Dear Editor,

Plasma cell (PC) dyscrasias, including multiple myeloma (MM), represent a spectrum of monoclonal gammopathies resulting from a clonal expansion of an abnormal plasma cell clone. MM is generally preceded by precursor conditions known as monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM) and is the most common hematologic malignancy in African Americans (AAs) and European Americans (EAs). It has been established that AAs, including Ghanaian men, display a 2–3-fold higher prevalence of MGUS with a reported similar risk of MGUS to MM progression compared to European Americans (EAs). An increased MM incidence has also been observed in individuals with a family history of MM, an effect that was greater for individuals who self-identify as black, suggesting that constitutional, MM susceptibility risk allele/s may explain the increased prevalence of MGUS among individuals of African ancestry. Interestingly, AAs also appear to have either a similar or in some cases superior survival outcome compared to EAs depending on patient age, specific treatment modalities and access to care including clinical trial enrollment. This disparity in outcome may be explained by genetic differences that predispose to specific acquired, cyogenetically defined subtypes, which can influence disease prognosis and response to treatment. These cytogenetic subtypes can be broadly classified into either hyperdiploid (characterized by gains of odd-numbered chromosomes) or translocations involving the immunoglobulin heavy chain (IgH) gene on chromosome 14. In the context of MM, hyperdiploidy and translocations t(11;14)(q13;q32) and t(6;14)(p21;q32) are typically associated with a favorable prognosis, while translocations t(4;14)(p16;q32), t(14;16)(q32;q23), or t(14;20)(q32;q12) translocations are generally associated with an unfavorable prognosis.

Many previous studies evaluating the mechanism of racial disparities in MGUS/MM have assessed race using self-reported demographic data rather than utilizing ancestry informative single-nucleotide polymorphisms (SNPs) as a method to determine the proportion of racial admixture. Using SNP data, we have recently identified a higher prevalence of IgH translocations t(11;14), t(14;16) and t(14;20) in individuals with ≥ 80% African ancestry. Enrichment of t(11;14) was confirmed in a more recent study. As an extension to our previous work, we investigated which, if any, of the germline risk alleles previously associated with MM or MGUS risk, survival or risk of development of t(11;14) (Supplemental Table 1) are enriched in individuals of African ancestry in our cohort of patients with plasma cell dyscrasias.

Genotype and ancestry information were obtained from the Precision Medicine Research Array (PMRA) data of 898 samples from patients with an abnormal plasma cell proliferative disorder fluorescence in situ hybridization (FISH) result and a concurrent conventional G-banded chromosome study (Supplemental materials and methods). Eight-hundred eighty-one of these samples were previously described. As expected, the patient demographics of the full 898 sample cohort were similar to prior results, including the increased...
risk of development of either a t(11;14), t(14;16) or t(14;20) in individuals with high African ancestry (≥80%, very African cohort) compared to individuals with low African ancestry (<0.1%, <30% Asian ancestry, European cohort) (Supplemental Tables 2 and 3).

Of the 18 previously reported SNPs examined within our cohort (Supplementary Table 1), 11 risk alleles were associated with European ancestry (<0.1% African and <30% Asian ancestries), involving variants at 2p23.3, 2q12.3, 3q26.2, 5q15, 6p21.33, 6q21, 10p12.1, 16q23.1, and 17p11.2 (Supplemental Table 4). Seven risk alleles were found associated with African ancestry (≥80% African ancestry) involving variants at 3p22.1, 3q26.2, 7p15.3, 8q24.21, 11q13.3, 16p13.11, and 17p11.2 (Supplemental Table 5). Of these seven variants, rs9344 at 11q13.3 encoding the CCND1 gene encodes the cyclin D1 protein, a member of the cyclin D family, which regulates cyclin-dependent kinases (Cdks). Cyclin D in concert with Cdks phosphorylate the retinoblastoma protein promoting cell cycle progression. MM tumors typically deregulate one of three cyclin D proteins and t(11;14) translocation is a common allele and does not contribute to t(11;14) risk in a fully penetrant manner, it is probable that additional variants present in individuals with ≥80% African ancestry also contribute t(11;14) risk.

The CCND1 gene encodes the cyclin D1 protein, a member of the cyclin D family, which regulate cyclin-dependent kinases (Cdks). Cyclin D in concert with Cdks phosphorylate the retinoblastoma protein promoting cell cycle progression. MM tumors typically deregulate one of three cyclin D proteins and t(11;14) translocation is a mechanism promoting cyclin D1 deregulation. The c.870G > A polymorphism is at chr11:69,462,910 (GRCh37/hg19) of the last nucleotide of exon 4 of CCND1 (NM_053056). Although both 870G and 870A encode the proline amino acid, the G allele has been reported to cause a novel splice donor site resulting in a longer cyclin D1a transcript. The A allele has been reported to hinder splicing of exon 4 resulting in intron 4 read-through creating a truncated D1b transcript producing a protein shorter than D1a and lacking the D1a carboxy-terminus. The lack of the carboxy-terminus of the D1b isoform results in nuclear retention. Most studies have associated the A allele with cancer risk and poor outcome, with only a few studies correlating the G allele to increased cancer risk. Of interest, the G allele has been associated with increased risk of cervical, head and neck and colorectal cancers, malignancies AAs have also been reported with increased incidence compared to EAs.

To our knowledge, our study includes the largest group of individuals of African ancestry with an abnormal
Table 1  rs9344 SNP in association with African ancestry in A and with t(11;14) in B.

(A)

| Gene     | Allele | SNP genotype associations with race | p-value       |
|----------|--------|-------------------------------------|---------------|
|          | Chr.   | GT       | European N = 238 | Other N = 537 | Very African N = 123 | Total N = 898 |
|          |        |          |                 |               |                   |               |
| rs9344   | 11q13.3| Missing  | 4 (16.7%)       | 5 (15.2%)     | 3 (4.2%)           | 12 (14.1%)    |
|          |        | AA       | 39 (16.7%)      | 81 (15.2%)    | 5 (4.2%)           | 125 (14.1%)   |
|          |        | AG       | 112 (47.9%)     | 266 (50.0%)   | 35 (29.2%)         | 413 (46.6%)   |
|          |        | GG       | 83 (35.9%)      | 185 (34.8%)   | 80 (66.7%)         | 348 (39.3%)   |
| Risk allele frequency | | 0.59 | 0.60 | 0.81 | 0.63 |

(B)

| rs9344   | Non-t(11;14) (N = 637) | t(11;14) (N = 261) | Total (N = 898) | p-value |
|----------|------------------------|-------------------|-----------------|---------|
|          |                        |                   |                 |         |
| Missing  | 6                      | 6                 | 12              | <0.0001 |
| AA       | 109 (87.2%)            | 16 (12.8%)        | 125 (14.1%)     |         |
| AG       | 308 (74.6%)            | 105 (25.4%)       | 413 (46.6%)     |         |
| GG       | 214 (61.5%)            | 134 (38.5%)       | 348 (39.3%)     |         |
| Risk allele frequency | | 0.58 | 0.73 | 0.63 |

A Chi-squared test was used to evaluate the differences across these groups. European (<0.1% African ancestry and <30% Asian ancestry), other (not European or African), very African (≥ 80% African ancestry). Chi-squared test was used to determine the overall comparison between the three ancestral groups and also between ancestral groups 1 vs. 2, and 2 vs. 3 using pairwise comparison. Pairwise comparison difference is considered statistically significant when p < 0.025 based on Bonferroni method for multiple comparison.
An alternatively spliced cyclin D1 isoform, cyclin D1b, is a nuclear oncogene. Cancer Res. 63, 7056–7061 (2003).