Genomic Landscape of Diverse Rare Tumors: Next-Generation Sequencing with Paired DNA and RNA analysis

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BACKGROUND

- In the U.S., rare tumors are defined as those with an incidence of fewer than 15 cases per 100,000 per year. Among rare tumors, cancers with prevalence <2000 or incidence of fewer than 2 cases per 100,000 are referred to as ultra-rare tumors.
- Rare tumors are infrequent by definition. However, when all subtypes of rare cancers are combined, they account for ~25% of adult malignancies. Hence the overall burden of rare tumors is significant.
- Clinical management of rare malignancies can be challenging due to the lack of information that can lead to difficulty making the diagnosis as well as a shortage of therapeutic options, both Food and Drug Administration approved and experimental on clinical trials.
- Thus patients with rare cancers tend to lack therapeutic approaches. Conceivably due to these limitations, patients with rare tumors are reported to have lower 5-year overall survival when compared to those with common tumors (47% versus 66%).
- Based on the unmet need for novel treatments for patients with rare cancers, genomic landscape of diverse rare tumors were investigated with next-generation sequencing. When available, paired DNA and RNA were sequenced.

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METHODS

- 380 patients with diverse rare tumors who underwent next-generation sequencing were evaluated (whole genome sequencing [N=274], whole exome sequencing [106]). Among them, 250 patients had paired DNA and RNA analysis.
- De-identified dataset with rare tumor diagnosis were collected from NantHealth database.
- Somatic-specific variants were identified using paired tumor/normal comprehensive NGS. Analysis was focused on the 200 most frequently mutated genes in this cohort. Deep whole transcriptomic sequencing (RNA-Seq) (~200x106 reads per tumor) was used to determine expression of observed somatic variants.

RESULTS

Patient characteristics (N=380)

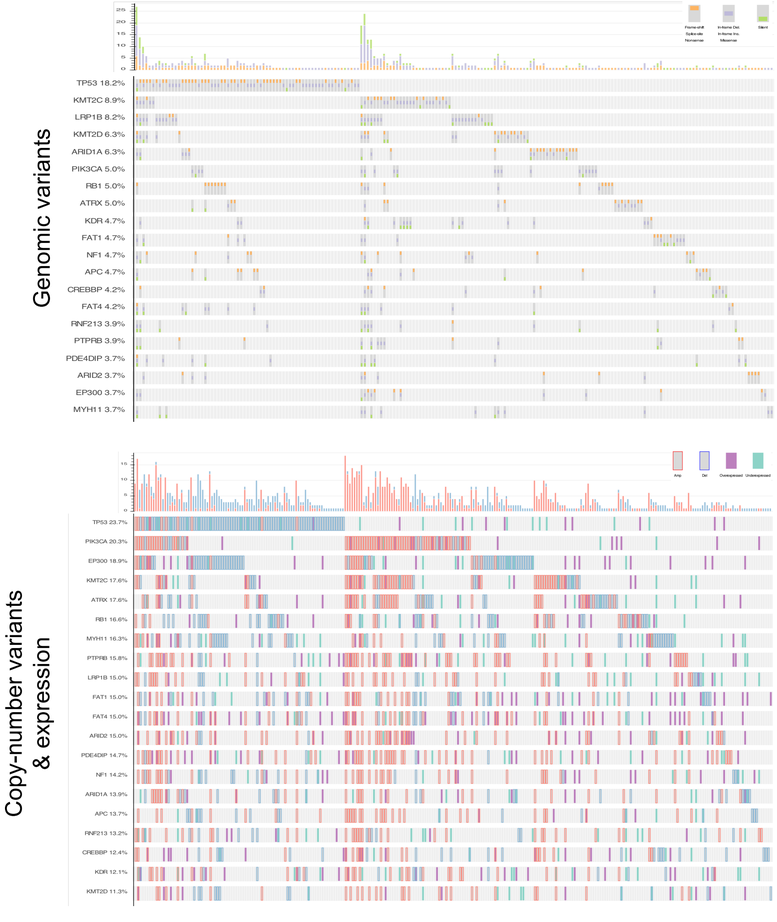
Cancer Type	Number of patients	Frequency
Bone and Soft Tissue Sarcoma	148	38.9%
Oral and Throat Cancers (Including Thyroid)	33	8.7%
Gall Bladder Cancer	32	8.4%
Cancer of Unknown Primary	28	7.4%
Thymic carcinoma	15	3.9%
Cervical cancer	15	3.9%
Adrenal carcinoma	9	2.4%
Skin cancer (Non-Melanoma)	9	2.4%
Mesothelioma	8	2.1%

Included in the table with N>5.
Testicular (N=4), Anal (N=4), Ampulla of Vater (N=3), Penile (N=1), Vaginal (N=2), Vulvar (N=2), Small Intestine (N=2), Urethral (N=1), Renal Pelvis and Ureter Cancers (N=1)

N=63 had unspecified cancer diagnosis.

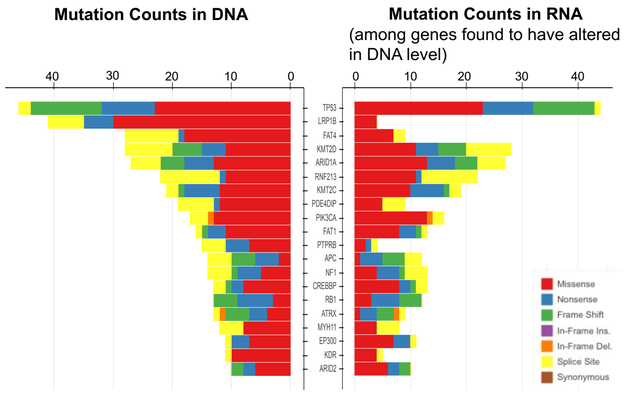
RESULTS

Overview of genomic alterations among diverse rare tumors (N=380)



RESULTS

Comparison between DNA and RNA alterations (N=250)



CONCLUSIONS

- Comprehensive genomic analysis is feasible among patients with rare tumors.
- Alterations were commonly seen in *TP53*, *KMT2C* and *PIK3CA*.
- Most patients had unique patterns of genomic alterations.
- Not all the genomic alterations observed in the level of DNA were transcribed.
- Further studies investigating the efficacy of an individualized precision therapy approach in patients with rare neoplasms using paired DNA/RNA analysis is warranted.

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