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Genetically determined telomere length in monoclonal gammopathy of undetermined significance, multiple myeloma risk and outcome

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Dear Editor,

The association between leukocyte telomere length (LTL) and cancer risk has been studied, with conflicting results [1]. One potential reason is heterogeneity in the study design and methodology to measure LTL. Retrospective and prospective studies tend to show different results, which could be caused by reverse causation bias [1].

LTL is genetically determined, and several studies used a polygenic score combining eleven single nucleotide polymorphisms (SNPs) as proxies for LTL measurement. The results of these studies are more homogeneous and show a trend towards longer genetically determined LTL (gdLTL) and increased risk of several cancers [1, 2]. More recently, our knowledge of the genetics of LTL has improved, with genome-wide association studies (GWAS) identifying 158 independent SNPs [3].

For multiple myeloma (MM) three studies have been published either using PCR-based methods for measuring directly LTL, or using SNPs as proxies showing a consistent effect of longer LTL and increased risk [4–6]. However, the role of LTL was not investigated in relation to monoclonal gammopathy of undetermined significance (MGUS). MGUS is an asymptomatic precursor of MM, defined by early clonal plasma cell expansion. MM and MGUS partially share genetic susceptibility [7]. All MM cases are thought to develop from MGUS, but only a small fraction of MGUS progresses to MM [8].

We investigated the role of gdTL in MGUS onset and progression to MM using SNP scores (hereafter called teloscores). Furthermore, considering that LTL has also been suggested to affect cancer survival, we tested the teloscores for association with MM overall survival (OS) [9].

This study was carried out within the International Lymphoma Epidemiology Consortium (InterLymph), [7]. We used 746 MGUS cases and 879 controls, and 2066 MM cases (1019 with survival data) and 2050 controls (supplementary material). All individuals were of European ancestry. Isotype information was available for 530 (71%) of the MGUS cases (supplementary material). A subset of 69 MGUS had available information on progression to MM (follow-up time and date of progression). Follow-up time was defined from the date of MGUS detection to date of MM diagnosis (progressors) or date of last known follow-up or death (non-progressors). Follow-up time for MM OS was defined from the date of MM detection to date of death or of last known follow-up. Genotyping was performed with SNP arrays by Affymetrix and Illumina. Genotype data were subjected to standard quality control measures and imputed. Additional information about study participants, genotyping and quality control is available in the supplementary material.

We computed two teloscores: one, including 38 SNPs identified through eight GWAS (basic score), and one consisting of the basic teloscore augmented with 115 SNPs identified by a single study carried out in UK Biobank (extended teloscore) [3]. We decided to use both scores because the extended score, even if consisting of more SNPs, was obtained predominantly from the UKBB and might be enriched for alleles that are specific only to UK. Therefore, we wanted to compare the performances and concordance of the two methods. The list of the selected SNPs is reported in the supplementary material.

An unweighted and a weighted score was built for each individual, for both the basic and the extended teloscore. The unweighted teloscore was computed by adding up the number of alleles associated with longer telomeres (according to the results of the literature). The weighted teloscore was computed by multiplying the number of alleles associated with LTL by their betas reported in the literature. The weighted score could reflect better the effect of each individual SNP without an overestimation of SNPs with low effect, however the unweighted score is easier to understand since it is only based on the allele count and makes the results more interpretable. All the teloscores were calculated only in subjects with a 100% call rate (MGUS: 746 cases and 879 controls; MM: 2066 cases and 2,050 controls for the basic teloscore and 1851 cases and 1606 controls for the extended teloscore). For MM survival analyses, the teloscores were computed for all the individuals with complete data on ISS stage and OS ($n = 1019$) with an average follow-up of 61.2 months (25%: 31.0, 75%: 84.2).

The scores were categorized in quintiles based on their distribution in the controls, whereas for survival analysis the quintiles were computed based on the distribution in all individuals with ISS stage and OS data. The association between the quintiles and MGUS and MM risk was tested with logistic regression. MGUS isotypes were classified according to a risk score, using the Mayo Clinic model, and analyzed in relation to progression to MM [10]. Sensitivity analysis of the association between gdLTL and MGUS risk was performed removing known MGUS progressors to MM ($n = 69$) to ensure that MGUS progressors were not driving the association. The progression of MGUS to MM was analyzed through logistic regression using non-progressed MGUS as controls. Additional subgroup analyses considering other risk factors using the Mayo Clinic model were also carried out [10]. All analysis on MGUS progression should be considered exploratory, given the low number of individuals employed. Survival analysis of MM cases was done using Cox regression. In all analyses, the first quintile (i.e., the individuals with the shortest telomere length) was used as the reference, with sex, age, subpopulation, the top 10 principal components, and ISS stage (only for survival analyses) as adjustment variables.

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Table 1. Results of the unweighted score analyses.

