Sézary syndrome shows whole genome duplication as a late event in tumor evolution

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Introduction

Sézary syndrome (SS) is an aggressive subform of cutaneous T cell lymphoma. The genetics of SS are already studied by 186 whole exome sequencing datasets. To date no highly recurrent point mutation is known while several recurrent copy-number variations (CNV) are described. We want to reanalysis existing data to build a model of genomic changes during SS tumor development.

CNV landscape of Sézary syndrome

Reanalysis and aggregation of genomic data from 76 SS patients from 3 studies starting from raw read data was carried out. Point mutation and absolute copy-number data for each sample was called (Fig1). 15 samples showed results indicating a whole-genome duplication (WGD). The relative CNV landscapes of non-WGD and WGD samples is comparable, hinting at occurrence of the WGD after accumulation of single chromosome CNVs.

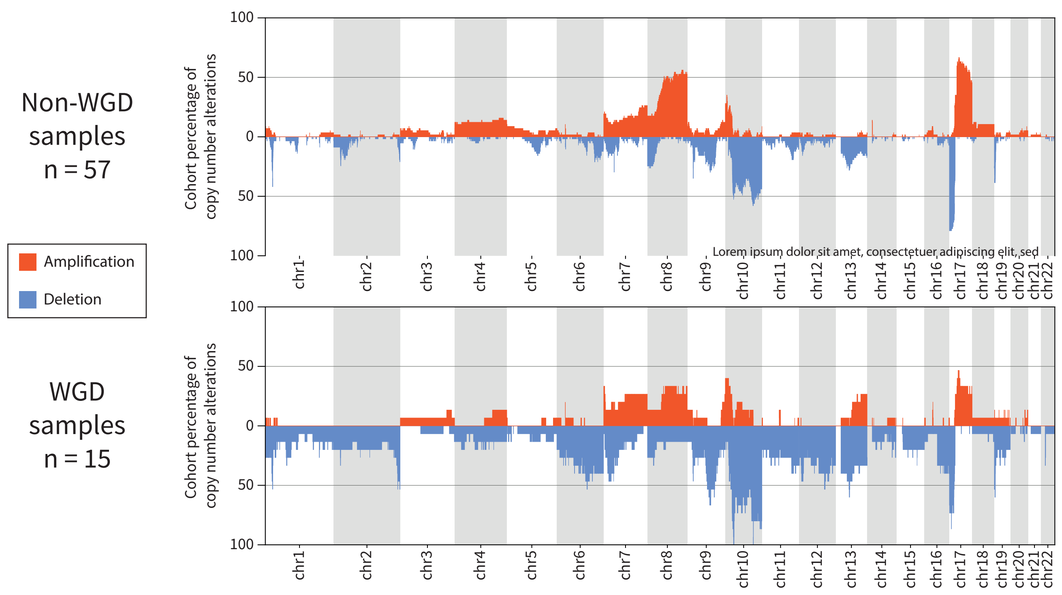

Figure 1: Copy number variation landscape of Sézary syndrome. The CNV landscape of 72 SS cases, separated in non-whole genome duplicated (WGD) and WGD, plotted against the genomic coordinates. Neutral copy number is 2 in the non-WGD and 4 in the WGD samples. Red areas above this level indicate amplifications and blue regions below this level indicate deletions.

Molecular timing of genomic amplifications

Genomic amplifications can be assigned a pseudo time indicating its occurance during tumor evolution. The used timing metric is the fraction of point mutations on one or multiple alleles. Early amplification shows point mutations on mostly one allele while later mutations show increasingly more point mutations on two alleles.

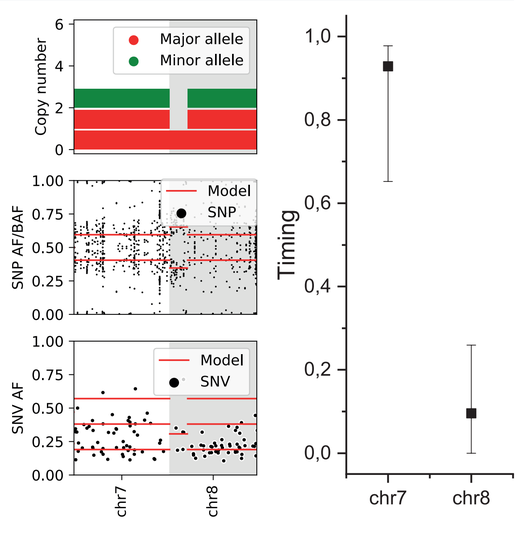

Figure 2: Example of molecular timing of amplifications. chr8 showed an early and chr7 a late amplification as indicated by their respective point mutation ploidy.

