Integrity of the pheochromocytoma susceptibility **TMEM127** gene in patients with pediatric malignancies

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Dear Editor:

Germline mutations of the tumor suppressor gene TMEM127 gene occur in the neural crest-derived tumors pheochromocytomas and paragangliomas (Neumann, et al. 2011; Qin, et al. 2010; Yao, et al. 2010), and have also been detected in renal cell carcinomas (Qin, et al. 2014). Genes involved in susceptibility to pheochromocytomas and renal cancers have been detected in other malignancies. To determine whether TMEM127 mutations also predispose to cancers affecting the pediatric population herein we investigated the integrity of TMEM127 in 155 samples from various cancer types from patients younger than 18 years of age. One group was comprised of 16 gastrointestinal stromal tumor (GIST) samples, four germline and 12 tumors, from 13 patients. A second group encompassed germline DNA from 139 pediatric patients and included: 53 hematologic malignancies (39 acute lymphoid leukemias, 3 acute myeloid leukemias, 5 Hodgkin’s and 6 non-Hodgkin’s lymphomas), 22 osteosarcomas, 15 central nervous system tumors (5 medulloblastomas, 1 astrocytoma, 2 gliomas, 1 craniopharyngioma, 1 atypical teratoid rhabdoid tumor, 5 with unspecified histology), 12 germ cell tumors, 8 Ewing’s sarcomas, 6 neuroblastic tumors, 5 Wilms’ tumors, 4 retinoblastomas, 3 rhabdomyosarcomas, 3 liver tumors (2 hepatoblastomas, 1 hepatocarcinoma), 1 synovial sarcoma, 1 fibrosarcoma, 1 mesothelioma, 1 adrenocortical carcinoma, 1 desmoid tumor, 1 non-Langerhans histiocytosis and 1 primitive mixoid mesenchymal tumor of nasal arch. Three patients had more than one tumor. Informed consent was obtained from all patients (approved by UTHSCSA and NIH IRB committees) and sequencing of the TMEM127 coding region was performed as described previously (Yao et al. 2010). Two germline TMEM127 missense variants were detected: c.67C>A, p.Leu23Met, a novel variant, in one patient with Ewing’s sarcoma and c.268G>A,
p.Val90Met in one case of craniopharyngioma (Fig.1). The Val90Met variant was previously reported in pheochromocytomas (Abermil, et al. 2012; Qin et al. 2010), but has also been listed in the NHLBI Exome Sequencing Project (ESP) and the Exome Aggregation Consortium (ExAC), Cambridge, MA (URL: http://exac.broadinstitute.org; March, 2015), two reference databases which include both healthy and disease cohorts, at 0.28% and 0.08% minor allele frequency (rs121908823), respectively. The patient with Ewing’s sarcoma carried a EWSR1 translocation which has been previously implicated in this tumor’s pathogenesis (Tsokos, et al. 2012). Tumor tissue was unavailable from either patient for loss of heterozygosity analysis. No family history of cancers, pheochromocytoma or paraganglioma was reported in these two cases and DNA from parents was not available for testing. No pathogenic variants were detected in the remaining samples. Previously, we found that ectopic expression of several mutant TMEM127 constructs can lead to a diffuse subcellular distribution of the protein, in contrast with the punctate, endomembrane-associated appearance of the wild-type TMEM127 product (Qin et al. 2014; Yao et al. 2010). To determine whether the variants detected in this study had aberrant distribution we engineered TMEM127 constructs expressing these changes fused to the GFP protein as previously reported (Qin et al. 2014). We found that subcellular localization of the constructs was similar to that of wild-type TMEM127 when transfected in HeLa cells (data not shown). These findings suggest that Leu23Met and Val90Met either disrupt a function of TMEM127 that is independent of its membrane association or that they are not pathogenic. Currently there are no established downstream studies to test other functions of TMEM127.
We also interrogated publicly available databases of sequenced data from cancers, including The Cancer Genome Atlas (TCGA, NIH, USA) and the Catalog of Somatic Mutations in Cancer (COSMIC, Sanger Institute, UK). In these predominantly adult cancer cohorts we identified 46 somatic TMEM127 mutations, some of which were recurrent and/or predicted to be pathogenically relevant, across multiple tumor types (Fig.1). Intriguingly, these variants were entirely non-overlapping with germline mutations reported in pheochromocytomas and renal cancer. Our study suggests that the overall contribution of TMEM127 to pediatric cancer predisposition is limited, if present at all, although the number of samples tested within individual tumor types was small. This finding may not be entirely surprising given that previously reported germline TMEM127 mutations occur predominantly in adult patients (Toledo, et al. 2014). However, further studies will be necessary to establish whether somatic TMEM127 variants have functional significance in pediatric or adult cancers.
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Germline TMEM127 mutations

Somatic TMEM127 mutations