		Results with basic score					Results with extended score				
	Quintile	**Controls**	**Cases**	**OR**	**95% CI**	**P_{value}**	**Controls**	**Cases**	**OR**	**95% CI**	**P_{value}**
MGUS risk	1	218	178	1.00	-	-	182	155	1.00	-	-
	2	161	128	0.97	0.70–1.35	0.873	180	151	1.07	0.77–1.48	0.683
	3	169	131	1.02	0.74–1.41	0.889	212	177	1.07	0.78–1.45	0.677
	4	210	177	1.02	0.76–1.38	0.879	130	111	1.20	0.84–1.71	0.318
	5	121	132	1.38	0.98–1.93	0.065	175	152	1.13	0.82–1.57	0.452
	Continuous[a]	879	746	1.06	0.98–1.14	0.123	879	746	1.04	0.96–1.11	0.356
MM risk	1	494	451	1.00	-	-	393	402	1.00	-	-
	2	350	327	1.03	0.82–1.30	0.811	277	274	0.92	0.68–1.23	0.568
	3	425	406	1.02	0.82–1.27	0.866	386	463	1.07	0.82–1.40	0.607
	4	443	502	**1.24**	**1.01–1.54**	**0.042**	244	296	1.23	0.91–1.65	0.177
	5	338	380	**1.31**	**1.04–1.65**	**0.02**	306	416	**1.33**	**1.01–1.74**	**0.044**
	Continuous[a]	2050	2066	**1.07**	**1.02–1.13**	**0.005**	1606	1851	**1.08**	**1.02–1.15**	**0.012**
	Quintile	**MGUS non-progressor**	**MGUS progressor**	**OR**	**95% CI**	**P_{value}**	**MGUS non-progressor**	**MGUS progressor**	**OR**	**95%CI**	**P_{value}**
MGUS progression to MM[c]	1	167	11	1.00	-	-	140	15	1.00	-	-
	2	113	15	1.96	0.85–4.48	0.112	143	8	0.49	0.19–1.24	0.131
	3	176	19	1.60	0.73–3.51	0.241	158	19	1.24	0.60–2.59	0.563
	4	102	11	1.68	0.69–4.07	0.251	104	7	0.64	0.25–1.66	0.364
	5	119	13	1.76	0.74–4.18	0.197	132	20	1.47	0.71–3.05	0.303
	Continuous[a]	677	69	1.1	0.92–1.32	0.301	677	69	1.12	0.94–1.34	0.199
	Quintile	**Alive**	**Deceased**	**HR**	**95% CI**	**P_{value}**	**Alive**	**Deceased**	**HR**	**95%CI**	**P_{value}**
MM survival	1	158	69	1.00	-	-	147	77	1.00	-	-
	2	183	93	1.08	0.79–1.48	0.629	151	72	0.92	0.66–1.27	0.601
	3	119	66	1.25	0.88–1.76	0.208	122	62	0.97	0.69–1.36	0.845
	4	97	62	1.19	0.84–1.68	0.339	131	75	1.13	0.82–1.56	0.456
	5	119	53	0.92	0.64–1.32	0.636	125	57	**0.70**	**0.49–0.99**	**0.046**
	Continuous[a]	676	343	0.99	0.92–1.08	0.940	676	343	0.96	0.89–1.03	0.235

[a]The measurement unit used in this analysis is the increase by one quintile. Results with a *P* value <0.05 are in bold.

Table 2. Results of the weighted score analyses.

		Results with basic score					Results with extended score				
	Quintile	**Controls**	**Cases**	**OR**	**95% CI**	**P_{value}**	**Controls**	**Cases**	**OR**	**95% CI**	**P_{value}**
MGUS risk	1	178	123	1.00	-	-	177	143	1.00	-	-
	2	177	162	1.33	0.95–1.86	0.093	176	140	0.98	0.70–1.37	0.905
	3	173	160	1.37	0.98–1.91	0.065	175	162	1.26	0.91–1.74	0.166
	4	176	133	1.12	0.80–1.58	0.503	176	129	1.01	0.72–1.41	0.972
	5	175	168	1.51	1.09–2.11	**0.015**	175	172	1.35	0.97–1.86	0.071
	Continuous[a]	879	746	1.07	0.99–1.15	0.085	879	746	1.07	0.99–1.15	0.085
MM risk	1	411	401	1.00	-	-	323	331	1.00	-	-
	2	412	348	0.97	0.69–1.09	0.227	321	329	0.98	0.73–1.32	0.897
	3	409	400	1.02	0.80–1.28	0.888	322	388	1.08	0.81–1.45	0.583
	4	411	478	1.18	0.95–1.48	0.137	320	371	0.96	0.72–1.28	0.771
	5	407	440	1.09	0.87–1.37	0.464	320	433	1.31	0.98–1.73	0.065
	Continuous[a]	2050	2067	1.05	0.99–1.10	0.065	1606	1852	1.05	0.99–1.12	0.108
	Quintile	**MGUS non-progressor**	**MGUS progressor**	**OR**	**95% CI**	**P_{value}**	**MGUS non-progressor**	**MGUS progressor**	**OR**	**95% CI**	**P_{value}**
MGUS progression to MM[c]	1	136	10	1.00	-	-	138	11	1.00	-	-
	2	137	11	1.02	0.41–2.50	0.973	135	9	0.82	0.33–2.08	0.680
	3	134	18	1.78	0.78–4.05	0.170	134	21	1.89	0.67–4.12	0.110
	4	135	13	1.22	0.51–2.90	0.654	135	14	1.22	0.53–2.81	0.634
	5	135	17	1.76	0.77–4.02	0.182	135	14	1.35	0.58–3.11	0.486
	Continuous[a]	677	69	1.14	0.95–1.36	0.172	677	69	1.09	0.91–1.31	0.340
	Quintile	**Alive**	**Deceased**	**HR**	**95% CI**	**P_{value}**	**Alive**	**Deceased**	**HR**	**95% CI**	**P_{value}**
MM survival	1	143	62	1.00	-	-	142	64	1.00	-	-
	2	143	61	0.98	0.69–1.41	0.929	143	60	1.04	0.73–1.48	0.846
	3	125	78	1.24	0.89–1.74	0.205	130	73	0.99	0.71–1.40	0.990
	4	126	78	1.35	0.96–1.89	0.081	122	82	1.29	0.93–1.80	0.130
	5	139	64	0.94	0.66–1.34	0.748	139	64	0.88	0.62–1.24	0.459
	Continuous[a]	676	343	1.02	0.95–1.10	0.620	676	343	0.99	0.92–1.07	0.929

