Online-Only Supplementary Material

Eleftheriou A., Petry C.J., Hughes I. A., Ong K.K. and Dunger D.B. The high-risk type 1 diabetes HLA-DR and HLA-DQ polymorphisms are differentially associated with growth and IGF-1 levels in infancy: the Cambridge Baby Growth Study.

Supplementary Table S1. Overview of studies on diabetes-associated HLA and early growth

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Supplementary Table S1. Overview of studies on diabetes-associated HLA and early growth

First author Year (Ref)	Study/ Country	N	Birth years	Study Design	No of HLA risk groups	Results
Stene 2001 (1)	Norway	969	1982-1998	Retrospective	5	▪ Homozygous DQB1*06:02 had highest BW versus DQ2/8 who had lowest BW. Mean ΔBW=354 g (95% CI 105 to 604).
Aroviita 2004 (2)	Finland	1,263	1999-2001	Retrospective	1	▪ DRB1*13 was more frequent among infants with highest relative BW (*P*=0.015).
Larsson 2005 (3)	DiPiS/Sweden	16,709	2000-2003	Prospective	7	▪ DQ2/8, DQ8/06:04, DQ8/X were associated with HrBW (*P*=0.0006). ▪ DQB1*06:03 was associated with increased frequency of HrBW (*P*=0.025).
Stene 2006 (4)	Norway	471 cases; 1,369 controls	1985-1999	Retrospective	4	▪ No association between BW and risk of type 1 diabetes even after adjusting for *HLA*. ▪ Hint of DQB1*06:02 carriers having higher BW.
Larsson 2007 (5)	DiPiS/Sweden	19,756	2000-2004	Prospective	7	▪ The effect of DQ8/DQ2 on HrBW was aggravated by gestational infections (*P*=0.003).
Locatelli 2007 (6)	DIABFIN/ Italy	4,349	1999-2005	Prospective	3	▪ No association between HLA and BW or BL. ▪ Length of gestation inversely correlated with HLA risk.
Larsson 2008 (7)	DiPiS/Sweden	58 cases; 155 controls	2000-2004	Prospective	2	▪ High HLA risk correlated with BL (*P*<0.01).

Jarvinen 2008 (8)	Finland	342	1987-1999	Retrospective	N/A (identified haplotypes)	▪ Carriers of Finnish-specific HLA haplotype (n=20) had higher BW (3,925 g, SD=446 g) versus non-carriers (3,676 g, SD=439 g). ▪ DR13 carriers tended to be heavier versus non-carriers.
Sterner 2011 (9)	TEDDY	5,461	2004-2010	Prospective	4	▪ Swedish infants were longer at birth if carrying DQ2/8 (*P*=0.023) or DQ8/8 (*P*=0.046) independent of parental height.
Peet 2012 (10)	DIABIMMUNE	7,931	2008-2010	Prospective	4	▪ No association between diabetes-associated HLA risk and BW.
Peet 2014 (11)	DIABIMMUNE	688	2008-2010	Prospective	4	▪ Length SDS was lower in carriers with very high-risk HLA at ages 12 mo and 24 mo, (*P*<0.05). ▪ Weight SDS was significantly lower in carriers of very high-risk genotypes vs. control groups at ages 12 mo, 18 mo and 24 mo (*P*<0.05)

BW, birth weight; BL, birth length; HrBW, high relative birth weight.

Supplementary Table S2. Anatomical sites where **s**kinfold thickness was measured

Name	Exact site of measurement
Triceps	The posterior midline of upper left arm, halfway between the acromial process and the olecranon.
Subscapular	The oblique angle below the left scapula.
Flank	The diagonal plane in line with the natural angle of the iliac crest taken in the posterior axillary line immediately posterior to the iliac crest.
Quadriceps	Found using a vertical line over the quadriceps muscle at midline of the left thigh, half-way between the top of the patella and the inguinal crease.

Each skinfold thickness was measured in triplicate by trained pediatric research nurses.

