Supplementary Table 1. Offspring from crosses of *Snrnp40* mutant mice

Cross	Offspring				
	Genotype	Number	Frequency		*P* value
			Actual	Expected	
Snrnp40$^{+/-}$ x *Snrnp40*$^{+/-}$	*+/-*	101	64.3%	50%	3.91 x 10^{-12}
	+/+	56	35.7%	25%	
	-/-	0	0%	25%	
Snrnp40$^{rplc/+}$ x *Snrnp40*$^{rplc/+}$	*rplc/+*	50	64.9%	50%	2.94 X 10^{-6}
	+/+	27	35.1%	25%	
	rplc/rplc	0	0%	25%	
Snrnp40$^{rplc/+}$ x *Snrnp40*$^{+/-}$	*rplc/+*	22	34.4%	25%	6.93 x 10^{-5}
	+/-	19	29.7%	25%	
	+/+	23	35.9%	25%	
	rplc/-	0	0%	25%	
Snrnp40$^{swp/swp}$ x *Snrnp40*$^{+/-}$	*swp/+*	72	100%	50%	2.15 X 10^{-17}
	swp/-	0	0%	50%	
Snrnp40$^{swp/swp}$ x *Snrnp40*$^{rplc/+}$	*swp/+*	1328	95.3%	50%	1.91 X 10^{-250}
	swp/rplc	66	4.7%	50%	
Snrnp40$^{swp/+}$ x *Snrnp40*$^{swp/+}$	*swp/+*	670	50.7%	50%	0.31
	+/+	344	26.0%	25%	
	swp/swp	307	23.2%	25%	

A chi-square test with the appropriate degrees of freedom was used to calculate *P* values.

Supplementary Table 2. Wild-type *Snrnp40* transcript expression level, viability, and phenotype of mice with *Snrnp40* allelic combinations

Genotype	% WT *Snrnp40* mRNA (normalized to +/+)*	Viability**	Phenotype
+/+	100%	Viable	Normal
swp/+	[55.1%]	Viable	Normal
rplc/+	[51.6%]	Viable	Normal
+/-	50%	Viable	Normal
swp/swp	10.2%	Viable	Immunodeficiency, reduced body size
swp/rplc	6.7%	Viable	Immunodeficiency, reduced body size, white-spotted ventral fur
swp/-	[5.1%]	Not viable	–
rplc/rplc	[3.2%]	Not viable	–
rplc/-	[1.6%]	Not viable	–
-/-	0%	Not viable	–

*The quantity of wild-type (WT) *Snrnp40* mRNA in *Snrnp40*$^{swp/swp}$ and *Snrnp40*$^{swp/rplc}$ splenic T cells was measured by RT-qPCR and expressed relative to that measured in *Snrnp40*$^{+/+}$ splenic T cells. Percentages in brackets were calculated based on the percentages for *Snrnp40*$^{swp/swp}$ and *Snrnp40*$^{swp/rplc}$ mice. Percentages of 50% and 0% were assumed for *Snrnp40*$^{+/-}$ and *Snrnp40*$^{-/-}$ mice, respectively.

**Genotypes were considered “viable” if any mice were born and survived to weaning age. Genotypes were considered “not viable” based on failure to observe any live mice at weaning age. Numbers and frequencies of offspring of each genotype are shown in Supplementary Table 1.

Supplementary Table 3. Splicing errors in EL4 cells

Splicing errors	*Snrnp40*-KO frequency* > WT frequency*	WT frequency* > *Snrnp40*-KO frequency*
Intron retention	214 (88.8%)	12 (30%)
Exon skipping	5 (2.1%)	18 (45%)
Cryptic splice site usage	22 (9.1%)	10 (25%)
Total	241	40

*The frequency of each type of splicing error (PIR or PSI) in mutant cells or wild-type (WT) cells was calculated by dividing the number of misspliced junctions by the total number of junctions detected in a given sample by RNA-seq. See Methods.

