Supplemental materials to

The effect of LPA Thr3888Pro on lipoprotein(a) and coronary artery disease is modified by the LPA KIV-2 variant 4925G>A

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Supplementary Methods

Description of the GCKD study

The GCKD [1,2] study includes German participants from nine recruiting centers suffering of moderate chronic kidney disease (CKD). Moderate CKD is classified as CKD Stage 3 with an estimated glomerular filtration rate (eGFR) according to the CKD_EPI equation [3] of 30-60 mL/min per 1.73 m\(^2\) or overt proteinuria and eGFR >60 mL/min per 1.73 m\(^2\). Overt proteinuria shows an albumin to creatinine ration of >300 mg/g or a protein to creatinine ratio in 24h urine of >500 mg/g. Individuals with active malignancy, NYHA IV heart failure, renal or any other transplantation, non-Caucasian origin and legal attendance were excluded. Study approval was done by the review boards of the participating institutions and informed consent was obtained from all participants.

Description of the KORA F3 and F4 studies

The KORA [4] (Cooperative Health Research in the Augsburg region, Kooperative Gesundheitsforschung in der Region Augsburg) F3 and F4 cohorts are follow-up studies of the previous studies KORA S3 and S4 and represent the general population in Augsburg and surrounding counties (Southern Germany). KORA F3 and F4 do not overlap. Inclusion criteria are German nationality and aged 25 to 74. Recruiting time for KORA F3 was 2004 and 2005 (n=3,184), for KORA F4 2006 and 2008 (n=3,080). Lp(a) concentrations and apo(a) isoforms were assessed for 3,516 participants in the KORA F3 and for 3,161 participants in the KORA F4 cohort. Available DNA samples at our institute were 3,161 from KORA F3 and 3,063 from KORA F4.

Lp(a) phenotyping

Lp(a) concentration was determined in mg/dL by ELISA [5,6]. A polyclonal affinity-purified rabbit anti-human apo(a) antibody was used for coating and a horseradish peroxidase-conjugated monoclonal anti-apo(a) antibody 1A2 for detection [7]. OD was quantified on two dilutions per sample (1:150 and 1:1500) and measurements within the linear range of the 7-point standard curve were accepted.

Apo(a) isoforms were assessed by Western blotting [6,8]. 150 ng Lp(a) were loaded and separated on a 1.46% agarose gel with 0.08% SDS for 18 h at 0.04 A constant current. A size standard containing apo(a) isoform 13, 19, 23, 27 and 35 KIV repeats (validated by fiber-FISH [9]) was applied in every seventh well of the gel. The gel was semi-dry electro-blotted to a PVDF membrane. The membrane was blocked with 1% BSA, 85 mM NaCl, 10 mM TRIS, 0.2% Triton X-100 for 30 min at 37°C and
incubated with horseradish-peroxidase-conjugated 1A2 antibody. Signals were detected with ECL substrate (WesternBright Chemilumineszenz Spray, Biozym, Vienna, AT) and recorded on autoradiography films (Amersham Hyperfilm™ ECL™, GE Healthcare, Chicago, IL, USA). A detailed protocol for ELISA and Western blotting has been published in [8].

Analysis of UK Biobank data

Genotypes of rs41272110 were retrieved from microarray genotyping data and 4925G>A carrier status was retrieved from whole exome sequencing data (n=199,126) using sequencing data reanalysis strategies detailed before [10]. Sequencing data were downloaded as CRAM data (UKB Data Field 23153) and all reads from the LPA KIV-2 region were extracted as defined in the bed files of Ebbert et al [10] (https://github.com/mebbert/Dark_and_Camouflaged_genes). The extracted sequencing reads were realigned to a single KIV-2 copy number as reference [10–12] and 4925G>A was called using a standard second-generation variant caller (https://github.com/seppinho/mutserve) capable to detect variants down to 1% mutation level [12].