Supplementary Table S3. Frequencies by genotypic group of HLA tag SNPs

Tag SNP	HLA	Major homozygote	Heterozygote	Minor homozygote
rs17426593	*DR4* (T>C)	366 (64)	189 (33)	14 (3)
rs2187668	*DR3* (G>A)	436 (75)	140 (24)	8 (1)
rs7454108	*DQ8* (T>C)	468 (81)	103 (18)	6 (1)

Data are n (%).

Supplementary Table S4. Skinfold thickness (mm) by age and anatomical site (n indicates sample with data)

	Triceps		Subscapular		Flank		Quadriceps	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Birth	565	5.6 ± 1.6	566	5.5 ± 1.3	567	6.1 ± 1.9	567	8.1 ± 2.6
3 months	517	8.5 ± 2.2	517	7.1 ± 1.5	517	10.1 ± 2.9	517	17.7 ± 3.4
12 months	466	9.8 ± 2.6	465	7.5 ± 1.8	466	10.4 ± 3.1	466	17.7 ± 3.7
18 months	446	9.8 ± 2.4	447	6.9 ± 1.5	443	10.4 ± 3.0	445	16.4 ± 3.6
24 months	429	9.5 ± 2.4	434	6.7 ± 1.7	431	10.2 ± 3.2	430	15.1 ± 3.6

Skinfold thickness (mm) at each anatomical site was converted to internal SDS adjusted for age (or gestational age for newborn measurements) by using the following formula: SDS = individual measurement minus the cohort mean, divided by the cohort SD.

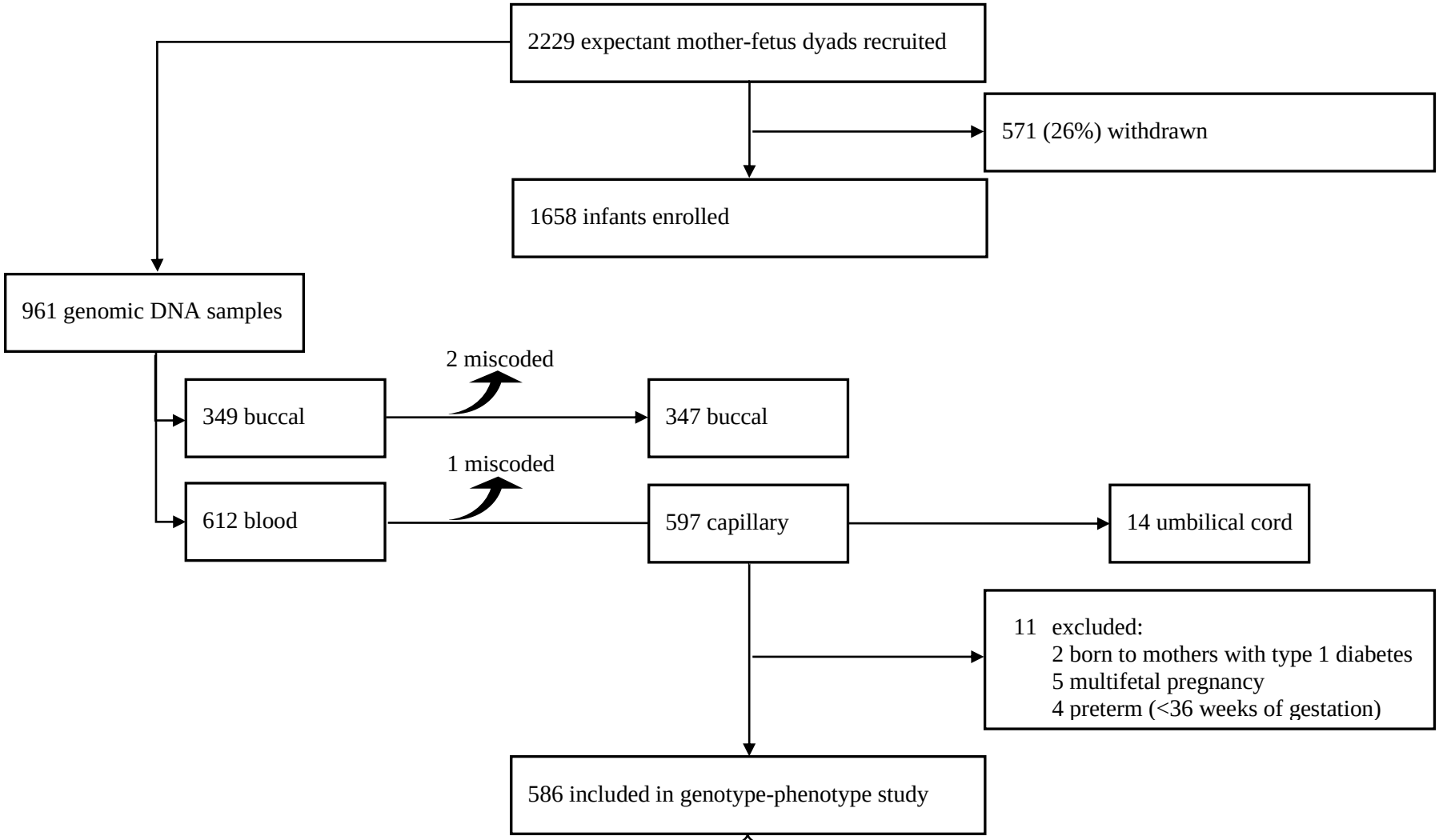
Supplementary Table S5. Comparison of non-genotyped and genotyped subcohorts (n indicates sample with data)