Supplementary Table 4. Candidate genes for aspects of the *skywarp* immunological phenotypes

Gene	Differential expression detected in cell type	Expression in mutant relative to wild-type cells*	RT-qPCR verification-cell types	Notes on encoded protein function and mouse mutant phenotypes
Themis	EL4 cells HSPCs T cells	16.5% 55.4% 80.5%	Verified-splenocytes, HSPCs	Plays a central role in late thymocyte development by controlling both positive and negative T-cell selection. Required to sustain and/or integrate signals required for proper lineage commitment and maturation of T cells. [provided by Uniprot] Homozygous null mice have defects in T cell positive selection that leads to very few alpha-beta T cells being found in the periphery. [provided by MGI]
Ikzf3	EL4 cells T cells	49.3% 139.9%	Verified-bone marrow cells	Transcription factor that plays an important role in the regulation of lymphocyte differentiation. Plays an essential role in regulation of B-cell differentiation, proliferation and maturation to an effector state. Involved in regulating BCL2 expression and controlling apoptosis in T-cells in an IL2-dependent manner. Homozygous mutants exhibit greatly reduced B cell populations in the peritoneum, marginal zone and recirculating bone marrow.
Il17a ***Il17f***	EL4 cells EL4 cells	2.3% 23.2%	Verified-EL4 cells	An intact IL-17 pathway is necessary for development of functionally competent NK cells, and mice deficient in IL-17RA, IL-17A, or IL-17F displayed impaired NK cell-mediated cytokine responses and increased susceptibility to MCMV.
Rag1	HSPCs	24.9%	Verified-HSPCs	Homozygotes for targeted null mutations exhibit arrested development of T and B cell maturation at the CD4-CD8- thymocyte or B220+/CD43+ pro-B cell stage due to inability to undergo V(D)J recombination. [provided by MGI]
Klf1	HSPCs	34.2%	Verified-HSPCs	Transcriptional activator. Homozygotes for an ENU-induced allele die as embryos; heterozygotes have reduced RBC, HCT, hemoglobin [1]. Homozygous null mice display defective erythropoiesis in fetal liver and die as embryos [2].
Gfi1b	HSPCs	41.7%	Verified-HSPCs	Transcriptional repressor. Homozygous null mice are embryonic lethal. Conditional knockout in bone marrow in adult mice results in reduced hemoglobin and platelets and causes death within 3 weeks [3, 4]. Impaired embryonic erythropoiesis in *Gfi1b*$^{-/-}$ chimeric mice [5].
Gata3	HSPCs T cells	63.5% 132.4%	Verified-HSPCs	Transcriptional activator which binds to the enhancer of the T-cell receptor alpha and delta genes. Binds to the consensus sequence 5'-AGATAG-3'. Required for the T-helper 2 (Th2) differentiation process following immune and inflammatory responses. [provided by Uniprot] Homozygous inactivation is embryonic lethal and show a variety of embryonic defects. [provided by MGI] Necessary for thymocyte development [6-8], early

				lineage T progenitor development [9].
Ets1	HSPCs	65.6%	Verified-HSPCs	Transcription factor. May control the differentiation, survival and proliferation of lymphoid cells. [provided by Uniprot] Homozygotes for targeted null mutations exhibit reduced numbers of peripheral CD8+ T cells, impaired TCR-mediated activation of both CD4+ and CD8+ T cells, increased numbers of IgM-secreting plasma cells, and severely impaired NK cell development [provided by MGI] [10-12].
Oas1a	HSPCs T cells	46.2% 50.3%	Verified-HSPCs	Interferon-induced, dsRNA-activated antiviral enzyme which plays a critical role in cellular innate antiviral response. [provided by Uniprot] Antiviral function induced by IFN-beta in acute ocular HSV-1 infection [13-15].
Il18	HSPCs	38.6%	Verified-HSPCs	A proinflammatory cytokine primarily involved in polarized T-helper 1 (Th1) cell and natural killer (NK) cell immune responses. Synergizes with IL12/interleukin-12 to induce IFNG synthesis from T-helper 1 (Th1) cells and natural killer (NK) cells. [provided by Uniprot] Mice homozygous for null alleles are deficient in producing IFN-gamma in response to infectious agents and have other impairments of the immune system. [provided by MGI]
Irf7	HSPCs T cells	24.7% 58.0%	Verified-HSPCs	Key transcriptional regulator of type I interferon (IFN)-dependent immune responses and plays a critical role in the innate immune response against DNA and RNA viruses [16]. Homozygous null mice are more vulnerable to viral infection (influenza PR8M [17], HSV-1 and EMCV [18]) and exhibit decreased serum interferon levels in response to viral infection. [provided by MGI]
Ifit1	HSPCs T cells	21.7% 33.3%	Verified-HSPCs	Interferon-induced antiviral RNA-binding protein that specifically binds single-stranded RNA bearing a 5'-triphosphate group (PPP-RNA), thereby acting as a sensor of viral single-stranded RNAs and inhibiting expression of viral messenger RNAs. [provided by Uniprot] Homozygous null mice display increased susceptibility to vesicular stomatitis virus infection. [provided by MGI

*Based on RNA-seq data.

