Supplementary description of Materials and Methods

Study design and patients

We conducted an unmatched case-control study nested within a prospective surveillance program in South Africa. The inclusion criteria for the primary study were as follows: cases consisted of infants who attended the hospital with an acute medical illness, and controls were infants residing in the same catchment area as the hospital who attended clinics for immunization visits and whose caregivers reported no signs or symptoms of any illness in the past 14 days, specifically the absence of fever, cough, runny nose, and diarrhea. From this pool of participants, we selected 129 infants who attended the hospital with symptomatic HRSV infection (case group) and 161 healthy infants (control group) who were less than one year old and had a blood sample stored at -80ºC.

All babies included in the current study were enrolled in four hospitals (case group) (Mapulaneng, Bushbuckridge; Matikwana, Mkhuhlu; Edendale, Pietermaritzburg; Klerksdorp-Tshepong, Klerksdorp) and two Health Centres (control group) (Jouberton, Klerksdorp; and Agincourt, Thulamahashe) across three provinces of South Africa from 2016 through 2018. All participants had informed consent signed by their parents or guardians. The research was done according to the Declaration of Helsinki, and the University of the Witwatersrand Human Research Ethics Committee approved this study (reference number M190216).

HRSV infection diagnosis

In the preliminary prospective surveillance study, combined nasopharyngeal and oropharyngeal swabs were collected for cases and controls at enrolment. Samples were stored at -80°C and transported on dry ice to The National Institute for Communicable Diseases (NICD) of South Africa, where all participants (cases and controls) were tested for several respiratory viruses.

Total nucleic acid from respiratory samples was extracted with the MagNA Pure 96 small-volume kit system (Roche Diagnostics, Basel, Switzerland) and tested by real-time polymerase chain reaction (qPCR) for HRSV and 17 other respiratory viruses using the FastTrack Diagnostics (FTD, Esch-sur-Alzette, Luxembourg) respiratory pathogens 33-plex assay. HRSV-positive samples were subtyped to identify HRSVA and HRSVB strains using an in-house reverse transcription-based qPCR method.

Outcome variables

The main outcome was the presence of symptomatic HRSV infection (hospital admission with confirmed HRSV PCR), dividing the study population into control group (healthy infants) and case group (symptomatic HRSV-infected infants). The secondary outcome was the bronchiolitis diagnosis at admission with confirmed RSV infection, stratifying the population into control group, case group without bronchiolitis, and case group with bronchiolitis.

Exposure variable

TNIP1 polymorphisms selection was carried out according to the following criteria: i) SNPs located within and flanking *TNIP1* gene previously associated with chronic inflammatory diseases; ii) a minor allelic frequency (MAF)>0.1 in the African population (AFR); iii) selection of tagSNPs among SNPs with high linkage disequilibrium in AFR populations (r2>0.85); iv) compatibility with other selected SNPs in the multiplex genotyping assay. Finally, six *TNIP1* SNPs (rs869976, rs4958881, rs73272842, rs3792783, rs17728338, and rs999011) were selected.

DNA purification and SNPs genotyping

Whole blood samples were collected on EDTA tubes at enrolment in the preliminary prospective surveillance study, shipped to NICD for PCR testing for multiple pathogens, and stored at -80°C until use. Next, blood samples in the current study were sent to the Centre for Proteomic and Genomic Research (CPGR; Cape Town, South Africa) for DNA genotyping. DNA was purified from 200µl whole blood using the QIAmp DNA Blood Mini QIAcube Kit using a QIAcube (Qiagen, Germany) following the manufacturer's guidelines.

The *TNIP1* genotyping reactions were prepared and ran on OpenArray ® plates according to the protocol in the Applied Biosystems® OpenArray ® Experiments User Guide (Applied Biosystems QuantStudio 12K Flex Real-Time PCR System). The DNA samples were diluted to 50 ng/µl as recommended by the manufacturer. Each diluted sample (2.5µl) was mixed with 2.5µl of TaqMan OpenArray Genotyping Master Mix in a 384-well plate. According to the manufacturer's recommendations, PCR amplification was performed in the QuantStudio 12K Flex Real-Time qPCR instrument. The genotype profiles were determined with the Thermo Fisher Connect™ Genotyping Analysis Module (2020.1.4-Q1-20-built1, https://apps.thermofisher.com/apps/spa/#/dashboard).

