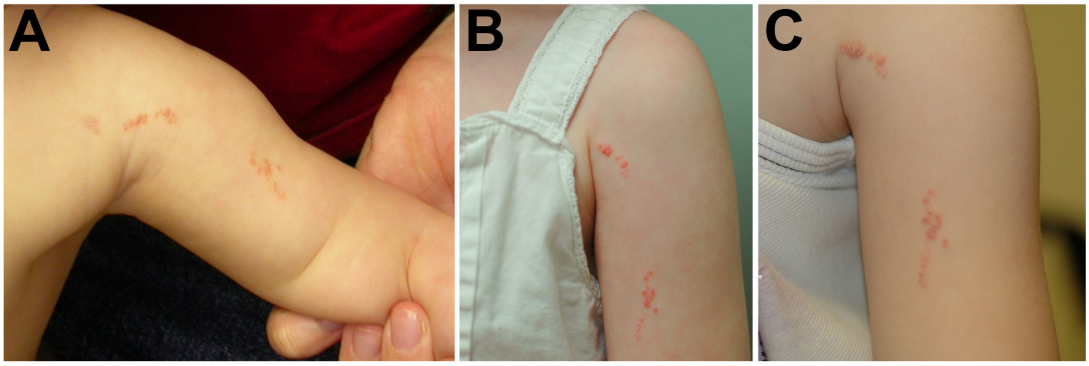
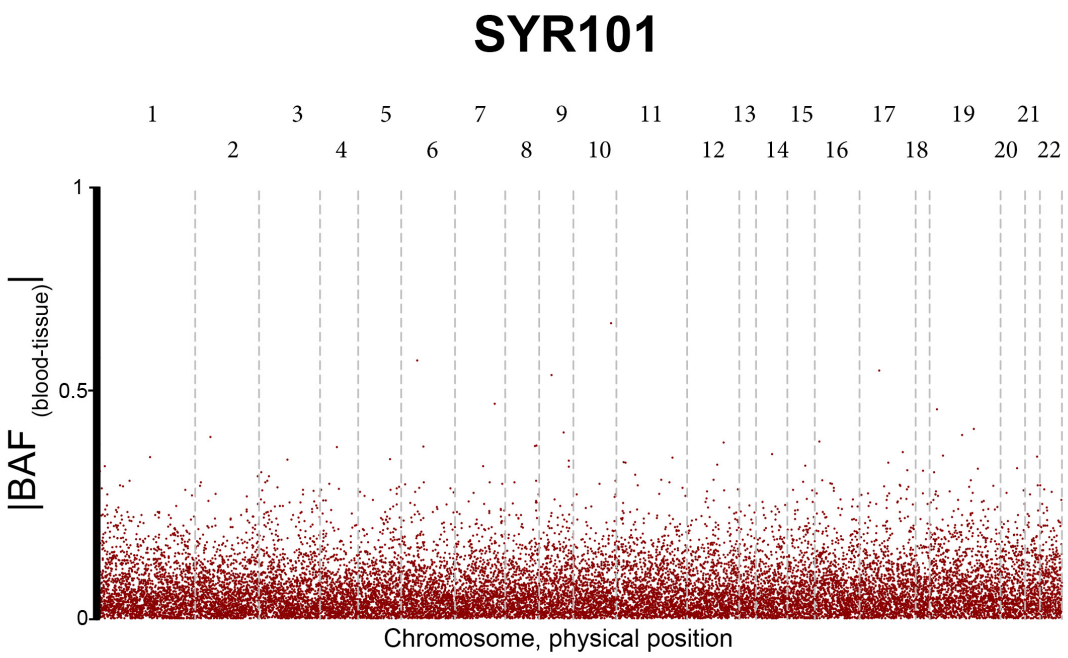
Sample	Mean Coverage	Bases Covered >8x	Bases Covered >20x	Mean Read Length
SYR101 Tissue	103.7x	98%	95%	74 bases
SYR101 Blood	78.4x	97%	90%	74 bases

