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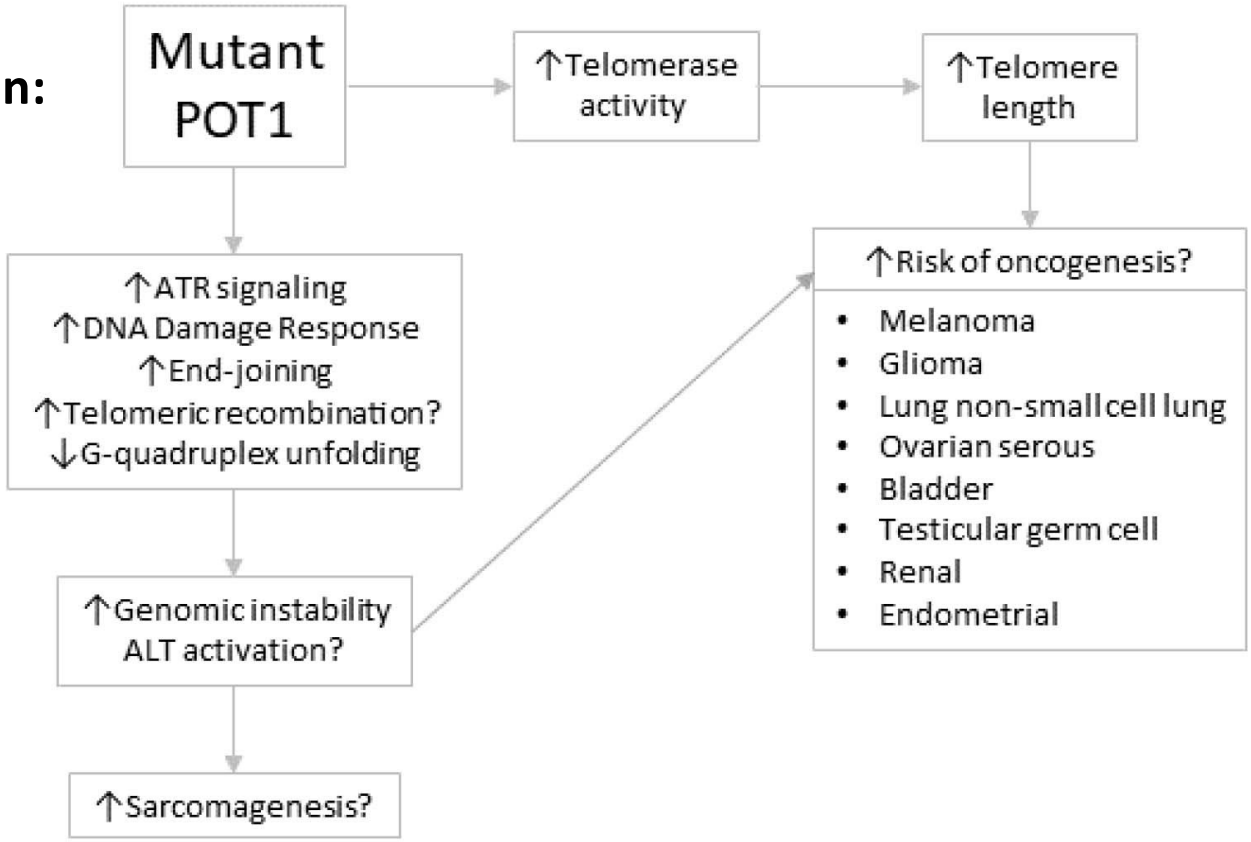
Germline and somatic POT1 mutations have been identified in a range of cancer types.
POT1 mutations are enriched in the **N-terminal OB-fold domains**.
Presumably non-benign POT1 mutations are present in approximately 3% of all tumors, with a **higher prevalence in angiosarcomas (20%)**, non-small-cell lung cancers, and cutaneous squamous cell carcinomas (9%) and melanomas.
POT1 germline variants are associated with cancer susceptibility in multiple familial cancer types, most notably in melanoma.

Speculation:



- POT1 is a negative regulator of telomerase.
- Experimentally induced complete loss of POT1 leads to rapid homologous recombination (HR)-mediated telomere elongation.
- Carriers of mutant POT1 genes have longer telomeres.
- POT1 suppresses ATR activation at telomeres.

Figure 3. Proposed roles of *POT1* mutations in development of cancer. We speculate here that the effects of *POT1* mutations differ according to the telomerase status of the cancer progenitor cells, with genomic instability and perhaps the activation of alternative lengthening of telomeres (ALT) being the predominant contributor to oncogenesis in cells that are telomerase-negative and therefore less able to counteract the deleterious effects of the *POT1* mutation on telomere cap function, and with increased telomere length being the predominant contributor when the progenitor cells have telomerase activity.

RESEARCH ARTICLE

CANCER GENOMICS

Heritable defects in telomere and mitotic function selectively predispose to sarcomas

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Cancer genetics has to date focused on epithelial malignancies, identifying multiple histotype-specific pathways underlying cancer susceptibility. Sarcomas are rare malignancies predominantly derived from embryonic mesoderm. To identify pathways specific to mesenchymal cancers, we performed whole-genome germline sequencing on 1644 sporadic cases and 3205 matched healthy elderly controls. Using an extreme phenotype design, a combined rare-variant burden and ontologic analysis identified two sarcoma-specific pathways involved in mitotic and telomere functions. Variants in centrosome genes are linked to malignant peripheral nerve sheath and gastrointestinal stromal tumors, whereas heritable defects in the shelterin complex link susceptibility to sarcoma, melanoma, and thyroid cancers. These studies indicate a specific role for heritable defects in mitotic and telomere biology in risk of sarcomas.

at the population level. For the most part, etic studies into sarcomas have used ei familial linkage approaches or genome-wide association studies (GWAS). Studies of rare sarcoma-associated syndromes have led to discovery of key cancer genes, such as the canonical tumor suppressor, *TP53* (*6*). Whole-exome sequencing (WES) or whole-genome sequencing (WGS) are now being used to catalog rare variants in known genes (*7*, *8*). In principle, combining both population- and family-based WGS approaches could uncover additional genes and pathways by integrating statistical methods with clinical information. In this study, we undertook a comprehensive, population-based, case-control study using WGS to identify penetrant genes and pathways that may explain sarcoma risk.

Results

Clinical findings

In total, 1644 sarcoma probands were recruited from sarcoma clinics in this international multi-institutional study, regardless of family history (tables S1 and S2). Subjects had a median age at first cancer diagnosis of 47 years, and 49 years at first sarcoma diagnosis. Soft-tissue sarcomas constituted 78.2% of diagnoses (Table 1 and table S3). Multiple primary cancers were common, including breast (n = 77), melanoma (n = 37), second connective tissue tumors (n = 37), nonmelanoma skin (n = 35), prostate (n = 23), colorectal (n = 21), and thyroid can-