Data were restricted to Caucasians (British, Irish or any other white ethnic background) with available exome data for 4925G>A and genotype data for rs41272110 (n=186,088). The impact of 4925G>A and rs41272110 on Lp(a) concentrations was investigated by quantile regression in 173,878 participants. The first reported diagnosis (International Classification of Disease version 10 ICD-10 I21-25) [13,14] of coronary artery disease (CAD) was used for survival analysis. CAD included acute myocardial infarction, subsequent myocardial infarction, complications following acute myocardial infarction (UKB macrogroup “certain current complications following acute myocardial infarction”, I23.0, I23.1, I23.2, I23.3, I23.5, I23.6, I23.8), other acute ischaemic heart diseases and chronic ischaemic heart diseases. The first occurrence was provided by UKB by mapping self-report at any assessment centre, inpatient hospital data, primary care or death record data. Hazard ratio for CAD was estimated as a function of the carrier status of the two SNPs independently from each other, as well as a joint model (one variant adjusted for the other) and additionally adjusted for sex (n=186,088). Age was used as timescale, meaning that the observation period starts from the year of birth and censored the data as of 1st of January 2020, including 13,335 incident CAD events, independently of their SNPs carrier status. One individual was excluded due to an implausible date of CAD event. UKB analyses were performed in R version 3.6.3 and the R package survival was used for survival analysis.
Supplementary Figures

Supplementary Figure I. Isoform distribution of the variant carriers in the different studies. Both variants are predominantly observed in isoforms with 20-25 KIV repeats in all three populations.
Supplementary Figure II. Lp(a) distribution in the four genotype combinations.

Lp(a) concentration of the different genotype combinations (wild type, rs41272110 only, 4925G>A only, double carriers) in GCKD, KORA F3 and KORA F4. Compared to wild type rs41272110 is significantly associated with increased Lp(a) concentrations, whereas no difference was observed between 4925G>A and double carriers. Since 4925G>A is associated with a defined isoform range [11], its effect becomes appreciable only after isoform stratification (Main Figure 1, Supplementary Figures III-IV). Median Lp(a) concentration and IQR for every genotype combination are given under the x-axis of the figure as well as in Supplementary Table IV. The box represents the IQR and the central line the median. Whiskers depict 1.5*IQR from the hinge.
Supplementary Figure III. Median and interquartile Lp(a) concentration of the four genotype combinations over the whole isoform range in KORA F3.

(A) Single distributions of all genotype combinations in the KORA F3 study; (B) Superimposed Lp(a) distributions of all genotype combinations in the KORA F3 study; compared to wild type Lp(a) concentrations are reduced in double carriers but increased in individuals carrying rs41272110 only. Solid line represents the median Lp(a) concentration. Shaded area represents the interquartile range.
Supplementary Figure IV. Median and interquartile Lp(a) concentration of the four genotype combinations over the whole isoform range in KORA F4.

(A) Single distributions of all genotype combinations in the KORA F4 study; (B) Superimposed Lp(a) distributions of all genotype combinations in the KORA F4 study; compared to wild type Lp(a) concentrations are reduced in double carriers, but increased in individuals carrying rs41272110 only. Solid line represents the median Lp(a) concentration. Shaded area represents the interquartile range.
**Supplementary Figure V.** Median and interquartile Lp(a) concentration of the four genotype combinations for the single isoforms in all study populations. Compared to wild type individuals, Lp(a) concentrations are reduced in double carriers, but increased in individuals carrying rs41272110 only. The solid line represents the median Lp(a) concentration. The shaded area represents the interquartile range.
Supplementary Figure VI. Lp(a) concentration of the genotype combinations distributed over the different isoform groups in GCKD.

Carriers of rs41272110 only (green) show mainly high Lp(a) concentrations, whereas the few individuals carrying 4925G>A only (yellow) and double carriers (orange) show mainly low Lp(a) concentrations. Grey shaded individuals represent wild type individuals; y-scale is restricted to 200 mg/dL, 6 individuals negative for both variants are omitted.
Supplementary Figure VII. Lp(a) concentration of the genotype combinations distributed over the different isoform groups in KORA F3.

