Genome-Wide Association With Postpartum Weight Change in Mothers on DTG or EFV in DolPHIN-2

985

Rebecca Jensen[1], Raymond Monk[2], Thokozile Malaba[3], Eunice Zhang[1], Duolao Wang[4], Sylvia Nassiwa[5], Catriona Waitt[2], Lucy Read[6], Jim Read[6], Helen Reynolds[2], Catherine Orrell[7], Landon Myer[3], Daniel F. Carr[1], Saye Khoo[2] for the DolPHIN-2 study group

1. Department of Pharmacology and Therapeutics, University of Liverpool, UK. 2 . Centre for Experimental Therapeutics, University of Liverpool, UK. 3. Division of Epidemiology and Biostatistics, School of Public Health, University of Cape Town. 4. Global Health Trials Unit, Liverpool School of Tropical Medicine. 5. Infectious Diseases Institute, Makerere University. 6. Global Health Trials Unit, Liverpool School of Tropical Medicine. 7. Desmond Tutu HIV Centre, Institute of Infectious Diseases & Molecular Medicine, University of Cape Town

BACKGROUND

- DolPHIN-2 (NCT 03249181) randomised mothers initiating ART in late pregnancy to efavirenz (EFV)- or dolutegravir (DTG) based regimens.
- We previously reported no significant differences between arms in weight change post-delivery to 48w postpartum (PP) but observed heterogeneity with numerically greater weight gain in women from South Africa [1].

AIM

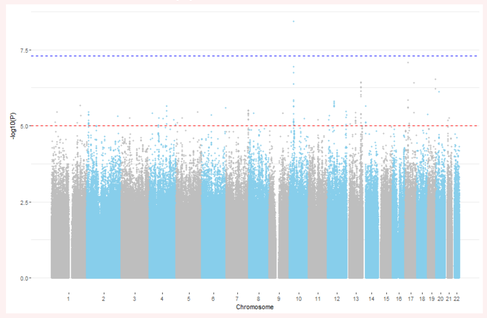
To undertake a genome-wide association study (GWAS) to identify genetic risk factors for weight change from delivery to 48w PP.

METHODS

- 159 participants were genotyped using the Illumina Infinium™ H3Africa Consortium Array v2 (2.27million variants).
- Linear regression was used for covariate selection using SPSS.
- After quality control of the genotyped data, 1.8 million variants across 128 mothers (61 EFV, 67 DTG) were included. Weights were recorded using standardised procedures at enrolment, <14 days of delivery and at 6, 12, 24 and 48 weeks PP. Weight change was calculated as a percentage from delivery to 48w PP.
- Genotype imputation was conducted using the 1000 Genomes phase III reference panel on the Michigan imputation server [2].
- The data shows logistic regression-derived log *p*-values of SNPs and the position of the SNP with the chromosome indicated, adjusted for the first four principal components for all arms and age for combined arms and DTG arm.
- Manhattan plots were prepared using an RStudio script and the top SNPs were extracted into text files.

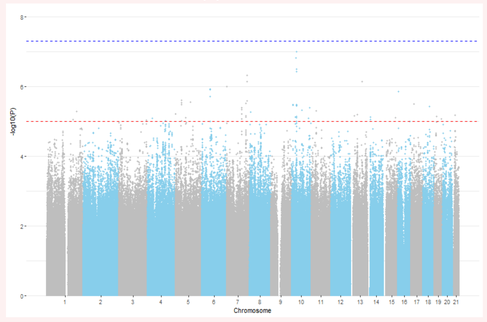
This is the **first genome-wide association study** looking at **weight change** from postpartum mothers on **EFV**- or **DTG**-based regimes. ***SLC47A2*** was identified as a putative genetic marker for weight gain in this population.

(1) Combined Arms



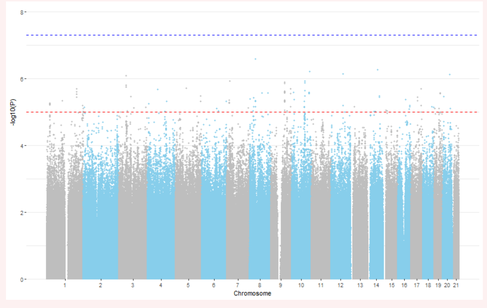
Chr	Gene	Function	p-value
10	*ZEB1*	Plays a role in transcriptional repression of interleukin 2	3.65E-09
17	*SLC47A2*	Belongs to a family of transporters involved in excretion of toxic electrolytes	8.08E-08
10	*MACORIS*	RNA Gene, and is affiliated with the lncRNA class	1.16E-07
19	*TPM3P9*	Pseudogene	2.95E-07
13	*LINC00554*	Long Intergenic Non-Protein Coding RNA 554	3.70E-07
17	*DDX5*	DEAD box protein, implicated in cellular processes involving alteration of RNA secondary structure.	3.75E-07
19	*ZNF765*	Involved in regulation of transcription by RNA polymerase II	5.90E-07
20	*ZNF133*	Involved in negative regulation of transcription by RNA polymerase II	7.50E-07
13	*ZIC2*	Regulate tissue specific expression of dopamine receptor D1	1.08E-06
12	*TMEM117*	Involved in intrinsic apoptotic signalling pathway in response to endoplasmic reticulum stress	1.56E-06