	Non-genotyped		Genotyped		
	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)	*P*
Newborn index					
Gestation (weeks)	1,061	39.7 ± 1.7	597	40.0 ± 1.4	0.002
Twins	1,061	39 (4)	597	5 (1)	0.001
Infant sex: male	1,061	537 (51)	597	321 (54)	0.2
Premature birth <36 weeks gestation	1,061	33 (3)	597	6 (1)	0.007
Birth weight (kg)	1,061	3.445 ± 0.554	594	3.528 ± 0.525	0.02
Birth weight SDS	1,061	0.07 ± 0.95	594	0.09 ± 1.03	0.6
Birth length (cm)	1,021	51.3 ± 2.6	578	51.6 ± 2.5	0.03
Birth length SDS	1,021	-0.07 ± 0.96	578	-0.07 ± 0.99	>0.9
Newborn mean skinfold (mm)	1,021	6.3 ± 1.6	578	6.3 ± 1.6	0.9
Pregnancy influences					
Maternal type 1 diabetes	1,044	3 (0)	594	2 (0)	0.9
Primiparous pregnancy	1,040	451 (43)	589	256 (43)	>0.9
Maternal smoking in pregnancy	1,014	61 (6)	561	25 (5)	0.2
Maternal height (cm)	740	165.7 ± 7.3	497	166.3 ± 7.0	0.1
Maternal pre-pregnancy weight (kg)	722	66.5 ± 14.1	481	65.9 ± 12.1	0.6
Maternal pre-pregnancy BMI (kg/m^2)	702	24.3 ± 4.9	471	23.8 ± 4.0	0.6
Maternal age at birth (years)	811	33.4 ± 4.4	527	33.6 ± 4.1	0.5
Paternal age at birth (years)	776	35.7 ± 5.4	515	35.7 ± 5.4	0.7
Post-pregnancy influences					
Birth delivery: cesarean	1,042	349 (34)	588	142 (24)	<0.0001
3-month feeding: breast milk only	793	324 (41)	526	233 (44)	0.2
Sociodemographic influences					
Index of multiple deprivation	542	9.1 ± 4.3	378	8.8 ± 4.2	0.5

Skinfold, skinfold thickness. Groups were compared by performing t-test or Mann-Whitney U test for continuous variables and chi-square tests for categorical variables.

