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Genome wide association meta study of diabetic foot ulcers

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Background and aims: Diabetic foot ulcers (DFUs) are a severe complication of diabetes mellitus. Globally, a lower limb is amputated due to diabetes every 30 seconds; foot ulceration precedes 85% of diabetes-related amputations. While several risk factors are known - including sensorimotor peripheral neuropathy (DSPN), peripheral artery disease, foot deformities, and poor glycemic control - the genetics of DFUs are poorly understood. In this study, we conducted the first genome-wide association meta-study of diabetic foot ulcers with the aim of identifying genetic loci associated with DFU risk in diabetic (type 1 and type 2) individuals with DSPN.

Materials and methods: A meta-analysis of DFUs was conducted, comprising four independent genome-wide association studies from diabetes cohorts of European ancestry (AfterEU, Denmark; SDR, Sweden; GoShare, Scotland; DCS, Netherlands). This case-control study comprised a total of 980 cases (with DFU and DSPN) and 6196 controls (no history of DFU, but with DSPN). DSPN was defined as bilateral vibration sensation threshold $\geq 25V$ or absent sensation to monofilament. Logistic regression models were applied adjusting for sex, duration of diabetes and principal components. Summary statistics from the four European cohorts were meta-analysed using fixed effects inverse-variance based meta-analysis.

Results: In the GWAS meta-analysis, we identified three common single nucleotide polymorphisms (SNPs) that were suggestive ($p\text{-value} < 1 \times 10^{-6}$), from three loci; an overview of these results is given in Table 1. Two common variants - rs11069845 (intronic), and rs1534545 (missense variant) - were located in *COL4A2* and *ALK*. The third, rs12129159, was located within 1mb from *HS2ST1* and *PKN2-AS1*.

Conclusion: Three suggestive loci associated with DFU risk were identified in the current ongoing study. Two loci were located in *COL4A2* and *ALK*, which have known roles in small vessel disease and neuronal development. Additional GWAS data from other participating centers will be added to the current analyses towards identification of loci associated with diabetic foot ulcers of neuropathic origin.

Table 1: Top SNPs from meta-analysis

SNP rsid	Gene/nearest gene	CHR	BP	A1	A2	EAF	OR	95% CI	p-value
rs11069845	COL4A2	13	111103362	C	A	0.305	1.294	[1.168;1.433]	$8.0 \cdot 10^{-7}$
rs1534545	ALK	2	29444076	T	G	0.204	0.746	[0.664;0.838]	$8.4 \cdot 10^{-7}$
rs12129159	HS2ST/PKN2AS1	1	88414544	T	G	0.278	0.735	[0.650;0.831]	$9.3 \cdot 10^{-7}$

Disclosure: S. Altintas: None.