statistical patterns of epistasis in genetic studies of human disease susceptibility. *J. Theor. Biol.* **2006**, *241*, 252–261. [CrossRef]
138. Gola, D.; Mahachie John, J.M.; van Steen, K.; König, I.R. A roadmap to multifactor dimensionality reduction methods. *Brief Bioinform.* **2016**, *7*, 293–308. [CrossRef]
139. Che, R.; Jack, J.R.; Motsinger-Reif, A.A.; Brown, C.C. An adaptive permutation approach for genome-wide association study: Evaluation and recommendations for use. *BioData Min.* **2014**, *7*, 9. [CrossRef]
140. Guo, Y.F.; Li, J.; Chen, Y.; Zhang, L.S.; Deng, H.W. A new permutation strategy of pathway-based approach for genome-wide association study. *BMC Bioinform.* **2009**, *10*, 429. [CrossRef] [PubMed]
141. Gauderman, W.; Morrison, J. QUANTO 1.1: A Computer Program for Power and Sample Size Calculations Genetic-Epidemiology Studies. 2006. Available online: <http://hydra.usc.edu/gxe> (accessed on 17 April 2023).
142. Ivanova, T.; Churnosova, M.; Abramova, M.; Plotnikov, D.; Ponomarenko, I.; Reshetnikov, E.; Aristova, I.; Sorokina, I.; Churnosov, M. Sex-Specific Features of the Correlation between GWAS-Noticeable Polymorphisms and Hypertension in Europeans of Russia. *Int. J. Mol. Sci.* **2023**, *24*, 7799. [CrossRef] [PubMed]
143. Pavlova, N.; Demin, S.; Churnosov, M.; Reshetnikov, E.; Aristova, I.; Churnosova, M.; Ponomarenko, I. Matrix Metalloproteinase Gene Polymorphisms Are Associated with Breast Cancer in the Caucasian Women of Russia. *Int. J. Mol. Sci.* **2022**, *23*, 12638. [CrossRef]
144. Golovchenko, I.; Aizikov, B.; Golovchenko, O.; Reshetnikov, E.; Churnosova, M.; Aristova, I.; Ponomarenko, I.; Churnosov, M. Sex Hormone Candidate Gene Polymorphisms Are Associated with Endometriosis. *Int. J. Mol. Sci.* **2022**, *23*, 13691. [CrossRef]
145. Ivanova, T.; Churnosova, M.; Abramova, M.; Ponomarenko, I.; Reshetnikov, E.; Aristova, I.; Sorokina, I.; Churnosov, M. Risk Effects of rs1799945 Polymorphism of the HFE Gene and Intergenic Interactions of GWAS-Significant Loci for Arterial Hypertension in the Caucasian Population of Central Russia. *Int. J. Mol. Sci.* **2023**, *24*, 8309. [CrossRef]
146. Li, M.J.; Yan, B.; Sham, P.C.; Wang, J. Exploring the function of genetic variants in the non-coding genomic regions: Approaches for identifying human regulatory variants affecting gene expression. *Brief Bioinform.* **2015**, *16*, 393–412. [CrossRef] [PubMed]
147. Butkiewicz, M.; Bush, W.S. In Silico Functional Annotation of Genomic Variation. *Curr. Protoc. Hum. Genet.* **2016**, *88*, 6.15.1–6.15.17. [CrossRef] [PubMed]
148. Watanabe, K.; Taskesen, E.; van Bochoven, A.; Posthuma, D. Functional mapping and annotation of genetic associations with FUMA. *Nat. Commun.* **2017**, *8*, 1826. [CrossRef] [PubMed]
149. Cheng, S.J.; Jiang, S.; Shi, F.Y.; Ding, Y.; Gao, G. Systematic identification and annotation of multiple-variant compound effects at transcription factor binding sites in human genome. *J. Genet. Genom.* **2018**, *45*, 373–379. [CrossRef] [PubMed]

150. Škunca, N.; Roberts, R.J.; Steffen, M. Evaluating Computational Gene Ontology Annotations. *Methods Mol. Biol.* **2017**, *1446*, 97–109. [[CrossRef](#)] [[PubMed](#)]
151. GTEx Consortium. The GTEx Consortium atlas of genetic regulatory effects across human tissues. *Science* **2020**, *369*, 1318–1330. [[CrossRef](#)] [[PubMed](#)]
152. Gene Ontology Consortium. The Gene Ontology resource: Enriching a Gold mine. *Nucleic Acids Res.* **2021**, *49*, D325–D334. [[CrossRef](#)]
153. Szklarczyk, D.; Kirsch, R.; Koutrouli, M.; Nastou, K.; Mehryary, F.; Hachilif, R.; Gable, A.L.; Fang, T.; Doncheva, N.T.; Pyysalo, S.; et al. The STRING database in 2023: Protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. *Nucleic Acids Res.* **2023**, *51*, D638–D646. [[CrossRef](#)] [[PubMed](#)]
154. Westra, H.J.; Peters, M.J.; Esko, T.; Yaghootkar, H.; Schurmann, C.; Kettunen, J.; Christiansen, M.W.; Fairfax, B.P.; Schramm, K.; Powell, J.E.; et al. Systematic identification of trans eQTLs as putative drivers of known disease associations. *Nat. Genet.* **2013**, *45*, 1238–1243. [[CrossRef](#)] [[PubMed](#)]
155. Kumar, P.; Henikoff, S.; Ng, P.C. Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. *Nat. Protoc.* **2009**, *7*, 1073–1081. [[CrossRef](#)] [[PubMed](#)]

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