Carriers of rs41272110 only (green) show mainly high Lp(a) concentrations, whereas the few individuals carrying 4925G>A only (yellow) and double carriers (orange) show mainly low Lp(a) concentrations. Grey shaded individuals represent wild type individuals.
Supplementary Figure VIII. Lp(a) concentration of the genotype combinations distributed over the different isoform groups in KORA F4. Carriers of rs41272110 only (green) show mainly high Lp(a) concentrations, whereas the few individuals carrying 4925G>A only (yellow) and double carriers (orange) show mainly low Lp(a) concentrations. Grey shaded individuals represent wild type individuals.
Supplementary Figure IX. Lp(a) distribution in the four genotype combinations in UK Biobank participants. (A) rs41272110 carrier, (B) 4925G>A carrier, (C) different genotype combinations (wild type, rs41272110 only, 4925G>A only, double carrier). Median Lp(a) concentration and IQR for every genotype combination is shown in Supplementary Table IX. The box represents the IQR and the central line the median. Whiskers depict 1.5*IQR from the hinge.
Supplementary Figure X. Impact of both variants on the CAD risk adjusted for Lipoprotein(a) concentrations.

The model is adjusted for sex and inverse-normal transformed Lp(a) concentration and restricted to individuals with Lp(a) measurements and data for both SNPs available (n=173,878). Age is taken as time scale and hazard ratio (HR) for Lp(a) is given for a 1-unit increase of the inverse-normal transformed Lp(a) concentration. In the joint model, the HR for CAD adjusted for Lp(a) was strongly alleviated and partially abolished. The HR of Lp(a) is highly significant and confirms the imperative role of the Lp(a) concentrations. adj.: adjusted
Supplementary Figure XI. Sensitivity analysis in UK Biobank: Hazard ratios (HR) of rs41272110 and 4925G>A in UK Biobank without genetic kinship to other participants (n=128,672). Rs41272110 (n=34,878) has no impact on CAD risk (total CAD events=8,922; 2,452 CAD events in rs41272110 carriers). 4925G>A carriers (n=22,373) show significantly reduced CAD risk (total CAD events=8,922; 1,480 CAD events in 4925G>A carriers). Conversely, in a joint model, hazard ratios show increased CAD risk in rs41272110 carriers (n=34,878) and reduced CAD risk in 4925G>A carriers (n=22,373). All Cox models for sensitivity analyses take participant age as timescale and are adjusted for sex and the first 30 principal components. adj.: adjusted
## Supplementary Tables

### Supplementary Table I. Study characteristics of previous investigations on rs41272110.

| Study                     | Study population                                                                 | n  | Ancestry       | Analysis stratified or adjusted for apo(a) isoforms | Effect on Lp(a) | Rs41272110 associated apo(a) isoform |
|---------------------------|----------------------------------------------------------------------------------|----|----------------|-----------------------------------------------------|----------------|-------------------------------------|
| Prins et al. (1997)[15]   | 153 subjects with symptomatic atherosclerosis, 153 controls                     | 306| White European | no                                                  | decreasing     | NR                                  |
| Prins et al. (1999)[16]   | healthy voluntary blood donors                                                  | 201| White European | yes                                                 | increasing     | 23-29                               |
| Ogorelkova et al. (2001)[17] | non-related healthy subjects                                                    | 130| White European | yes                                                 | decreasing     | 21-25                               |
|                           |                                                                                  | 104| White European | yes                                                 | increasing     | 21-25                               |
| Chretien et al. (2006)[18] | patients receiving incident dialysis (CHOICE cohort)                            | 534| European Americans | yes                                          | decreasing     | 17-21                               |
|                           |                                                                                  | 249| African Americans | yes                                          | decreasing     | NR                                  |
| Deo et al. (2011)[19]     | community-based observational study of cardiovascular disease (Jackson Heart Study) | 4464| African Americans | no                                                  | no beta reported | NR                                  |
| Lee et al. (2016)[20]     | multiethnic, probability-based sample of the Dallas County population          | 1792| Black participants | yes                                                 | decreasing     | NR                                  |
|                           |                                                                                  | 1030| White participants | yes                                                 | increasing     | NR                                  |
|                           |                                                                                  | 597 | Hispanic participants | yes                                                 | increasing     | NR                                  |
| Yahya (2019)[21]          | dyslipidemia patients on statin treatment, mostly familial hypercholesterolemia | 81 | Primarily white European | no                                                  | no significant effect on Lp(a), but ~5 mg/dL higher median Lp(a) in carriers | NR |
Supplementary Table II. Quantile regression analysis of rs41272110 and 4925G>A on Lp(a) concentration in GCKD, KORA F3 and KORA F4. In GCKD both models were further adjusted for eGFR.

