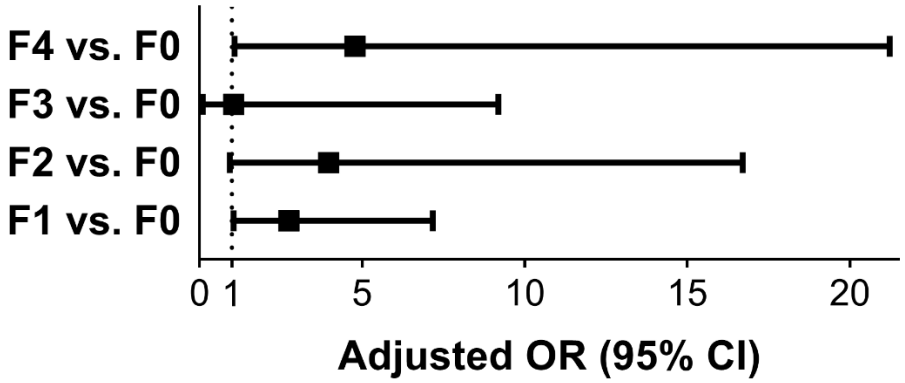
Online-only supplement of Strnad et al. – "Heterozygous carriage of the alpha1-antitrypsin Pi*Z variant increases the risk to develop liver cirrhosis."

SUPPLEMENTARY FIGURES



Supplementary figure 1: Nominal regression analysis of the different fibrosis stages in the first German-Austrian non-alcoholic fatty liver disease (NAFLD) cohort.
The odds ratio and their corresponding 95% confidence intervals are depicted. All nominal regression analyses were adjusted for sex, age, BMI, diabetes, *PNPLA3*, *TM6SF2*, and *MBOAT7*.

SUPPLEMENTARY TABLES

Study	Etiology	Outcome	Association of the Pi*Z variant with advanced liver fibrosis/cirrhosis
a) genotyping studies			
Valenti et al., 2006	NAFLD	Biopsy	No
Al-Jameil et al., 2017	Multiple (ESLD)	Clinical	No
Schaefer et al., 2018	Multiple (ESLD)	Clinical	Yes
b) phenotyping studies			
Eriksson et al., 1975	Multiple (population-based)	Biopsy	Yes
Hodges et al., 1981	Multiple	Biopsy	No
Bell et al., 1990	Multiple	Clinical	No
Propst et al., 1992	Multiple	Clinical	Yes
Eigenbrodt et al., 1997	Multiple (ESLD)	Clinical	Yes
Elzouki et al., 1997	Multiple	Biopsy	No
Graziadei et al., 1998	Multiple (ESLD)	Clinical	Yes
Fischer et al., 2000	Multiple	Biopsy	Yes
Regev et al., 2006	Multiple	Biopsy, Clinical	No
Goltz et al., 2014	ALD	Biopsy	Yes

Supplementary table 1: Overview of studies investigating the association of the Pi*Z variant with alcoholic/non-alcoholic fatty liver disease (ALD/NAFLD) or with liver diseases of multiple aetiologies. A) Studies, where all patients have been genotyped for the presence of the alpha1-antitrypsin (AAT) Pi*Z variant. B) Selected studies using primary non-genetic approaches (i.e., isoelectric focusing, assessment of AAT serum levels and/or liver histology/immunohistochemistry to detect the presence of AAT inclusions). The term "clinical" in the outcome column refers to studies where presence

of advanced/end-stage liver disease (ESLD) was based on clinical grounds as opposed to studies that performed liver biopsies. Some of the studies marked as "no" in the last column suggested an association between Pi*Z and advanced liver disease, but this relationship was not statistically significant.