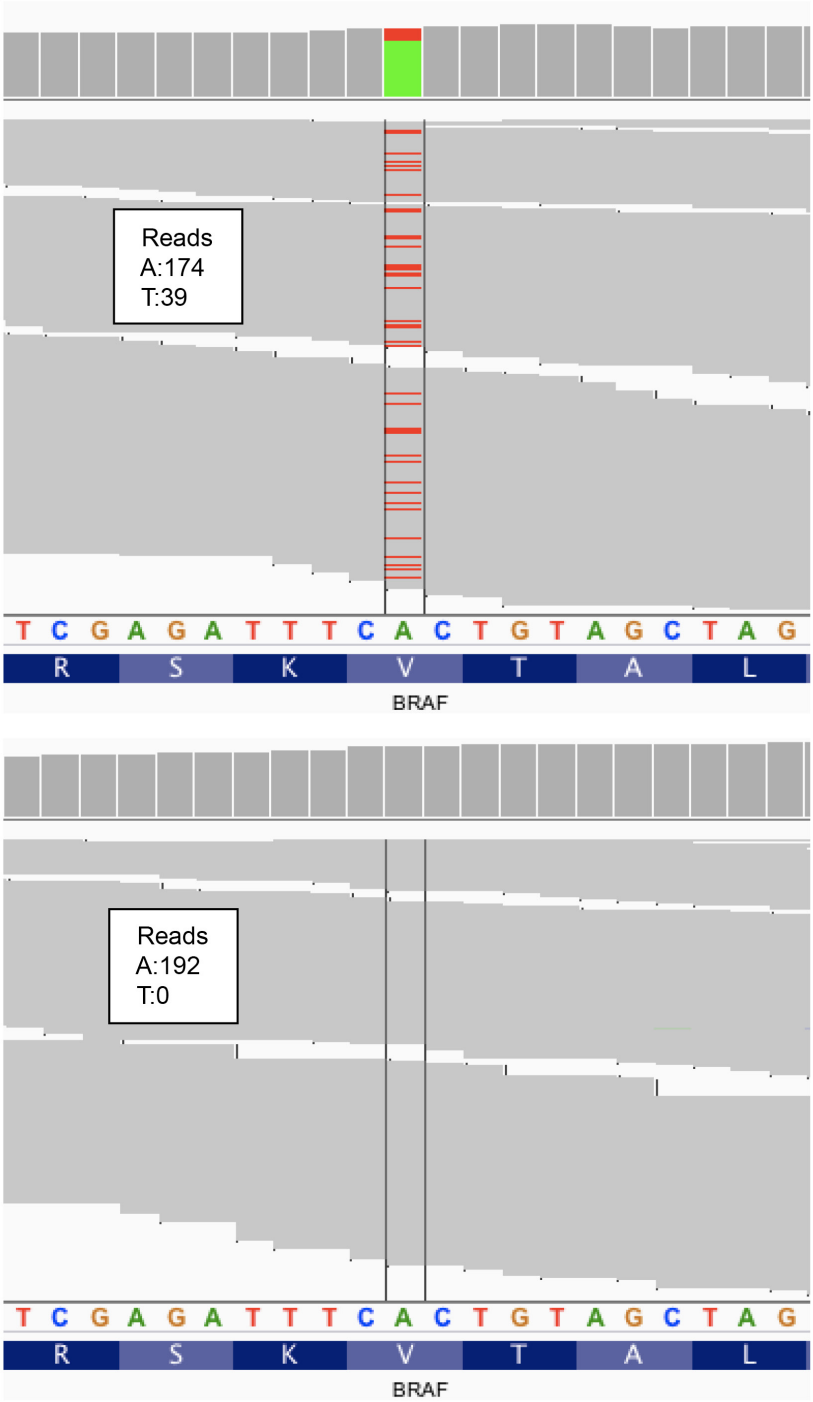
Supplementary Table 1. Exome sequencing run statistics. Tissue and blood was covered at an average depth of 103.7x and 78.4x, with 20x coverage of 95% and 90%, respectively.



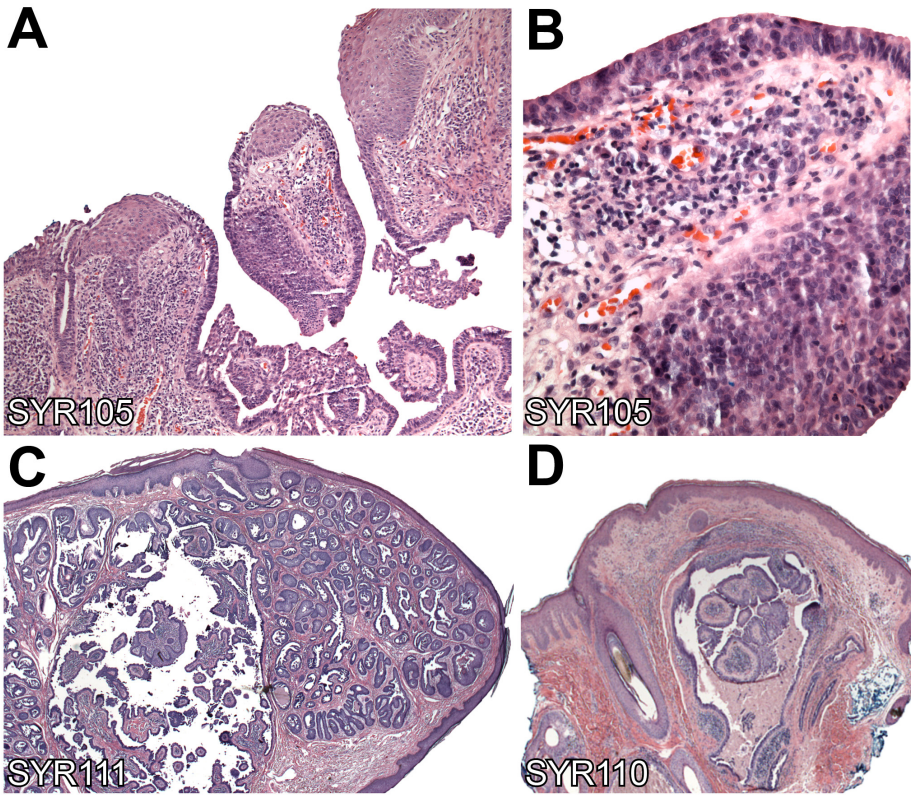
Supplementary Figure 1. Clinical appearance of SYR101 over time. The linear syringocystadenoma presents in the same pattern along the arm of the patient present as an infant (A), as a 6-year-old (B), as an 8-year-old (C).