[a]The measurement unit used in this analysis is the increase by one quintile. Results with a *P* value <0.05 are in bold.

We observed an increased MGUS risk between the individuals with the longest gdLTL compared to those with shortest gdLTL. The association of the basic teloscore was statistically significant for the weighted teloscore (OR = 1.51, 95% CI 1.09–2.11, $P = 0.015$), but the P value did not reach the statistical significance threshold in the extended teloscore (OR = 1.35, 95% CI 0.97–1.86, $P = 0.071$). The unweighted teloscores showed the same trend, without statistically significant associations (Tables 1 and 2). Similar results were obtained with the analysis restricted to non-progressor MGUS cases, without statistical significance (supplementary materials). None of the teloscores were associated with progression status (Table 1) and also the analysis using the Mayo Clinic model [10] did not provide reliable results (supplementary material).

There was a consistent association between longer gdLTL and increased MM risk, in both unweighted scores (Table 1). Similar results were obtained with the weighted score, although the associations were not formally significant (Table 2).

An association between longer gdLTL and longer survival in 1019 MM cases was observed only for the unweighted extended score (Tables 1 and 2). Supplementary Fig. 1 reports the Kaplan-Meier curve of the highest vs lowest quintile of the analysis of MM OS using the extended score.

Taken together, the results confirm the association of longer gdLTL with increased risk of developing MM [6]. Our findings are consistent with other studies conducted using gdLTL as marker for cancer risk and progression [1, 2]. A common explanation of the association between long LTL and increased risk of developing cancer is that longer LTL are potential markers of cells with greater division potential, making them more susceptible to acquiring new mutations that could promote malignant transformation [11], rather than an intrinsic effect of longer versus shorter telomeres. This could be particularly relevant for pre-malignant conditions such as MGUS.

In this study, we report for the first time an association between longer gdLTL and risk of developing MGUS, that was statistically significant in the unweighted basic teloscore suggesting that LTL may play a role in the chance of developing MGUS and the following progression towards MM. Nakao and colleagues identified an association between longer LTL and increased risk of clonal hematopoiesis of indeterminate potential which is a precursor of several myeloid malignancies [12]. Thus, our observation strengthens the relation between preneoplastic conditions and blood malignancy risk through telomere length. However, we did not observe any association for the MGUS progressors vs. non-progressors, probably due to the limited number of MGUS progressors that were included in this study. Additionally, no statistically significant differences in teloscore medians across different MGUS isotypes were observed, nor did teloscores vary significantly with disease progression status.

We observed a statistically significant association between longer gdLTL in the unweighted extended teloscore and better MM survival. This association is in line with the results observed in a study conducted in the context of the International Multiple Myeloma Research (IMMEnSE) consortium [6].

Limitations of this study include the European origin of all study subjects, which makes it difficult to generalize the results to other ethnicities, as well as the relatively small number of individuals in some of the analysis that were carried out, particularly the MGUS cases progressing to MM. Furthermore, the lack of smoldering myeloma patients in our dataset also represents a possible limitation to the understanding of the effect of gdLTL in the natural history of the disease. Additionally, using SNPs instead of direct PCR-based methods, even though it decreases possible bias, captures only a modest fraction of the variance of the trait.

In conclusion, we suggest that longer gdLTL may be a marker for MM risk, possibly increasing the risk of developing MGUS, and that longer telomeres are potentially associated with improved survival in MM patients.

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AUTHOR CONTRIBUTIONS

DC, CMV, FC, and FG conceived and designed the study. MGi performed the data analysis and drafted the first version of the manuscript. AICG and RL contributed to the data analysis. AM, MGe, EEB, MJM, SJC, MATH, ADN, EM, SVR, JNH, SIB, PB, GGG, EZ, SKK, NJC, WC, and SLS provided critical insights and comments. All authors reviewed and approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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