Entities *versus* diseases: Myers *et al*. propose distinct aspects of adult T-cell lymphoma/leukemia

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In this issue of *Haematologica*, Myers *et al*.[1] argue that the characteristics of adult T-cell lymphoma/leukemia (ATLL) differ based on the geographic location of the patients affected. ATLL is a well-established entity, whose diagnostic criteria have remained substantially unchanged in the International Consensus Classification[2] and 5th Edition of the WHO Classification of Haemato-lymphoid Tumours[3] as compared to those in the 2017 WHO Classification.[4]

Although ATLL is recorded in different geographic areas, all in which the retrovirus human T-lymphotropic virus type 1 (HTLV-1) is endemic, most information in the literature is based on Japanese cases. Accordingly, the prototypic description of ATLL includes four subtypes (acute, lymphomatous, chronic, and smoldering), with different clinical characteristics, aggressiveness, cytological atypia, and prognosis. The average age of patients is 58 years. On molecular grounds, Japanese cases show frequent gain-of-function in T-cell receptor/NF-κB signaling, including activating mutations of *PLCG1* and *PRKCB*, *CTLA4/ICOS-CD28* fusions, and *REL* truncations.[5] Recurrent alterations of the *CD274* locus correlate with PD-L1 overexpression.[5] Further abnormalities affect transcriptional regulation, T-cell trafficking (*CCR4* and *CCR7* truncating mutations), tumor suppression (*TP53*) and epigenetic modification (*ARID2* and *EP300*).[5] Aggressive subtypes are characterized by more genetic alterations, while indolent subtypes frequently carry *STAT3* mutations.[5] Patients with *CCR4* mutations may respond to mogamulizumab,[5] while those with single nucleotide variations and copy number alterations of *TP53* have an inferior overall survival, regardless of the type of treatment.[5]

The paper by Myers *et al*. sheds new light on the topic of ATLL.[1] It focuses on the characteristics of cases occurring in Western populations and compares them with those of Japanese cohorts. One-hundred sixty-five ATLL cases were collected in South American and Caribbean countries as well as in France and USA, the latter corresponding to patients of African descent. Such a cohort has never been gathered before in the Western hemisphere and it was also noteworthy for the quantity of biological samples collected which allowed the application of a refined multi-omics approach. In addition, pre-and post-relapse material was available for 12 patients.

The confirmed worse outcome of Western ATLL cases compared to Japanese ones might be due to the economic conditions of African, Caribbean and South-American countries, which impede access to *ad hoc* designed trials, expensive therapies and personalized medicine programs. However, the study by Myers and co-workers[1] highlights many other factors that could affect the prognosis of patients with ATLL in the Western world. Clinically, there is a higher prevalence of aggressive subtypes (acute, lymphomatous and chronic with unfavorable features), occurring at a younger age. Most importantly, the study shows a significantly different molecular scenario, as depicted by the integration of whole-exome sequencing, copy-number variation data and RNA sequencing (Figure 1).[1]

Deletions or mutations of the putative driver genes *INPP4B*, *ANKRD11*, *CBLB* and *FOXO3* were significantly more common in Western cases than in Japanese ones, whereas the opposite was recorded for *CCR4* (explaining the poorer response to mogamulizumab), *PTPRN2* and *TRRAP*. Interestingly, a novel *FOXO3* hotspot was detected which occurred only in Western patients of African descent with the aggressive leukemic subtype of ATLL. In addition, combined mutational analysis and *in vitro* experiments indicated *ANKRD11* and *FOXO3* as potential driver genes, for the first time. Genetic alterations of *TP53*, *CD58*, *PRKCB*, *FAT1*, *FHIT*, *ARID2*, *CARD11*, *NOTCH1*, *INPP4B* and *ANKRD11* were associated with significantly increased overall mortality. Interestingly, *FAT1* mutations were previously found to be associated with a worse response to chemotherapy in peripheral T-cell lymphoma (PTCL), not otherwise specified.[6] *GATA3* deletion was significantly associated with unfavorable chronic cases, which were indeed numerous in the series