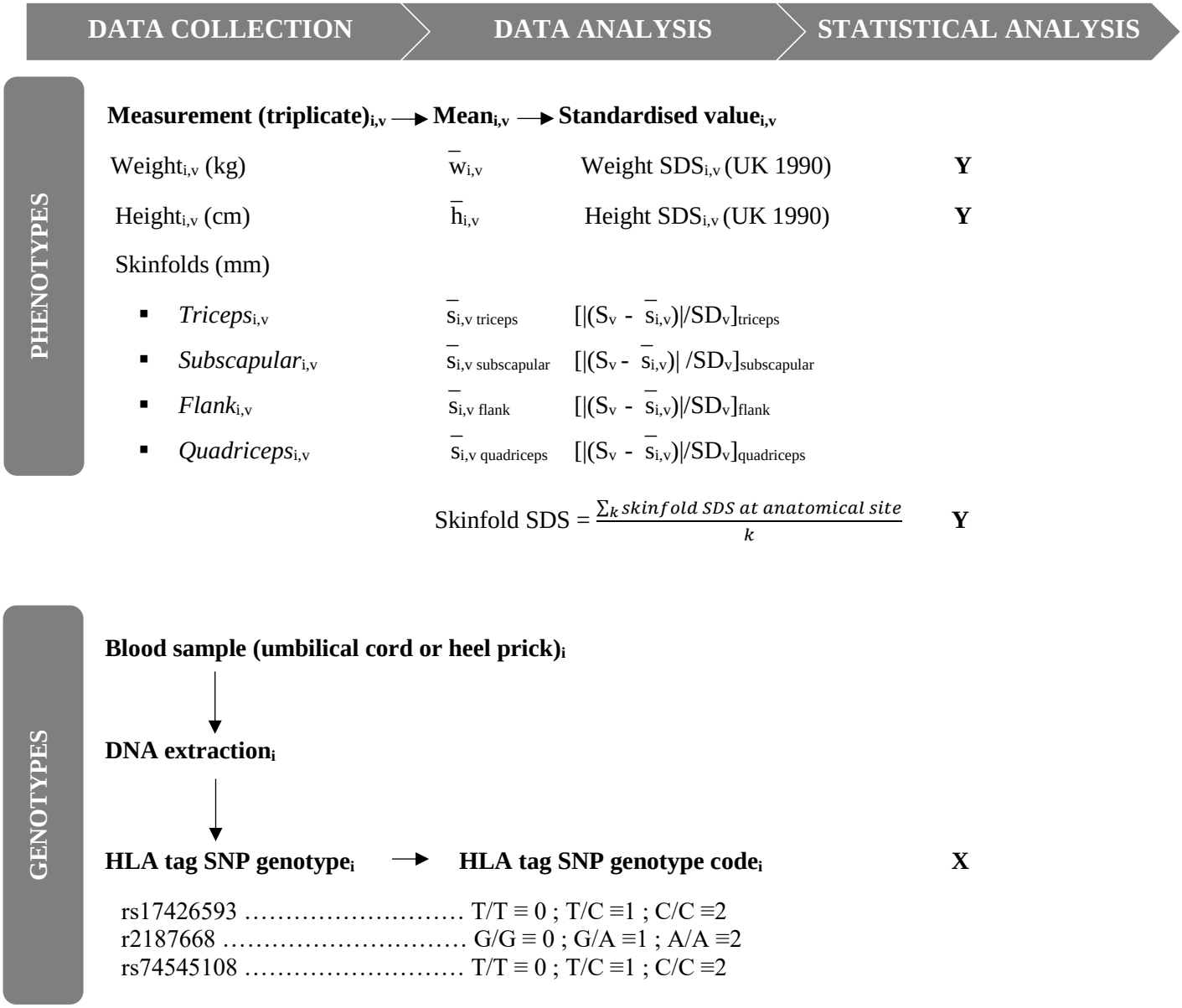
SUPPLEMENTARY MATERIAL

Supplementary Figure S1. Study flow chart



Counts (n) of subjects					
Age	**Weight**	**Height**	**Skinfold**	**IGF-1**	**IGFBP-3**
Birth	584	569	567	Blood not sampled	
3 mo	517	511	517	212	212
12 mo	468	464	466	166	161
18 mo	448	448	448	135	133
24 mo	432	427	434	89	85

Supplementary Figure S2. Method algorithm (i ≡ participating child; v ≡ study visit)



k, number of anatomical sites with skinfold thickness data available; SD, cohort standard deviation; S, cohort mean skinfold thickness; skinfold, skinfold thickness; X explanatory variable; Y, explained variable.

SUPPLEMENTARY MATERIAL

Supplementary Material References

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