Supplementary Information

Comprehensive germline genomic profiles of children, adolescents, and young adults with solid tumors

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## Supplementary Table 1 Demographic and clinical characteristics of patients

| DNA Type | CCF | PCGP | SJLIFE |
|----------|-----|------|--------|
| Sequencing Assay | Whole Exome Sequencing | Whole Exome Sequencing | Whole Exome Sequencing |
| #Total Patients | 50 | 193 | 1269 |
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| Age Group | Children | Adolescent | Young Adult | Children | Adolescent | Young Adult | Unknown | Children | Adolescent | Young Adult | Unknown |
| Gender/Male | 16/15 | 4/8 | 0/7 | 64/62 | 5/4 | NA | 14/13* | 520/505 | 58/85 | 5/8 | NA |
| Average Age of onset | 7.8 ± 4.2 | 17.7 ± 1.2 | 22.3 ± 2.9 | 6.4 ± 4.7 | 16.5 ± 1.1 | NA | NA | 6.1 ± 4.5 | 16.9 ± 1.3 | 22.2 ± 2.5 | NA |
| All Solid Tumors (1507) | 31 | 12 | 7 | 126 | 9 | 0 | 53 | 1025 | 143 | 13 | 88 |
| Central Nervous System (323) | 1 | | | | | | | 265 | 23 | 2 | 32 |
| Wilms Tumor (207) | 1 | | | | | | | 188 | 2 | | 15 |
| Neuroblastoma (190) | 2 | 1 | 21 | 2 | 25 | | | | 135 | | 4 |
| Rhabdomyosarcoma (134) | 3 | | 26 | 2 | 1 | | | | 85 | 12 | 1 | 4 |
| Osteosarcoma (129) | 8 | 4 | 2 | | 2 | | | | 70 | 38 | 3 | 2 |
| Retinoblastoma (98) | | | | | | | | | 84 | | | 14 |
| Ewing's Sarcoma (95) | 3 | 2 | 1 | | | | | | 55 | 25 | 4 | 5 |
| Soft Tissue Sarcoma (93) | 6 | 1 | 1 | | | | | | 63 | 16 | 2 | 4 |
| High Grade Glioma (80) | 2 | 3 | | 61 | 5 | | 9 | | | | | |
| Germ Cell Tumor (74) | 1 | | | | | | | 56 | 11 | 1 | 5 |
| Low Grade Glioma (24) | 1 | | | | | | | 15 | | 7 |
| Adrenocortical Carcinoma (22) | 1 | | | | 18 | | 1 | | | | 2 |
| Carcinoma (14) | | | | | | | | 7 | 7 |
| Giant Cell Tumor (3) | | | | | | | | | 3 |
| Renal Cell Carcinoma (3) | | 1 | | | | | 2 |
| Low Malignant Potential Renal Tumors (2) | | | | | | | 2 |
| Basal Cell Carcinoma (1) | | | | | | | 1 |
| Paraganglioma (1) | | | | | | | 1 |
| Other Solid Tumor (10) | | | | | | | 3 | 4 | | 3 |
| Non-Malignant Tumor (4) | | | | | | | 2 | 1 |

CCF, Cleveland Clinic Foundation; PCPG, Pediatric Cancer Genome Project; SJLIFE, St. Jude Life Cohort.

* Gender data were not available for all the patients in this group.
Supplementary Figure 1 Analysis Workflow. Abbreviations: XHMM, eXome-Hidden Markov Model; IGV, Integrative Genomic Viewer; PCGP, Pediatric Cancer Genome Project; SJLIFE, St. Jude Lifetime
Supplementary Figure 2 Examples of Sanger sequencing confirmations of KCPG and candidate variants in CCF series

CCF12237, BRCA2
c.4284dupT
p.Q1429fs*9

CCF12237, TP53
c.916C>T
p.R306*

CCF11848, ARMC4
c.2495+1G>A
Reverse Strand

CCF11950, LIFR
c.1231_1234delAATG
p.N411fs*13

CCF10770, CHD7
c.6199C>A
p.Q2067K

CCF11946, ACADS
c.2T>C ; p.M11T
Reverse Strand

CCF11930, ITAGA8
c.2937+2T>C
Reverse Strand

CCF11835, GLRA1
c.737G>A ; p.R163Q
Reverse Strand
Supplementary Figure 3 Copy number variation analysis in CCF C-AYA cases. a *DDX10* duplication in a patient with osteosarcoma, VarSeq (left panel) and XHMM (right panel) platforms. b *SUZ12* duplication in a patient with Wilms Tumor, VarSeq (left panel) and XHMM (right panel) platforms. In VarSeq, Thick blue line in CNV state shows the duplicated area. In XHHM, green line is the target case, and all gray lines are other CCF cases in the series. Related to Figure 1.
Supplementary Figure 4 Lollipop plots of top KCPC with germline P/LP variants in C-AYA patients with solid tumors. Related to Figure 2.
Supplementary Figure 5 Lollipop plots of top candidate genes with germline P/LP variants in C-AYA patients with solid tumors. Related to Figure 2.
Supplementary Figure 6  Top genes with P/LP mutations in each C-AYA solid tumors.  

**a** Top altered KCPG genes in each tumor type.  

**b** Top altered candidate genes in each tumor type. Abbreviations: ACT, adrenocortical carcinoma; CNS, central nervous system; EWS, Ewing sarcoma; GCT, germ cell tumor; HGG, high-grade glioma; LGG, low-grade glioma; NBL, neuroblastoma; OS, osteosarcoma; RB, retinoblastoma; RHB, rhabdomyosarcoma; STS, soft tissue sarcoma; WLM, Wilms tumor. Related to Figure 3.
Supplementary Figure 7 Congenital heart defect (CHD) related genes with germline P/LP alterations in each C-AYA related solid tumor. a Oncoplots of CHD related genes. Each column represents one patient and its affected genes. b Heatmaps of CHD-related genes in each C-AYA related solid tumor. Scale refers to log10 (frequency of P/LP variants in specified genes in each tumor type). Abbreviations: ACT, adrenocortical carcinoma; CA, carcinoma; CNS, central nervous system; EWS, Ewing sarcoma; GCT, germ cell tumor; HGG, high-grade glioma; LGG, low-grade glioma; NBL, neuroblastoma; OS, osteosarcoma; OST, other solid tumors; RB, retinoblastoma; RHB, rhabdomyosarcoma; STS, soft tissue sarcoma; WLM, Wilms tumor. Related to Supplementary Table 6.
Supplementary Figure 8 Genes mutated in cell cycle, Notch, Wnt, and Hippo pathways, and the number of patients affected in our cohort. Red font: tumor suppressor genes; Blue font: oncogenes. Related to Figure 4.
Supplementary Figure 9 Lower expression of Col7A1 in kidney related tumors. Related to Figure 3.
Data extracted from gene expression profiling interactive analysis (GEPIA) website (Tang et al., 2017).
log2(TPM + 1) have been used for log-scale. Line in the box shows median expression, top & bottom of the box are quartiles, and external lines show the range. Dots outside of the range are outliers. p-value Cutoff was 0.01 and Log2fc cutoff was 1.