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Abstract Title:- Molecular profiling of soft-tissue sarcomas using Next Generation Sequencing for definitive diagnosis

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Aims:-Soft tissue sarcomas are a heterogeneous group of tumors with numerous subtypes. Molecular profiling helps in accurately diagnosing and subtyping the tumor, which is essential for determining the most appropriate treatment plan.

Methods:- We present the molecular profiling data of soft tissue sarcoma patients (n = 95) who underwent testing using a laboratory-developed, CAP-accredited Next Generation Sequencing (NGS)-based Soft Tissue Sarcoma Panel from MedGenome Labs, which accurately identifies single nucleotide variants (SNVs), small insertions and deletions (InDels), and gene fusions in 101 genes curated using WHO 2021 and the latest NCCN guidelines. Fusions are screened using RNA sequencing, and therefore all known and unknown partners are detected with 98% sensitivity.

Results:- Among 95 patients (62.1% male and 38.9% female), 51 were below 40 years of age, including 12 pediatric patients, and the average age was 41.1 years. The cohort exhibited highly heterogeneous histological subtypes like rhabdomyosarcoma, synovial sarcoma, Ewing's sarcoma, round cell tumors, myxoid tumors, spindle cell sarcoma, and others. 75.7% (72/95) of patients exhibited at least one clinically relevant genomic alteration with a fusion event in 36.8% (35/95) patients, offering definitive diagnostic and management information. Interestingly, EWSR1 fusions were found in 10 patients with different fusion partners (ERG (1), FLI (1), ATF (1), PATZ (1), and WT (1)). EWSR1/ATF1 fusion is exclusively found in clear cell sarcoma, and similarly, EWSR1/WT1 fusion is specific to desmoplastic round cell tumors. Also, COL1A1/PDGFB fusion was detected in two Dermatofibrosarcoma protuberans patients, SS18-related fusions in three synovial sarcomas, BCOR-related fusions (BCOR/CCNB3 (2), ZC3H7B/BCOR (3)) in five spindle cell sarcomas, WWTR1/CAMTA1 fusion in epithelioid hemangioendothelioma, YAP1/KMT2A fusion in sclerosing epithelioid fibrosarcoma, and DDIT3/FUS fusion in two myxoid liposarcoma. Interestingly, BCOR-ITD alteration was detected in a patient with a primitive myxoid mesenchymal tumor of infancy and helped in the definitive diagnosis. Additionally, NTRK-related fusions were reported in three patients (NTRK3/ETV6, NTRK3/MYH9, and TPR/NTRK1), indicating the targeted treatment options. TP53 gene mutations were observed in 27 patients, with 21 patients with VAF >30%, indicating the probability of germline predisposition.

Conclusions:- This data presents the significance of a molecular approach in the diagnosis and treatment of soft tissue sarcomas, offering solutions to the challenges of differential diagnosis by identifying novel fusion partners using an RNA sequencing-based NGS test.

Keywords:- Soft Tissue Sarcoma, Fusions, Next Generation Sequencing, RNA-Seq