**SUPPLEMENTARY FIGURE LEGENDS**

**Supplementary Figure 1.** Evidence supporting multiple lncRNA transcript isoforms mapping to chromosome 6p22.3. (**a)** Graphical representation of the multiple *CASC15* isoforms annotated in the Ensembl Genome Browser. Note that CASC14 is transcribed in the antisense direction. (Vertical bars denote exons). The long (CASC15-003) and short isoforms of *CASC15* (CASC15-004) are highlighted in red and blue, respectively. (**b**) RNA paired-end tagged transcripts (cytosolic fraction: top, nuclear fraction: bottom) in SK-N-SH neuroblastoma cells indicate the presence of capped and polyadenylated *CASC15* transcripts. Reads spanning the short *CASC15* isoform are denoted by the red arrows, and were found in both the nucleus and cytosol.

**Supplementary Figure 2.** Bioinformatical support for *CASC15-S* as a long noncoding transcript. (**a**) The genomic region containing the *CASC15-S* transcript indicates a capped and polyadenylated product as illustrated by CAGE and PolyA-Seq, respectively. In addition, the 5’ region of *CASC15-S* appears conserved by 100 vertebrate multiple sequence alignment and placental mammal chain alignments from the UCSC browser. (**b**) *CASC15-S* expression using an *in vitro* transcription/translation assay did not produce protein product (3rd lane), in contrast to a luciferase control (right). (**c**) *CASC15-S* also exemplifies non-coding status by coding-potential assessment tool (CPAT) analysis. Shown for reference are GAPDH (a known coding transcript) and XIST (a verified lncRNA) (**d**) Nuclear localization by quantification of RNA-PET in the SK-N-SH cell line. (**e**) Quantification of RNA sequencing across 51 ENCODE cell lines illustrates robust expression of *CASC15-S* isoforms in neuroblastoma cell lines (red text), but much weaker expression in most other cell types.

**Supplementary Figure 3.** (**a**) Results of Sanger sequencing from 5’ and 3’-RACE products of *CASC15-S*. This isoform matches a cDNA clone (FLJ37399, clone BRAMY2027587) derived from amygdala, but is truncated at the 3’ end of the gene to form a 1181nt product. (Exons 1-4 shown as different colors) Exon 2-4 align with exons 10-12 of the long *CASC15* isoform (NR\_15410.1). (**b**)RNA fluorescent in-situ hybridization (RNA-FISH) conducted in NB-69 cells labeled with probes for *CASC14* or full-length (**c**) *CASC15* transcripts demonstrated very low or no observable levels (40x magnification).

**Supplementary Figure 4.** rs6939340 genotype and expression of 6p22.3 gene products. (**a**) Exon array expression data from patient samples (n=134) failed to demonstrate a significant correlation between risk and non-risk genotypes and expression lncRNAs (*CASC15*, *CASC15-S* or *CASC14*) at the 6p22.3 locus*.* We also observed no significant correlation using either of the two previously published SNPs in high LD (rs4712653 and rs9295536, not shown) (**b**) Neuroblastoma cell line genotypes for rs6939340. Cell line expression of gene products at 6p22.3 did not correlate with genotype (p=0.87, see **Figure 2c** for expression levels).

**Supplementary Figure 5.** Additional expression data for CASC15 isoforms in neuroblastoma cell lines and patients. (**a**) Expression of CASC15-S is not significantly different between MYCN amplified and non-amplified tumors (n = 251, *p* = 0.29) (**b**) High-risk patients with low *CASC15-S* expression exhibited significantly poorer overall survival compared to high-risk patients with 1.9-fold higher *CASC15-S* levels (n=146 for group “low”, n=74 for group “high”, *adj. p* = 0.002). (**c**) Full length *CASC15* (n=12 unique probes) expression from patient tumors (n=250) hybridized to Affymetrix Human Exon 1.0ST arrays demonstrates significantly less expression of *CASC15* compared to *CASC15-S* (n=1 unique probe). (**d**) Similar to what was observed with *CASC15-S*,low levels of full-length *CASC15* correlate with poor overall survival (*p* = 0.007). (**e**) Low expression of full length *CASC15* correlates significantly with stage 4 disease (p<0.0001).

**Supplementary Figure 6.** Additional cell lines showing increased neuroblastoma cell growth following *CASC15-S* depletion. (**a**) IMR-5 and (**b**) SK-N-SH cells were transfected with 50nM siRNA specific for *CASC15-S* and monitored for real time cell growth. siPLK-1, was used as a positive control. (**c**) Kelly and (**d**) Ebc1 neuroblastoma cells also exhibit an increased cell growth rate following CASC15-S however depletion of *CASC14* has no effect. . (**e**) SK-N-SH and (**f**) NGP neuroblastoma cells were stably depleted of *CASC15-S* and exhibited a robust increase in cell growth compared to controls. (\*\*\* p < 0.0001)

**Supplementary Figure 7.** Depletion of the long isoform of *CASC15* does not impact neuroblastoma cell viability. (**a and c**) NB-16 and SK-N-AS neuroblastoma cells were transfected in triplicate with 50nM siRNA specific for the long isoform of *CASC15* (n271792), *GAPDH*, *PLK-1* or a scrambled control. Cell viability was assessed via the Cell TiterGlo Assay (Promega) 72 hours after transfection. No change in cell viability was observed despite substantial depletion of full length *CASC15* (**b and d**). (**e**)shCASC15-S cells demonstrate substantial depletion of *CASC15-S* levels*.* SK-N-BE2, NB-16 and SK-N-SH cells were assayed for CASC15-S by Taqman PCR compared to their empty vector counterparts.

**Supplementary Figure 8.** Cell viability assays for neuroblastoma cell lines stably depleted of CASC15-S. (**a**) SK-N-BE2, (**b**) SK-N-SH and (c) NGP cells plated in triplicate at 8x103 cells/well in a 96-well plate were cultured for 72h and then read using the Cell TiterGlo cell viability assay (Promega). Neuroblastoma cells stably depleted of CASC15 showed a significant increase in cell viability and cell number as measured by intracellular ATP.

**Supplementary Table 1.** List of imputation results at the 6p22.3 region with the initial thirty-two candidate polymorphisms selected based on GWAS p-value shown. The filtration strategy used resulted in candidate SNPs (highlighted in green) failing to meet criteria being discarded (shown in red). The only SNP to emerge from this strategy was rs9295534 (shown in bold). Column descriptions are as follows: SNP = rsID or indel identifier from dbSNP for given single nucleotide variant or indel; GWAS p-value = p-value for European-American discovery cohort; DNase HS = DNAse hypersensitivity data from Roadmap Epigenomics project summed across all cell types and tissues; Fetal Adrenal H3K27Ac = Score obtained from Roadmap Epigenomics fetal adrenal H3K27Ac ChIP-Seq. This is derived from the public .wig file; Cons +/-5bp = Placental mammal sequence conservation. Taken +/- 5 base pairs; DNase +/-100bp = SK-N-SH DNAse hypersensitivity: how many reads aligned +/-100 base pairs; Homo / Het OR = GWAS Odds Ratio; GWAS MAF = Minor allele frequency of this allele; GWAS Infoscore = Genotype imputation information score; R2 value = R2 value in reference to rs4712656 taken from the LocusZoom 1000 genomes data (EUR population). .

**Supplementary Table 2.** Full Table for the *CASC15-S* Cox Statistical Model