Timing of CNVs in Sézary syndrome

Molecular timing of amplifications was carried out for all 72 samples for single chromosome CNV events and for a combined WGD event if applicable (Fig3a) using mutationTimeR (Gerstung et al., 2020). Aggregated timing data from individual chromosomes showed early amplification of chromosomes 4, 8, 10 and, 17 and late occurrence of the WGD event (Fig3b).

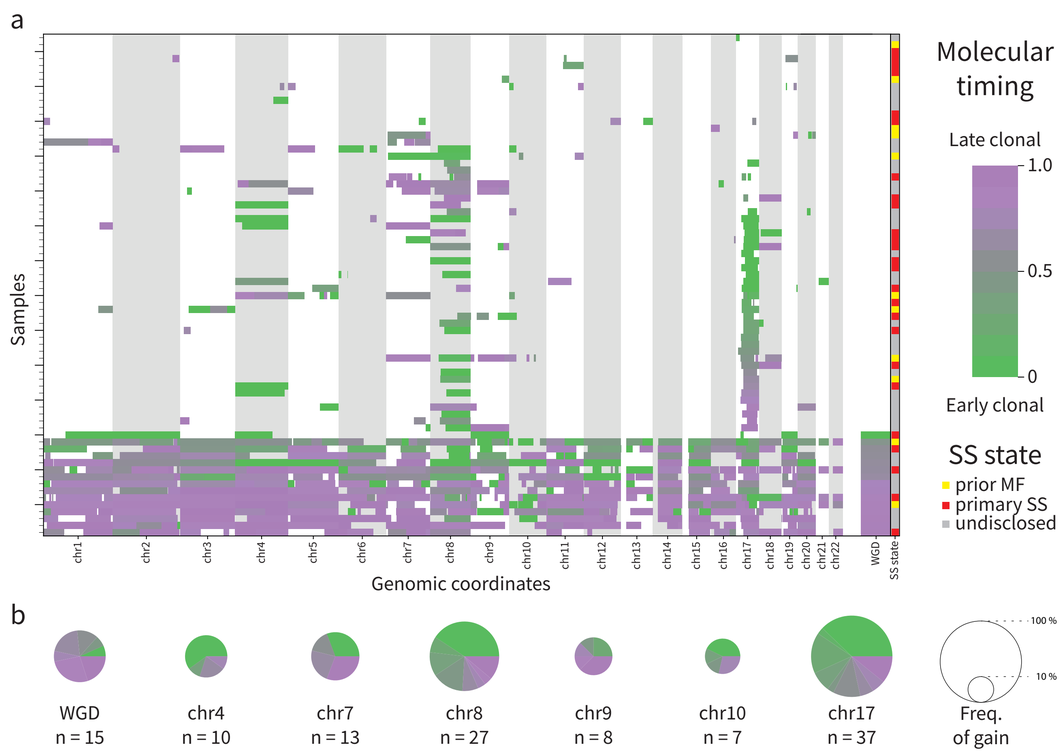

Figure 3: Molecular timing of amplification in Sézary syndrome patients. The amplifications of 72 SS patients were timed with MutationTimeR (Gerstung et al., 2020). This included all amplification with 3 or more SNVs as well as all whole genome duplications. Results are plotted against their genomic coordinates (a) or aggregated for the WGD event and the most recurrently amplified chromosomes (b). Initial diagnosis for individual patients (prior mycosis fungoides, primary SS) is indicated if this data was available.

Summary and Outlook

Our data suggests a rough model for the genomic changes in SS tumor evolution: Initial mutations are early amplification on chromosomes 4, 8, 10 and, 17. Afterwards multiple other point mutations and CNV accumulate and in about 20 % of cases a WGD occurs late into tumor evolution. This model explains the recurrence of individual CNVs as well as the lack of recurrent point mutations and the general heterogeneity of the genomic changes in this disease. Further focus should be directed to adding deletions to this model and analysing the early mutations in the much more common disease mycosis fungoides.

Literature

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