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Germline whole-exome sequencing of patients with neuroendocrine neoplasms (NENs) reveals pathogenic or likely pathogenic variants in a large subset of patients

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BACKGROUND

We conducted whole-exome sequencing (WES) of germline(g) and somatic(s) DNA from a prospective cohort of patients with NENs (n=151) to study the genetic predisposition to NENs.

METHODS

Variants obtained from gWES were filtered using a standard bio-informatics pipeline. Variant Effect Predictor (Release 107) was applied to obtain population allele frequencies. Variants were restricted to those among 974 genes obtained by combining publicly available gene lists. Fisher's exact tests were used to compare the frequencies of pathogenic/likely pathogenic germline variants with a reference population (n=74,023) from gnomad V3.1 Non-Cancer. Analysis of gene ontology was performed using the DAVID algorithm. Multiplex immuno-fluorescence (mIF) of samples with g*MUTYH* was performed.

RESULTS

The primary site of NEN was pancreas/duodenum (47%), small intestine/unknown (38%) and lung (9%). The stage at diagnosis was limited in 56% and metastatic in 44%. Well-differentiated NETs constituted 90% of the sample and poorly-differentiated carcinomas were 10%. After excluding 7 samples for insufficient data, a total of 144 germline samples were sequenced and 3,400 variants were identified; 75 pathogenic and 99 likely pathogenic. Pathogenic/Likely Pathogenic variants were present in 78% of patients (112/144), among 127 genes. Pathogenic variants were present in 45% of patients (65/144), with 15% (22/144) patients having at least one pathogenic variant in a gene included on current clinical cancer genetics testing panels. Recurrent alterations were found in 37 genes (frequency, false discovery rate): MEN1 (5%, 1.22E-17), MUTYH (5%, 0.003), PKD1 (5%, 0.003), ATP4A (4%,0.04), PAH (4%,0.003). The three most commonly involved pathways were DNA repair (26%), cellular calcium signaling (14%) and epigenetic regulation (7%). Germline *MUTYH* alterations were associated with a high somatic tumor mutation burden in three out of six patients. Two out of five of these subjects with g*MUTYH* showed a high degree of CD3+ and CD11c+ immune infiltration on mIF.

CONCLUSIONS

We identified that around 45% of patients with neuroendocrine neoplasms have pathogenic variants in the germline whole-exome. A subset of patients with g*MUTYH* alterations have a high TMB and robust immune infiltration with important implications for treatment with immunotherapy.

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