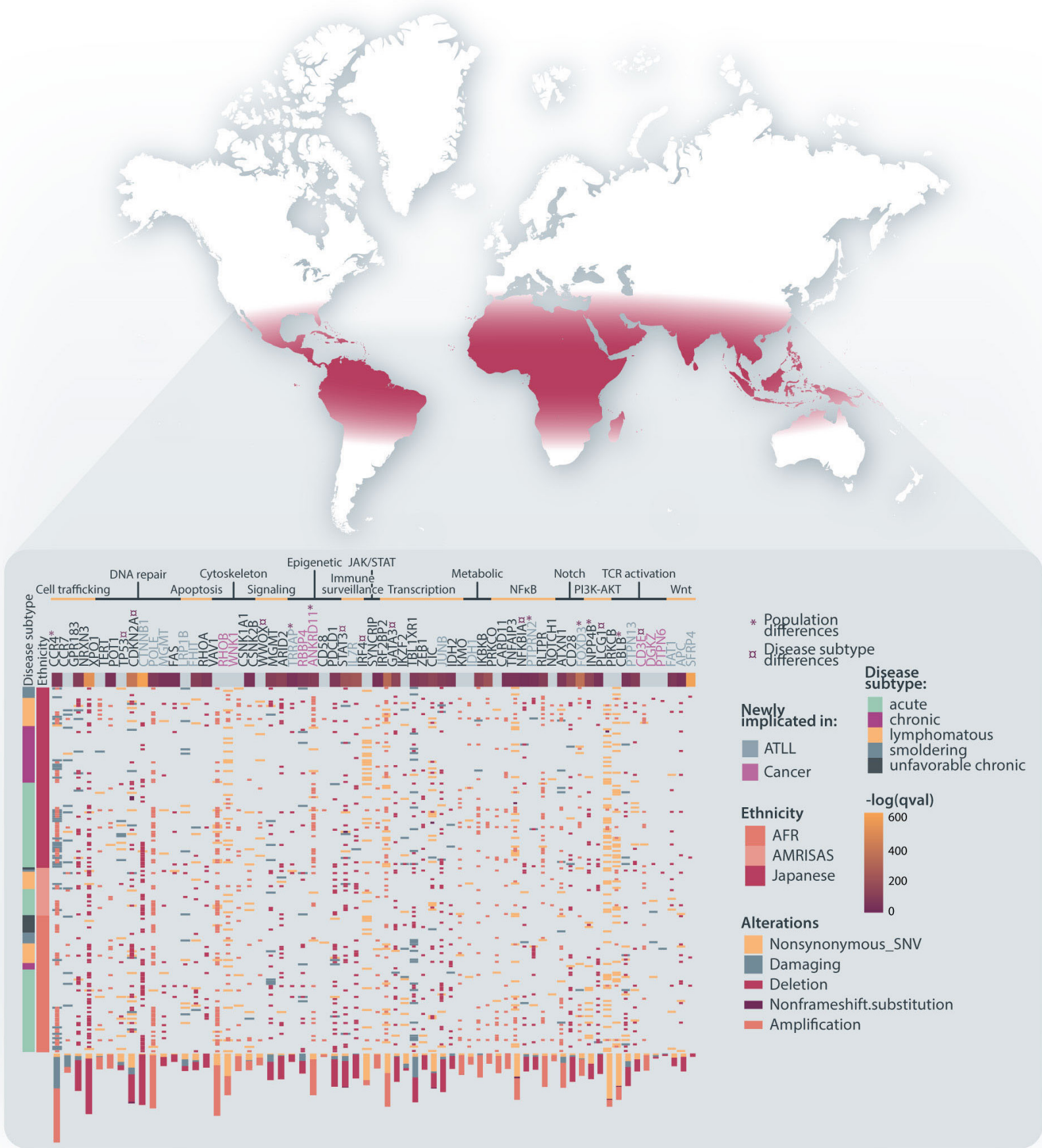

Figure 1. The molecular characteristics of adult T-cell lymphoma/leukemia vary between different geographic areas. The plot is taken from Figure 2A of the paper by Myers *et al.*,[1] to which one should refer for further details. TCR: T-cell receptor; ATLL: adult T-cell lymphoma/leukemia; AFR: African; AMRISAS: Native American/Southeast Asian; SNV: single nucleotide variation.

reported by Myers *et al*. *CDNK2A* loss heralded a complete response to chemotherapy, although the global mortality rate remained unchanged. In relapsed cases with material available, clonality identity with the samples at the time of diagnosis was shown. In addition, recurrent mutations of *CARD11* and *IRF4* were acquired in disease-relapse samples after treatment with zidovudine-interferon.

The observations of Myers and co-workers[1] might pave the way for novel therapeutic approaches in ATLL patients in the Western hemisphere. In fact, the recorded enrichment of mutations affecting *FOXO3*, *INPP4B*, *CBLB*, *DGKZ* and *PTPN6* points to the potential role of deregulation of the PI3K-AKT-mTOR pathway in the process of lymphomagenesis. PI3K inhibitors have been approved by regulatory agencies for different types of tumors, including malignant lymphomas. In recent trials, they have produced promising

results in PTCL.[7] Thus, they might represent an additional therapeutic option for ATLL patients, with particular reference to Western ones.

Among others, the paper by Myers and co-workers[1] has the merit of highlighting the concept that there is a difference between entities as described in the literature and diseases as occurring in real life. For instance, geographic area and ethnicity influence the characteristics of a certain pathological process by producing deviations from its prototypic description, in terms of prevalence, pathobiology, behavior, and response to therapy. This underlines the need for the inclusion of underrepresented populations, especially in the field of genomic research, as Myers and co-workers did. Besides the discrepancies between Japanese and Western ATLL cases, there are other examples of geographic variation of PTCL. The prevalence of ALK-negative anaplastic large cell lymphoma is significantly higher in South America than in Europe and North America.[8] The opposite holds true for Epstein-Barr virus-positive NK/T-cell lymphoma, nasal-type. Notably, the prevalence of the latter varies between the western and eastern coasts of South America, being definitely higher in the former.[8] This might reflect different ethnicities and migration flows, which occurred millennia ago. On the same line, the incidence of T follicular helper cell-related tumors varies among continents and even among countries belonging to the same continent (e.g., France *vs*. the rest of Europe).[9] Social and environmental factors can affect such variability. Thus, the question is: should we stand on prototypic descriptions or be aware of the many facets that the same disease can show? In-depth knowledge of the diversity of ethnic and molecular mechanisms at work for the same tumor in the different parts of the world is pivotal for the development of personalized medicine programs as well as for the appropriate usage of the new drugs, which often imply costs that are not easily affordable even by the public health systems of industrialized countries.

Disclosures

No conflicts of interest to disclose.

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