Supplementary Table 1. Characteristics of *TNIP1* polymorphisms in cases (symptomatic RSV infection) and controls (healthy infants).

		Distribution of genotypes (1)			HWE (p-values) (2)	
SNPs	**Genotype**	**Controls**	**Cases**	***p*-value**	**Controls**	**Cases**
rs869976	n=281					
	AA	72 (46.2%)	52 (41.6%)	0.508	0.281	0.843
	AG	63 (40.4%)	59 (47.2%)			
	GG	21 (13.5%)	14 (11.2%)			
rs4958881	n=253					
	CC	43 (30.1%)	35 (31.8%)	0.858	0.402	0.700
	CT	66 (46.2%)	52 (47.3%)			
	TT	34 (23.8%)	23 (20.9%)			
rs73272842	n=261					
	AA	41 (28.3%)	48 (41.4%)	0.076	0.999	0.428
	AG	73 (50.3%)	50 (43.1%)			
	GG	31 (21.4%)	18 (15.5%)			
rs3792783	n=256					
	AA	29 (19.7%)	17 (15.6%)	0.146	0.618	0.684
	AG	77 (52.4%)	49 (45.0%)			
	GG	41 (27.9%)	43 (39.4%)			
rs17728338	n=247					
	AA	8 (5.7%)	3 (2.8%)	0.448	0.461	0.999
	AG	45 (31.9%)	30 (28.3%)			
	GG	88 (62.4%)	73 (68.9%)			
rs999011	n=284					
	CC	142 (90.4%)	98 (77.2%)	**0.002**	0.999	0.224
	CT	15 (9.6%)	25 (19.7%)			
	TT	0 (0.0%)	4 (3.1%)			

Statistic: (1), Differences in the genotype's distribution between case and control groups; (2), Hardy-Weinberg equilibrium. P-values were calculated by chi-squared or Fisher test when it was appropriated.

Abbreviations: RSV, respiratory syncytial virus; HWE: Hardy-Weinberg equilibrium; TNIP1: TNFAIP3-interacting protein 1; SNP: single nucleotide polymorphism.

Supplementary Table 2. Genetic association of *TNIP1* polymorphisms with clinical outcomes.

