Association of VEGF Gene polymorphisms with Diabetic Retinopathy in GoDARTS Cohort

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Introduction

❖Retinopathy is a frequent microvascular complication in diabetic individuals in the productive age group.

❖Diabetic Retinopathy develops in one third of diabetic population and a similar proportion will progress to severe retinopathy.[2]

❖Proportion of blindness in England and Wales due to retinopathy is 14.4%.[3]

❖ Development and progression of retinopathy varies between individuals.

❖ The reason for this variability is not clear and requires further research.

❖ Vascular endothelial growth factor (VEGF) is a mitogen that causes increased vascular permeability and neovascularisation in the diabetic retina.[4]

❖VEGF gene codes for protein that promotes angiogenesis and belongs to the same family as the platelet derived growth factor.

❖ In studies, *VEGF* was shown to have a significant association with circulating levels of vascular endothelial growth factor.[4]

❖PPAR -α agonists such as Fenofibrate have shown promise in clinical trials.[5]

Methods

❖We analysed GoDARTS diabetes eye data (n=5099).

❖ Novel and traditional *VEGF* SNPs were identified from studies.

❖Retinopathy grades were categorised according to Scottish retinopathy classification.

❖Secular trends in retinopathy such as prevalence and cumulative incidence were explored.

❖Differences in distribution of risk factors at diabetes diagnosis visualized with future retinopathy using ANOVA.

❖SNPs for the analysis were extracted from GenomeDB. [6]

❖Survival analysis computed for 10 year incidence of retinopathy with SNPs as the exposure and adjusted for sex, HbA1c,blood pressure and BMI.

❖Significant SNPs were adjusted in the final model.

❖ Cox diagnostic test for proportional hazards was conducted to confirm constant hazards.

❖ Any known incident retinopathy in relation to the SNPs was analysed using an extended Cox model due to the absence of proportional hazards.

Figure1.Trends in the prevalence of retinopathy

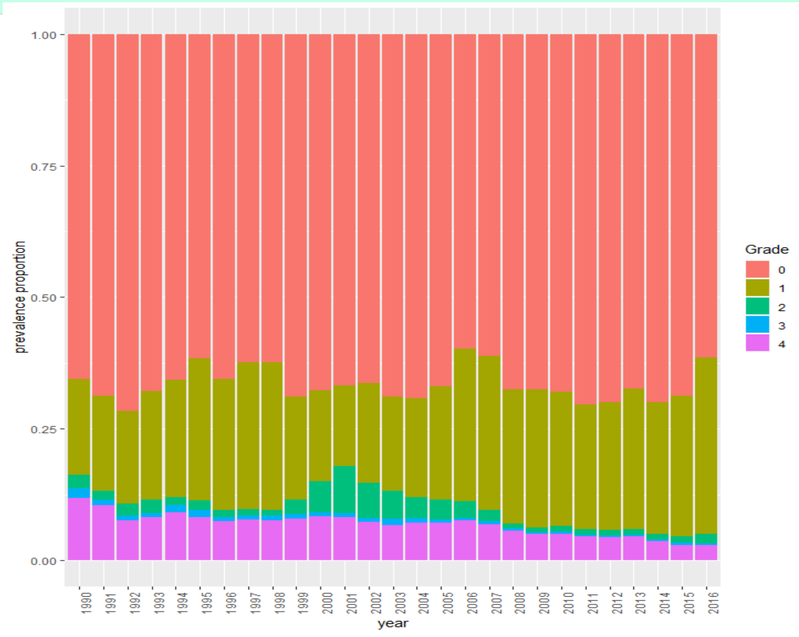


Figure2.Distribution of risk factors at diagnosis of diabetes versus Retinopathy Grades