| study   | group  | variant   | carrier [n] | β [mg/dL] | 95% CI [mg/dL] | p-value | β [mg/dL] | 95% CI [mg/dL] | p-value |
|---------|--------|-----------|-------------|-----------|----------------|---------|-----------|----------------|---------|
|         |        |           |             |           | Model 1: adjusted for age and sex |          |           | Model 2: adjusted for age, sex and smaller apo(a) isoform |          |
|         |        |           |             |           | 95% CI [mg/dL] | p-value | 95% CI [mg/dL] | p-value |         |
| GCKD    | All    | rs41272110| 1,151       | -0.13     | -0.87, 0.61   | 0.733   | -12.79    | -14.41, -11.16 | 2.13E-52 |
|         |        | 4925G>A   | 926         | -2.47     | -3.36, -1.58  | 5.93E-08| -22.67    | -24.25, -21.09 | 2.67E-160|
|         | LMW    | rs41272110| 402         | -26.75    | -32.93, -20.58| 6.01E-17| -26.47    | -32.40, -20.54 | 7.46E-18 |
|         |        | 4925G>A   | 310         | -48.51    | -51.95, -45.08| 3.80E-129| -47.65    | -51.23, -44.07 | 6.14E-118|
|         | HMW    | rs41272110| 749         | +1.55     | 1.06, 2.03    | 4.14E-10| -1.15     | -1.76, -0.54   | 0.0002   |
|         |        | 4925G>A   | 616         | +0.76     | 0.15, 1.38    | 0.015   | -3.30     | -4.29, -2.31   | 6.52E-11 |
|         |        |           |             |           | Model 1: adjusted for age and sex |          |           | Model 2: adjusted for age, sex and smaller apo(a) isoform |          |
|         |        |           |             |           | 95% CI [mg/dL] | p-value | 95% CI [mg/dL] | p-value |         |
|         |        |           |             |           | GCKD   All    | rs41272110| 795       | +0.68     | -0.19, 1.54  | 0.124   | -12.49    | -13.75, -11.23 | 1.75E-79 |
|         |        |           |             |           |         | 4925G>A   | 687       | -1.27     | -2.37, -0.17 | 0.0243  | -19.10    | -20.87, -17.32 | 2.18E-92 |
|         |        |           |             |           | LMW    rs41272110| 252       | -27.08    | -34.10, -20.07 | 1.23E-13| -26.95    | -33.87, -20.03 | 7.92E-14 |
|         |        |           |             |           |         | 4925G>A   | 208       | -44.83    | -48.49, -41.17| 1.09E-92| -44.95    | -48.73, -41.17 | 1.17E-88 |
|         |        |           |             |           | HMW    rs41272110| 542       | +2.42     | 1.67, 3.17 | 3.44E-10| -0.50     | -1.38, 0.38   | 0.263    |
|         |        |           |             |           |         | 4925G>A   | 478       | +1.49     | 0.64, 2.33  | 0.000574| -2.86     | -4.00, -1.72  | 8.78E-07 |
|         |        |           |             |           | KORA F4 All | rs41272110| 753       | -0.64     | -1.39, 0.11 | 0.0967  | -11.34    | -13.28, -9.40 | 1.20E-29 |
|         |        |           |             |           |         | 4925G>A   | 642       | -3.04     | -4.10, -1.98 | 2.07E-08| -19.75    | -21.29, -18.22 | 4.95E-127|
|         |        |           |             |           | LMW    rs41272110| 242       | -21.07    | -25.21, -16.94| 4.53E-22| -20.01    | -24.09, -15.93 | 1.30E-20 |
|         |        |           |             |           |         | 4925G>A   | 199       | -38.34    | -42.27, -34.41| 5.61E-66| -35.67    | -39.83, -31.51 | 1.47E-53 |
|         |        |           |             |           | HMW    rs41272110| 511       | +1.19     | 0.52, 1.86 | 0.0005  | -1.50     | -2.44, -0.56  | 0.00187 |
|         |        |           |             |           |         | 4925G>A   | 443       | -0.41     | -1.29, 0.47 | 0.359   | -4.70     | -5.97, -3.43  | 5.89E-13 |
**Supplementary Table III.** Sensitivity analysis: Quantile regression of rs41272110 and 4925G>A on Lp(a) concentration in a restricted dataset without relatives and adjusted for the first 10 (GCKD) and 8 (KORA F3) principal components. In GCKD both models were further adjusted for eGFR.