			Symptomatic RSV infection [(a)]			Bronchiolitis [(b)]		
SNPs	**Inheritance**	**Genotypes**	**OR (95%CI)**	**p-value**	**q-value**	**OR (95%CI)**	**p-value**	**q-value**
rs869976	Dominant	AG/GG vs. AA	1.20 (0.75 - 1.93)	0.445	0.630	1.2 (0.76 - 1.91)	0.436	0.604
	Recessive	GG vs. AA/AG	0.81 (0.39 - 1.67)	0.569	0.698	0.81 (0.4 - 1.64)	0.552	0.710
	Additive	G vs. A allele	1.05 (0.74 - 1.48)	0.780	0.780	1.05 (0.75 - 1.47)	0.780	0.886
rs4958881	Dominant	CT/TT vs. CC	0.92 (0.54 - 1.58)	0.765	0.780	0.97 (0.57 - 1.63)	0.899	0.899
	Recessive	TT vs. CT/CC	0.85 (0.47 - 1.54)	0.589	0.698	0.94 (0.52 - 1.7)	0.828	0.886
	Additive	T vs. C allele	0.92 (0.65 - 1.29)	0.616	0.698	0.97 (0.69 - 1.35)	0.837	0.886
rs73272842	Dominant	GA/GG vs. AA	0.56 (0.33 - 0.94)	**0.027**	**0.140**	0.6 (0.37 - 0.99)	**0.045**	**0.198**
	Recessive	GG vs. GA/AA	0.68 (0.36 - 1.28)	0.230	0.489	0.71 (0.38 - 1.34)	0.289	0.473
	Additive	G vs. A allele	0.68 (0.48 - 0.97)	**0.033**	**0.140**	0.72 (0.51 - 1.01)	0.055	0.198
rs3792783	Dominant	AG/AA vs. GG	0.59 (0.35 - 1.01)	0.052	0.177	0.62 (0.37 - 1.03)	0.066	0.198
	Recessive	AA vs GG/AG	0.75 (0.39 - 1.45)	0.395	0.610	0.76 (0.4 - 1.45)	0.407	0.604
	Additive	A vs. G allele	0.72 (0.5 - 1.04)	0.076	0.215	0.74 (0.52 - 1.05)	0.090	0.231
rs17728338	Dominant	AG/AA vs. GG	0.75 (0.44 - 1.28)	0.292	0.498	0.73 (0.43 - 1.23)	0.240	0.461
	Recessive	AA vs. GG/AG	0.48 (0.13 - 1.87)	0.293	0.498	0.46 (0.12 - 1.75)	0.256	0.461
	Additive	A vs. G allele	0.75 (0.48 - 1.17)	0.208	0.489	0.73 (0.47 - 1.14)	0.164	0.369
rs999011	Dominant	CC/CT vs. TT	N/A	-	-	0.13 (0.02 - 0.77)	**0.025**	0.150
	Recessive	CC vs. TT/CT	0.36 (0.18 - 0.7)	**0.003**	**0.026**	0.35 (0.19 - 0.65)	**0.001**	**0.009**
	Additive	C vs. T allele	0.36 (0.19 - 0.67)	**0.001**	**0.017**	0.37 (0.22 - 0.64)	**<0.001**	**<0.001**

Statistics: Data were calculated by logistic binomial regressions (a) and logistic ordinal regressions (b). P-values adjusted by False Discovery Rate (q-value). Significant differences are shown in bold.

Abbreviations: 95%CI: 95% confidence interval; OR: odds ratio; aOR: adjusted odds ratio; TNIP1: TNFAIP3-interacting protein 1; RSV, respiratory syncytial virus.

Supplementary Table 3. Association of *TNIP1* haplotypes (rs73272842 and rs999011) with outcome variables.

TNIP1		**Symptomatic RSV infection**			**Bronchiolitis**		
haplotypes	**Freq.**	**OR (95% CI)**	***p*-value**	***p*-value [(a)]**	**OR (95% CI)**	***p*-value**	***p*-value [(a)]**
AC	0.540	1.24 (0.87 - 1.76)	0.234	-	1.11 (0.84 - 1.46)	0.466	-
AT	0.035	4.4 (1.42 - 13.58)	**0.010**	0.077	2.79 (1.41 - 5.5)	**0.003**	0.081
GC	0.371	0.53 (0.37 - 0.77)	**0.001**	**0.002**	0.62 (0.46 - 0.84)	**0.002**	**0.002**
GT	0.053	2.88 (1.24 - 6.69)	**0.014**	0.108	2.43 (1.39 - 4.24)	**0.002**	0.108

Statistics: Data were calculated using Stata's *Haplologit* package. (a), p-values were validated by BCa Bootstrap. Significant p-values are shown in bold.

Abbreviations: 95%CI: 95% confidence interval; OR: odds ratio; TNIP1: TNFAIP3-interacting protein 1; RSV, respiratory syncytial virus.

Supplementary Figure 1. Pairwise linkage disequilibrium (LD) pattern for *TNIP1* polymorphisms. The intensity of red or grey decreases with decreasing D´ and r2 values. The genomic location of SNPs is indicated on top. The diagonal represents an SNP, and the square represents a pairwise comparison between two SNPs, indicating the magnitude of LD (D´ and r^2). D´ and r^2 vary from 0 (absence) to 100 (complete). **Abbreviations**: D´: D-prime or proportion of the possible linkage disequilibrium that was present between two SNPs; r^2: square of the correlation coefficient; TNIP1: TNFAIP3-interacting protein 1.