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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* occur in the neural-crest-derived tumors, pheochromocytomas and paragangliomas (Qin *et al*. 2010, Yao *et al*. 2010, Neumann *et al*. 2011), and have also been detected in renal cell carcinomas (Qin *et al*. 2014). Genes involved in susceptibility to pheochromocytomas and renal cancers are also mutated 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 of various cancer types from patients younger than 18 years of age. One group comprised 16 gastrointestinal stromal tumor samples, four germline and 12 tumors, from 13 patients. A second group encompassed germline DNA from 139 pediatric patients and included 53 hematological malignancies (39 acute lymphoid leukemias, three acute myeloid leukemias, five Hodgkin's and six non-Hodgkin's lymphomas), 22 osteosarcomas, 16 CNS tumors (five medulloblastomas, one astrocytoma, two gliomas, one craniopharyngioma, one atypical teratoid rhabdoid tumor, and five with unspecified histology), 12 germ cell tumors, eight Ewing's sarcomas, six neuroblastic tumors, five Wilms' tumors, four retinoblastomas, three rhabdomyosarcomas, three liver tumors (two hepatoblastomas and one hepatocarcinoma), one synovial sarcoma, one fibrosarcoma, one mesothelioma, one adrenocortical carcinoma, one desmoid tumor, one non-Langerhans histiocytosis, and one primitive myxoid mesenchymal tumor of nasal arch. Three patients

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Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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 has been previously reported in pheochromocytomas (Qin *et al.* 2010, Abermil *et al.* 2012), and has also been listed in the NHLBI Exome Sequencing Project and the Exome Aggregation Consortium, Cambridge, MA, USA (URL: http://exac.broadinstitute.org; March, 2015), two reference databases that include both healthy and disease cohorts, at 0.28 and 0.08% minor allele frequency (rs121908823) respectively. The patient with Ewing's sarcoma carried an *EWSR1* translocation that has been previously implicated in this tumor's pathogenesis (Tsokos *et al.* 2012). Tumor tissue was not available 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 WT TMEM127 product (Yao *et al.* 2010, Qin *et al.* 2014). 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 reported previously (Qin *et al.* 2014). We found that subcellular localization of the constructs was similar to that of WT TMEM127 when transfected into HeLa cells (data not shown). These findings indicate either that Leu23Met and Val90Met 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 sequence 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. The results of our study indicate 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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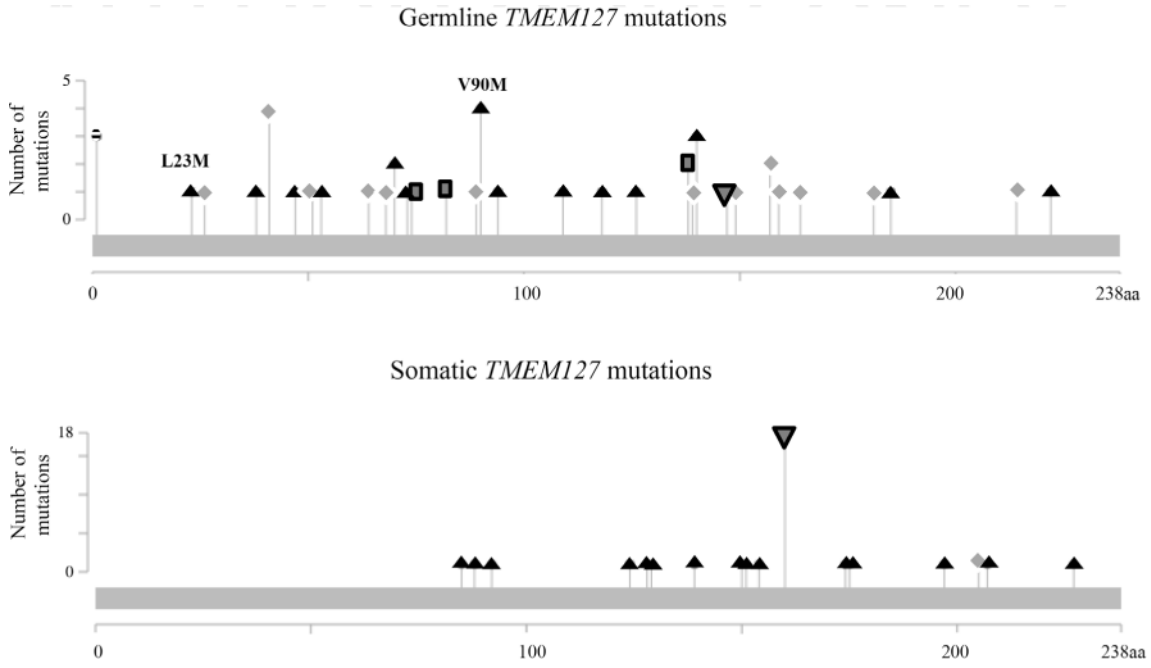

Figure 1.

'Lollipop' plot displaying the number (vertical axis) and position of *TMEM127* gene mutations along its protein sequence. The upper panel depicts germline mutations. The two mutations found in this study are indicated. The Val90Met (V90M) variant has been found previously in three pheochromocytomas. The lower panel shows somatic mutations found in breast, brain, liver, pancreas, skin, stomach, and endometrial cancers from publicly available databases searchable at the Memorial Sloan Kettering Cancer Center cBioPortal for Cancer Genomics site (http://www.cbioportal.org/public-portal/). Key: missense mutations, triangles; nonsense or frameshift mutations, diamonds; splice mutations, squares; inframe insertions or deletions, inverted triangles; start codon loss/change, circles. The plot was designed using the Mutation Mapper tool of the cBioPortal.