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Supplementary Table 5. RT-PCR primers used for the validation of intron retention and RT-qPCR primers used for the validation of differential expression of genes identified by RNA-seq

Target	Sequence (5′ – 3′)	Target	Sequence (5′ – 3′)
Amdhd2-e7-F	TTCCACCACCGTGACCCAG	*Isg15* (fwd)	GCAGACTCCTTAATTCCAGGG
Amdhd2-e8-R	AGTGTATGGCGGCCATTGC	*Isg15* (rev)	TGGAGTTAGTCACGGACACCAG
Trp53-e8-F	TTCTGGGACGGGACAGCTTT	*Rsad2* (fwd)	ACACAGCCAAGACATCCTTC
Trp53-e9-R	TGGTTTTTTCTTTTGCGGGG	*Rsad2* (rev)	CAAGTATTCACCCCTGTCCTG
Rpl10-e6-F	GCTCCAGACAGGGATGCGTG	*Irf7* (fwd)	TTGATCCGCATAAGGTGTACG
Rpl10-e7-R	CCGCTTCTCAGCAACCATGT	*Irf7* (rev)	TTCCCTATTTTCCGTGGCTG
Mapk8ip3-e21-F	ATGTTCCTAGACAGTGATGTGAACCC	*Oas1a* (fwd)	AGAGATGCTTCCAAGGTGC
Mapk8ip3-e22-R	TTCTGTGGATTGGGACGGGT	*Oas1a* (rev)	ACTGATCCTCAAAGCTGGTG
Ddx27-e5-F	GTGAGGATGAGGCAGGCTCC	*Oas2* (fwd)	GCCTGAATACTGAGTCACCTG
Ddx27-e6-R	GGAGAGGTTCATGTCCTGGAAGG	*Oas2* (rev)	TTCAGTAAGTGGCTTGGAGTG
Ergic3-e11-F	AGGACTAACCAGTTCTCCGTGACCA	*Oas3* (fwd)	TGCTACTGGTCAAACACTGG
Ergic3-e12-R	CTGTAAACATGCCCCCAATGAT	*Oas3* (rev)	CTGAACTTTTGCTCTCCACAG
Polrmt-e19-F	GACACATGCCGCTGACATCC	*Oasl1* (fwd)	CTGTATCTACTGGACCAAGCAC
Polrmt-e20-R	TCCTGCAGCTTGGTGACCAG	*Oasl1* (rev)	GCCACTATGTCCCATCTGTAG
Rsbn1l-e7-F	GCCTGATCAACCCCGAGTAACC	*Oasl2* (fwd)	ATCATTGTCCTTACCCACAGAG
Rsbn1l-e8-R	GCTGAATCCTGGCATAGCGAA	*Oasl2* (rev)	TGCTGGTTTTGAGTCTCTGG
Eif4a3-e10-F	CCGGGTGCTCATCTCCACA	*Treml4* (fwd)	TTCTCAGAAACATCAGCCTGG
Eif4a3-e11-R	CCCTGAGAATCCGGATGTCATC	*Treml4* (rev)	GATGGAAGAGTCAGTGGTCTC
Fkbp1a-e1-F	ACGAGAGGGACGAAGCCGA	*Il18* (fwd)	GCCTCAAACCTTCCAAATCAC
Fkbp1a-e2-R	TAGTGCACCACGCAGGTCTGGC	*Il18* (rev)	GTTGTCTGATTCCAGGTCTCC
Sec61a1-e3-F	ATTCTGTGTCATCTTGCCGGAA	*Klf1* (fwd)	CCTCCATCAGTACACTCACC
Sec61a1-e4-R	TCACTCGCATCCAGTAGAACGG	*Klf1* (rev)	CCTCCGATTTCAGACTCACG