| study       | group | variant    | carrier [n] | β [mg/dL] | 95% CI [mg/dL] | p-value | β [mg/dL] | 95% CI [mg/dL] | p-value |
|-------------|-------|------------|-------------|-----------|----------------|---------|-----------|----------------|---------|
| **Model 1: adjusted for age and sex** |        |            |             |           |                |         |           |                |         |
| GCKD        | All   | rs41272110 | 1151        | -0.26     | -0.30, -0.21  | 0.438   | -12.83    | -14.50, -11.16 | 2.78E-50 |
|             |       | 4925G>A    | 926         | -2.38     | -3.25, -1.52  | 7.56E-08 | -22.53    | -13.63, -11.00 | 1.58E-168 |
| LMW         | rs41272110 | 402        | -26.98      | -32.71, -21.25 | 1.28E-19 | -25.86    | -31.04, -20.68 | 9.50E-22 |
|             | 4925G>A | 310        | -47.71      | -51.09, -44.32 | 8.32E-129 | -47.16    | -50.48, -43.83 | 5.09E-130 |
| HMW         | rs41272110 | 749      | +1.29       | 0.83, 1.75  | 4.77E-08   | 1.19     | -1.70, -0.67   | 7.19E-06 |
|             | 4925G>A | 616        | +0.72       | 0.02, 0.10  | 0.022      | -3.19    | -4.17, -2.20   | 2.72E-10 |
| **Model 2: adjusted for age, sex and smaller apo(a) isoform** |        |            |             |           |                |         |           |                |         |
| GCKD        | All   | rs41272110 | 750         | +0.72     | -0.09, 1.54  | 0.083   | -12.32    | -13.63, -11.01 | 1.24E-71 |
|             | 4925G>A | 649       | -1.44       | -2.50, -0.37 | 0.008    | -19.01   | -20.83, -17.20 | 2.61E-87 |
| KORA F3     | All   | rs41272110 | 238         | -26.32    | -32.80, -19.84 | 7.83E-15 | -25.82   | -32.50, -19.15 | 1.17E-13 |
|             | 4925G>A | 197       | -44.21      | -47.86, -40.55 | 9.99E-90 | -43.75   | -47.52, -39.99 | 1.04E-84 |
| LMW         | rs41272110 | 511      | +2.39       | 1.82, 2.95  | 2.47E-16   | -0.87   | -1.53, -0.21   | 0.009   |
|             | 4925G>A | 451       | +1.38       | 0.52, 2.23  | 0.00161   | -3.03   | -4.19, -1.88   | 2.93E-07 |
Supplementary Table IV. Quantile regression analysis of rs41272110 and 4925G>A on Lp(a) concentration by adjusting one variant for the other (joint model) in GCKD, KORA F3 and KORA F4. In GCKD both models were further adjusted for eGFR.