	Total *n*=643	**Pi*MZ** *n*=36 (5.6%)	**Pi*MS** *n*=29 (4.5%)
Fibrosis stage F0	362	9 (2.5)	14 (3.9)
Fibrosis stage F1	144	12 (8.3)	6 (4.2)
Fibrosis stage F2	35	5 (14.3)	2 (5.7)
Fibrosis stage F3	34	1 (2.9)	4 (11.8)
Fibrosis stage F4	68	9 (13.2)	3 (4.4)

Supplementary table 2: Histologic fibrosis stages in the first German-Austrian non-alcoholic fatty liver disease (NAFLD) cohort.
The absolute count (n) and relative frequency (%) of the analysed individuals are displayed. Only individuals carrying the Pi*MZ or Pi*MS genotype are displayed as there were no individuals with the Pi*ZZ, Pi*SS, or Pi*SZ genotype. Abbreviations: Pi*MZ=heterozygous for the Pi*Z variant; Pi*MS=heterozygous for the Pi*S variant; Pi*ZZ=homozygous for the Pi*Z variant; Pi*SS=homozygous for the Pi*S variant; Pi*SZ=compound heterozygous for the Pi*S and the Pi*Z variant.

	NAS 1-2 (*n*=379)	**NAS 3-4** (*n*=109)	**NAS 5-8** (*n*=61)	***p* value** (NAS 1-2 vs. 3-8)	***p* value** (NAS 1-2 vs. 5-8)
Pi*MZ genotype	14 (3.7)	9 (8.3)	1 (1.6)	.241	.416
Pi*ZZ genotype	0 (0)	0 (0)	0 (0)	NA	NA
Pi*MS genotype	16 (4.2)	5 (4.6)	3 (4.9)	.756	.830
Pi*SS genotype	0 (0)	0 (0)	0 (0)	NA	NA
Pi*SZ genotype	0 (0)	0 (0)	0 (0)	NA	NA

Supplementary table 3: Distribution of the common AAT genotypes within the first German-Austrian NAFLD cohort according to the NAFLD activity score.
Liver biopsies from 549 patients with non-alcoholic fatty liver disease (NAFLD) have been examined for the NAFLD activity score (NAS). The frequencies of the studied AAT genotypes are given as absolute count (n) and relative frequency (%).
Abbreviations: Pi*MZ=heterozygous for the Pi*Z variant; Pi*ZZ=homozygous for the Pi*Z variant; Pi*MS=heterozygous for the Pi*S variant; Pi*SS=homozygous for the Pi*S variant; Pi*SZ=compound heterozygous for the Pi*S and the Pi*Z variant; NA=not applicable.

	OR [95% CI]	***P* value**
Fibrosis stage F1 vs. F0	2.75 [1.05-7.18]	.039
Fibrosis stage F2 vs. F0	3.97 [0.94-16.71]	.060
Fibrosis stage F3 vs. F0	1.05 [0.12-9.19]	.963
Fibrosis stage F4 vs. F0	4.78 [1.08-21.23]	.040

Supplementary table 4: Nominal regression analysis of the various fibrosis stages in the first German-Austrian non-alcoholic fatty liver disease (NAFLD) cohort.
All nominal regression analyses were adjusted for sex, age, BMI, diabetes, *PNPLA3*, *TM6SF2*, and *MBOAT7*. Abbreviations: OR, odds ratio; CI, confidence interval.

	Total *n*=541	**Pi*Z heterozygous** *n*=22 (4.1%)	**Pi*Z homozygous** *n*=2 (0.4%)
Fibrosis stage F0	256 (47.3)	6 (2.4)	1 (0.4)
Fibrosis stage F1	165 (30.5)	8 (4.8)	0 (0)
Fibrosis stage F2	67 (12.4)	3 (4.5)	0 (0)

Fibrosis stage F3	27 (5.0)	1 (3.7)	0 (0)
Fibrosis stage F4	26 (4.8)	4 (16.0)	1 (4.5)

Supplementary table 5: Histologic fibrosis stages in the second German-Austrian non-alcoholic fatty liver disease (NAFLD) cohort.
The absolute count (n) and relative frequency (%) of the analysed individuals are displayed.