Ssb-e5-F	AAAGGTTTCCCAACTGACGCC	*Gfi1b* (fwd)	CTTTGCCTGTGATGTCTGTG
Ssb-e6-R	TCTCCACAAACTTCTTTGCAGACTG	*Gfi1b* (rev)	GGGTGGATGAACGCTTGAAG
Eif5a-e6-F	ATCACAGTGCTGTCTGCCATG	*Gata1* (fwd)	CCCAATGCACTAACTGTCAAAC
Eif5a-e7-R	AGGGTCTCCCCGACAGTTTG	*Gata1* (rev)	ATCTTTCCTCATGGTCAGTGG
Ubap2-e28-F	CTGCAGCGGCCCCCGGCTAC	*Gata3* (fwd)	CAACCTCTACCCCACTGTG
Ubap2-e29-R	TCAGGGTCTAGTTTGTCCAG	*Gata3* (rev)	GATGTCCCTGCTCTCCTTG
Cope-e8-F	CCCTGAGACCCTCATCAATC	*Ets1* (fwd)	AGTCTTGTCAGTCCTTTATCAGC
Cope-e10-R	AAGCACTGGGCGCATACTGC	*Ets1* (rev)	TTTTCCTCTTTCCCCATCTCC
Slc25a11-e5-F	GGCTGCATCCCTACCATGGC	*Stat1* (fwd)	GCCGAGAACATACCAGAGAATC
Slc25a11-e6-R	CTAGTTTTGACGATGTCCAC	*Stat1* (rev)	GATGTATCCAGTTCGCTTAGGG
Cd8a (fwd)	CATCACTCTCATCTGCTACCAC	*Xrcc5* (fwd)	TGACTGCTCAGGACGTTTTC
Cd8a (rev)	TTTTCTCTGAAGGTCTGGGC	*Xrcc5* (rev)	CCTTGGTGATGTTCCCTTCTG
Cd8b1 (fwd)	TGGCCGTCTACTTTTACTGTG	*Themis* (fwd)	GAACAATAAATCTGCCCAAGTCTC
Cd8b1 (rev)	GGCGCTGATCATTTGTGAAAC	*Themis* (rev)	CTCTCCACATCAGCCACATC
Rag1 (fwd)	TTTGGGCATTGAGGACTCTC	*Nt5e* (fwd)	GCTTCAGGGAATGCAACATG
Rag1 (rev)	CAATGTGCTAGGTGCTAGGAG	*Nt5e* (rev)	TGCCACCTCCGTTTACAATG
Icos (fwd)	AGAAATACGGATCCAGTGTGC	*Arg1* (fwd)	AAGAATGGAAGAGTCAGTGTGG
Icos (rev)	CTAGTCCATGCGTTTCCTCTG	*Arg1* (rev)	GGGAGTGTTGATGTCAGTGTG
Hemgn (fwd)	ACATCACAATGGCTCCTTGG	*Slamf6* (fwd)	GGCAGACACAGGATCATACAC
Hemgn (rev)	CCCTTTCCCTTTCTGTTTGTG	*Slamf6* (rev)	AGGTCCCATTCTCTAGCAGG
Il6 (fwd)	CAAAGCCAGAGTCCTTCAGAG	*Tnfsf10* (fwd)	TCTGTGGCTGTGACTTACATG
Il6 (rev)	GTCCTTAGCCACTCCTTCTG	*Tnfsf10* (rev)	AAGCAGGGTCTGTTCAAGATC
Cd83 (fwd)	CTTTCAGGAAGTACAGGGCAG	*Cd226* (fwd)	AACCCACTTATCTGCAAGGAG
Cd83 (rev)	GAAAAGCTTGTTCCGTACCAG	*Cd226* (rev)	TGTCCCACAATGTCTCTTCAC
Ifit1 (fwd)	AGAGTCAAGGCAGGTTTCTG	*Ikzf3* (fwd)	GTCATATTAAACTGCACACGGG
Ifit1 (rev)	TGTGAAGTGACATCTCAGCTG	*Ikzf3* (rev)	AGAACTCACACTTGTACGGC
Ifit3 (fwd)	AGCACAGAAACAGATCACCAT		
Ifit3 (rev)	CACCCTGTCTTCCATATGACTG		