(2) DTG Arm



Chr	Gene	Function	p-value
10	*MACORIS*	RNA Gene, and is affiliated with the lncRNA class	1.01E-07
10	*ZEB1*	Plays a role in transcriptional repression of interleukin 2	1.51E-07
7	*MGAM*	Encodes maltase-glucoamylase, a brush border membrane enzyme that plays a role in the final steps of starch digestion	4.76E-07
13	*OBI1-AS1*	RNA Gene, and is affiliated with the lncRNA class	7.04E-07
6	*PRIM2*	Encodes subunit of DNA primase, an enzyme that plays a key role in the replication of DNA	1.17E-06
16	*DNASE1, TRAP1*	Encodes a member of the DNase family. Encodes a mitochondrial chaperone protein that is a member of the HSP90 family	1.41E-06
5	*C7*	Complement component 7 is a protein involved in the complement system of the innate immune system.	2.41E-06
5	*PAM*	Encodes a multifunctional protein with the preproprotein processed to generate the mature enzyme	2.83E-06
7	*EXOC4*	Encodes for part of a multiple protein complex essential for targeting exocytic vesicles to specific docking sites on the plasma membrane	3.02E-06
17	*SLC47A2*	Belongs to a family of transporters involved in excretion of toxic electrolytes	3.20E-06

(3) EFV Arm



Chr	Gene	Function	p-value
8	*RNF5P1*	Pseudogene	2.57E-07
14	*RGS6*	Encodes a member of the RGS (regulator of G protein signalling) family of proteins	5.40E-07
10	*FGFR2*	Encodes a protein member of the fibroblast growth factor receptor family	6.18E-07
20	*PTGIS*	Encodes a member of the cytochrome P450 superfamily of enzymes	7.56E-07
3	*C3orf18*	Chromosome 3 open reading frame 18	8.06E-07
7	*ASS1P11*	Pseudogene	1.16E-06
10	*PANK1*	Encodes a member of the pantothenate kinase family which are key regulatory enzymes in the biosynthesis of coenzyme A	1.17E-06
9	*ROR2*	Encodeds for a receptor protein tyrosine kinase and type I transmembrane protein that belongs to the ROR subfamily of cell surface receptors	1.28E-06
10	*SLC16A12*	Encodes a transmembrane transporter that likely plays a role in monocarboxylic acid transport	1.30E-06
3	*CACNA2D2*	encodes the alpha-2/delta subunit of the voltage-dependent calcium channel complex.	1.57E-06

Figures 1, 2, 3. GWAS Manhattan plots of weight change, (1) combined arms (n=128), (2) DTG (n=67), (3) EFV (n=61). Suggestive genome-wide threshold ($p < 1 \times 10^{-5}$) (blue line), genome-wide significance ($p < 5 \times 10^{-8}$) (red line).

RESULTS

- SNP QC thresholds used: MAF, 0.02 (2%); Geno, 0.05 (95%); HWE, $1x10^{-7}$. After imputation, 22077386 variants pass filters and SNP QC.
- Linear regression:
  - Combined arm: adjusted R^2 0.03 (*p*, 0.017)
  - DTG arm: adjusted R^2 0.44 (*p*, 0.049)
  - EFV arm: adjusted R^2 0.001 (*p*, 0.306)
- Analysis identified several loci which reached the suggestive genome-wide threshold ($p < 1 \times 10^{-5}$) across the arms with each arm having different top SNPs associated with weight change.
- *SLC47A2* was seen in the DTG-arm (β 0.77; *p* 3.2×10^{-6}) and combined arms (β 0.71; *p* 8.1×10^{-8}) which encodes for multidrug and toxin extrusion transporter 2-K (MATE2-K) which has previously been linked to the interindividual variability in the change in serum creatinine after starting dolutegravir [3].
- After imputation, *HK1* was no longer in the top genes for the combined (β 0.45; *p* 4.7×10^{-3}) or separate arms.

CONCLUSIONS

- These findings suggest that there are genetic variants which may be associated with changes in postpartum weight in women receiving DTG- or EFV-based treatments.
- Further work will include validating the top SNPs of interest using SNP genotyping and validation by replication in another cohort.

REFERENCES

[1] Malaba TR, Nakatudde I, Kintu K, Colbers A, Chen T, Reynolds H, Read L, Read J, Stemmet LA, Mrubata M, Byrne K, Seden K, Twimukye A, Theunissen H, Hodel EM, Chiong J, Hu NC, Burger D, Wang D, Byamugisha J, Alhassan Y, Bokako S, Waitt C, Taegtmeyer M, Orrell C, Lamorde M, Myer L, Khoo S; DolPHIN-2 Study Group. 72 weeks post-partum follow-up of dolutegravir versus efavirenz initiated in late pregnancy (DolPHIN-2): an open-label, randomised controlled study. Lancet HIV. 2022 Aug;9(8):e534-e543. doi: 10.1016/S2352-3018(22)00173-4. PMID: 35905752.

[2] Das S, Forer L, Schönherr S, Sidore C, Locke AE, Kwong A, Vrieze SI, Chew EY, Levy S, McGue M, Schlessinger D, Stambolian D, Loh PR, Iacono WG, Swaroop A, Scott LJ, Cucca F, Kronenberg F, Boehnke M, Abecasis GR, Fuchsberger C. Next-generation genotype imputation service and methods. Nat Genet. 2016 Oct;48(10):1284-1287. doi: 10.1038/ng.3656. Epub 2016 Aug 29. PMID: 27571263; PMCID: PMC5157836.

[3] Mpofu R, Kawuma AN, Wasmann RE, et al. Determinants of early change in serum creatinine after initiation of dolutegravir-based antiretroviral therapy in South Africa. Br J Clin Pharmacol. 2024; 90(5): 1247-1257. doi:10.1111/bcp.16009

Unpublished work © 2025 Rebecca Jensen, University of Liverpool. All rights reserved.
r.jensen@liverpool.ac.uk

UNIVERSITY OF LIVERPOOL

DolPHIN2