Supplementary Figure 2. The is no evidence of loss-of heterozygosity in SYR101 Absolute value of b-allele frequency (BAF) differences between tissue and blood across the genome is plotted for SYR101 against genomic position. No large regions demonstrate changes in BAF as we would expect to see in the case of large deletions or CNVs. CoNIFER was employed to detect CNVs without using BAF, and also found no regions of LOH.



Supplementary Figure 3. Exome reads at *BRAF* V600E locus of SYR101 samples. Using Integrative Genome viewer, exome reads are visualized at exon 15 of BRAF demonstrating 39 non-reference out of 213 total reads in tissue that manifest in a V600E mutation. Blood demonstrates no non-reference reads out of 192 total reads.



Supplementary Figure 4. Histologic features of archival V600E positive SCAP. SCAP lesions demonstrate papillomatosis with columnar cells lying upon cuboidal epithelia lining the papillae. Plasma cell infiltration is also present.

Materials and Methods

Human Subjects.

This study was approved by the Yale Human Investigation Committee, and complies with the Declaration of Helsinki guidelines. Subjects provided written informed consent, except in the case of archival tissue samples, which were provided anonymized.

DNA Extraction.

For linear SCAP, DNA was directly extracted from a punch biopsy of and excised lesion. Fat and underlying dermis were trimmed to leave clinically homogeneous lesional tissue.

For archival SCAP specimens, 2-3 1mm cores were taken from the center of lesional tissue based upon a hematoxylin-eosin stained slide from an adjacent section. DNA from formalin-fixed paraffin-embedded (FFPE) archival tissue samples was extracted using an FFPE extraction kit (QIAGEN, Valencia, CA). DNA was extracted from fresh tissue and blood via standard methods.

Whole Exome Sequencing.

DNA was sheared, and captured using EZexome V2 capture probes (Roche). Paired-end sequencing was performed on an Illumina HiSeq2000. Raw reads were aligned to the hg19 reference genome using BWA-mem [1]. PCR duplicates were excluded and reads were trimmed to fit the targeted regions. Variants (SNVs and indels) were called using SAMtools [2], and common variants (dbSNP 137) were excluded. A Perl script was used to identify mutations with increased non-reference reads in tissue versus blood, and manually filtered for novel, coding mutations with $\geq$4 non-reference reads in tissue and $\leq$3 non-reference reads in blood. Mutations were manually inspected using the Integrative Genomics Viewer to ensure that reads were not mismapped [3].

Copy Number Variation and Loss-of-Heterozygosity

Copy number variation and loss-of-heterozygosity events were evaluated using CoNIFER [4] (267 control exomes, SVD 20).

Sanger Sequencing.

Kapa 2G polymerase was used for PCR. The following primers were used for amplification and sequencing:

BRAF_exon11_F: TTCTGTTTGGCTTGACTTGAC
BRAF_exon11_R: GACTTGTCACAATGTCACCAC
BRAF_exon15_F: TCATAATGCTTGCTCTGATAGGA
BRAF_exon15_R: GGCCAAAAATTTAATCAGTGGA
HRAS_exon2_F: CTCCTTGGCAGGTGGGGCAG
HRAS_exon2_R: AGCCCTATCCTGGCTGTGTCCTG
KRAS_exon2_F: TGAGTTTGTATTAAAAGGTACTGGTGGAG
KRAS_exon2_R: AACTTGAAACCCAAGGTACATTTCAG

Supplemental References

1. Li H, Durbin R (2009) Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics 25: 1754-1760.
2. Li H, Handsaker B, Wysoker A, Fennell T, Ruan J, et al. (2009) The Sequence Alignment/Map format and SAMtools. Bioinformatics 25: 2078-2079.
3. Thorvaldsdottir H, Robinson JT, Mesirov JP (2013) Integrative Genomics Viewer (IGV): high-performance genomics data visualization and exploration. Brief Bioinform 14: 178-192.
4. Krumm N, Sudmant PH, Ko A, O'Roak BJ, Malig M, et al. (2012) Copy number variation detection and genotyping from exome sequence data. Genome Res 22: 1525-1532.