| study | group | variant | carrier [n] | \(\beta\) [mg/dL] | 95% CI [mg/dL] | p-value | \(\beta\) [mg/dL] | 95% CI [mg/dL] | p-value |
|-------|-------|---------|-------------|-------------------|-----------------|---------|-------------------|-----------------|---------|
| GCKD  | All   | rs41272110 | 1,151       | +8.36             | 3.90, 12.82     | 2.44E-04 | +4.28             | 2.78, 5.79     | 2.50E-08 |
|       |       | 4925G>A   | 926         | -10.91            | -15.46, -6.37   | 2.56E-06 | -26.94            | -28.85, -25.02 | 2.47E-155 |
|       | LMW   | rs41272110 | 402         | +3.30             | -2.99, 9.59     | 0.304    | +4.71             | -1.92, 11.35   | 0.164    |
|       |       | 4925G>A   | 310         | -51.29            | -58.09, -44.48  | 2.77E-45 | -51.96            | -59.05, -44.88 | 3.92E-43 |
|       | HMW   | rs41272110 | 749         | +4.52             | -10.59, 19.63   | 1.62E-14 | +4.09             | 2.96, 5.21     | 1.20E-12 |
|       |       | 4925G>A   | 616         | -3.80             | -5.12, -2.49    | 1.58E-08 | -7.10             | -8.64, -5.57   | 1.97E-19 |
| KORA F3 | All  | rs41272110 | 795         | +11.48            | 5.78, 17.17     | 7.95E-05 | +5.48             | 2.15, 8.82     | 0.00126 |
|       |       | 4925G>A   | 687         | -12.99            | -18.78, -7.20   | 1.15E-05 | -24.61            | -28.29, -20.92 | 4.56E-38 |
|       | LMW   | rs41272110 | 252         | +9.93             | 6.01, 13.85     | 8.69E-07 | +10.91            | 6.02, 15.80    | 1.43E-05 |
|       |       | 4925G>A   | 208         | -54.56            | -59.55, -49.58  | 2.58E-78 | -55.29            | -61.42, -49.17 | 6.34E-58 |
|       | HMW   | rs41272110 | 542         | +7.58             | 5.80, 9.35      | 1.14E-16 | +6.02             | 3.86, 8.17     | 4.83E-08 |
|       |       | 4925G>A   | 478         | -6.44             | -8.25, -4.64    | 3.65E-12 | -8.88             | -11.26, -6.49  | 3.78E-13 |
| KORA F4 | All  | rs41272110 | 753         | +9.03             | 3.63, 14.42     | 0.00105 | +4.22             | 1.38, 7.07     | 3.64E-03 |
|       |       | 4925G>A   | 642         | -12.99            | -18.5, -7.48    | 8.33E-06 | -23.92            | -27.12, -20.72 | 5.67E-47 |
|       | LMW   | rs41272110 | 242         | +1.75             | -3.56, 7.06     | 0.519    | +4.78             | -1.35, 10.92   | 0.127    |
|       |       | 4925G>A   | 199         | -40.01            | -46.98, -33.03  | 5.04E-27 | -41.16            | -48.82, -33.50 | 3.44E-24 |
|       | HMW   | rs41272110 | 511         | +7.51             | 3.98, 11.03     | 3.14E-05 | +5.87             | 3.98, 7.76     | 1.35E-09 |
|       |       | 4925G>A   | 443         | -7.93             | -11.58, -4.27   | 2.25E-05 | -10.48            | -12.62, -8.33  | 3.09E-21 |
**Supplementary Table V.** Median Lp(a) concentration and IQR of the different genotype combinations in GCKD, KORA F3 and KORA F4. Populations were stratified into four genotype combination categories: individuals carrying only rs41272110, carrying only 4925G>A, carrying both variants (double carriers) and carrying neither of both (wild type).