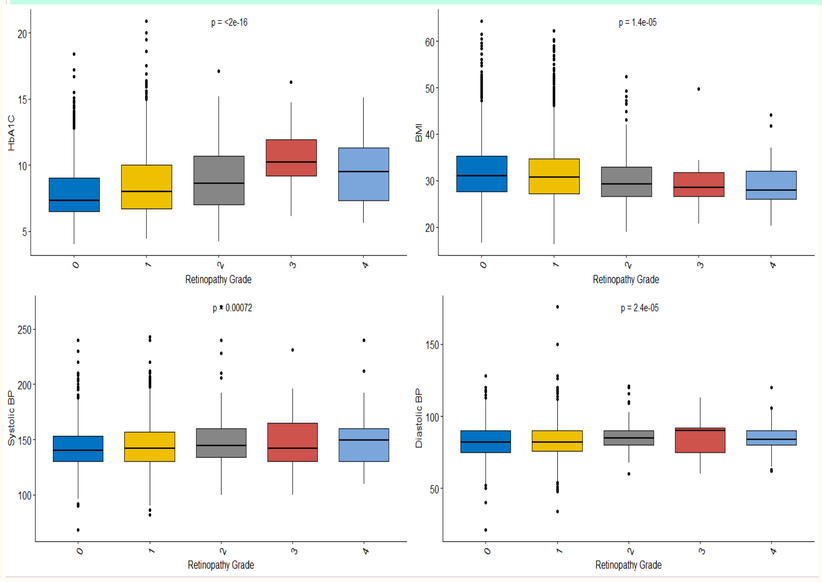


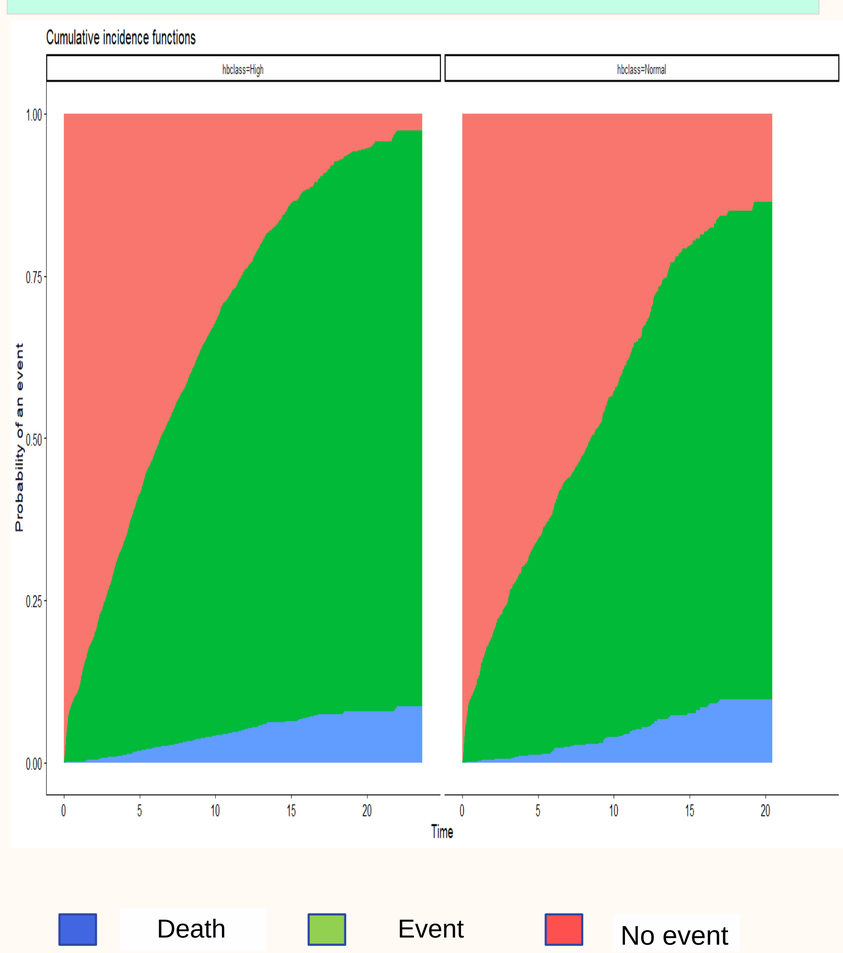
Table1: SNP associations in multivariate extended Cox Proportional Hazard Model for 10 year incidence of retinopathy

SNP	Chromosome	Gene	Minor Allele	MAF	N(%)	Marginal Hazard Ratio (CI)	Adjusted Hazard Ratio (CI)	P Value*
rs6921438	6	LOC100132354	A	0.49	4506	1.03 (0.978 -1.089)	1.032 (0.973- 1.095)	0.290
rs114694170	5	MEF2C	C	0.046	4679	1.03 (0.919 -1.173)	1.025 (0.896- 1.171)	0.716
rs4782371	16	ZFPM1	G	0.299	4699	1.02 (0.966- 1.086)	1.064 (0.992- 1.141)	0.081
rs10761741	10	JMJD1C	T	0.406	5084	0.999 (0.948-1.054)	1.086 (1.022- 1.155)	0.007 **
rs7043199	9	VLDLR-AS1	A	0.215	4255	0.993 (0.927- 1.063)	1.091 (1.020- 1.168)	0.011 *
rs2639990	18	ZADH2	C	0.075	4602	0.945 (0.849-1.051)	0.987 (0.873- 1.116)	0.8440
rs74506613	10	JMJD1C	G	0.0027	4677	1.158 (0.625- 2.142)	1.104 (0.640- 1.905)	0.719
rs1740073	6	C6orf223	C	0.391	4568	1.004 (0.950- 1.061)	0.979 (0.919 -1.043)	0.525
rs6993770	8	ZFPM2	T	0.274	5026	0.981 (0.926- 1.039)	0.995 (0.930- 1.065)	0.901
rs2375981	9	KCNV2	G	0.433	4426	1.008 (0.953-1.065)	1.022 (0.966- 1.082)	0.432
Rs10761741 (Final Model)	10	JMJD1C	T	0.406	5084	0.999 (0.948- 1.054)	1.086 (1.016- 1.160)	0.014 **
Rs7043199 (Final Model)	9	VLDLR-AS1	A	0.215	4255	0.993 (0.927- 1.063)	1.087 (1.016- 1.164)	0.015 *

*Adjusted for Sex, HbA1C, SBP, DBP,BMI

* Final model adjusted for significant SNPs and covariates

Figure3.Multistate graph depicting competing events stratified by levels of HbA1C



Conclusions

❖The prevalence of higher retinopathy grades has decreased over time (Fig 1).

❖In this study, the Risk of retinopathy rises with increase in duration of diabetes.

❖More than half, (57.7%) of the participants had developed retinopathy within 10 years of diagnosis.

❖*VEGF* polymorphisms were associated with incidence of diabetic retinopathy in this cohort.

❖The effect of various SNPs on retinopathy risk can be significant when different polymorphisms are considered together.

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Disclaimer: The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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