| study     | Genotype combination | n     | n (%) with Lp(a) concentration >50 mg/dL | median Lp(a) [mg/dL] | IQR [mg/dL] |
|-----------|----------------------|-------|----------------------------------------|----------------------|-------------|
| GCKD      | Wild type            | 3,413 | 586 (17.2)                             | 11.58                | 3.96, 35.44 |
|           | rs41272110 only      | 236   | 94 (39.8)                              | 35.44                | 12.24, 66.52 |
|           | 4925G>A only         | 11    | 2 (18.2)                               | 11.66                | 7.64, 25.04 |
|           | Double carriers      | 915   | 75 (8.2)                               | 9.87                 | 6.82, 18.54 |
| KORA F3   | Wild type            | 2,135 | 310 (14.5)                             | 10.92                | 4.09, 31.27 |
|           | rs41272110 only      | 117   | 58 (49.6)                              | 49.55                | 17.31, 79.70 |
|           | 4925G>A only         | 9     | 0 (0)                                  | 21.81                | 12.10, 23.92 |
|           | Double carriers      | 678   | 50 (7.4)                               | 10.29                | 6.71, 17.48 |
| KORA F4   | Wild type            | 2,130 | 294 (13.8)                             | 12.11                | 4.38, 32.54 |
|           | rs41272110 only      | 119   | 43 (36.1)                              | 37.52                | 17.32, 63.93 |
|           | 4925G>A only         | 8     | 0 (0)                                  | 7.82                 | 6.21, 10.36 |
|           | Double carriers      | 634   | 34 (5.4)                               | 9.80                 | 6.34, 17.63 |
**Supplementary Table VI.** Quantile regression analysis of different genotype combinations on Lp(a) concentration in GCKD, KORA F3 and KORA F4. Populations were stratified into four genotype combination categories: individuals carrying only rs41272110, carrying only 4925G>A, carrying both variants (double carriers) and carrying neither of both (wild type). The wild type group is the reference group in the regression model. Effect given in mg/dL. Table continues on next page. In GCKD both models were further adjusted for eGFR.

| study   | group | Genotype combination | carrier [n] | β [mg/dL] | 95% CI [mg/dL] | p-value | β [mg/dL] | 95% CI [mg/dL] | p-value |
|---------|-------|----------------------|-------------|-----------|----------------|---------|-----------|----------------|---------|
| **Model 1: adjusted for age and sex** | | | | | | | | | |
| GCKD    | All   | Wild type            | 3,413       | reference | 24.41          | 22.37, 26.45 | 5.53E-115 | 9.93          | 7.78, 12.07 | 1.63E-19 |
|         |       | rs41272110 only      | 236         | 24.41     | 22.37, 26.45   | 5.53E-115 | 9.93      | 7.78, 12.07   | 1.63E-19 |
|         |       | 4925G>A only         | 11          | 0.57      | -8.56, 9.70    | 0.903    | -20.12    | -29.66, -10.58 | 3.61E-05 |
|         |       | Double carriers      | 915         | -1.84     | -2.96, -0.71   | 0.0014   | -21.93    | -23.19, -20.68 | 6.28E-230 |
| LMW     | Wild type | reference            | 726         | reference    | 8.22        | 2.94, 13.50 | 0.0023    | 9.65        | 4.13, 15.15   | 0.0006   |
|         | rs41272110 only | 95          | 8.22      | 2.94, 13.50 | 0.0023    | 9.65      | 4.13, 15.15   | 0.0006   |
|         | 4925G>A only   | 3           | NA        | NA         | NA         | NA        | NA        | NA          | NA      |
|         | Double carriers | 307        | -47.74   | -51.04, -44.44 | 4.44E-134 | -46.6     | -50.03, -43.15 | 5.89E-121 |
| HMW     | Wild type | reference            | 2,687       | reference   | 7.44       | 5.86, 9.02  | 4.84E-20  | 5.93        | 4.29, 7.55   | 1.40E-12 |
|         | rs41272110 only | 141        | 7.44      | 5.86, 9.02  | 4.84E-20  | 5.93      | 4.29, 7.55   | 1.40E-12 |
|         | 4925G>A only   | 8           | 1.7       | -4.75, 8.16 | 0.605     | -1.52     | -8.17, 5.12  | 0.654      |
|         | Double carriers | 608        | 1.02      | 0.20, 1.84  | 0.0149    | -2.71     | -3.66, -1.75 | 2.80E-08   |
| **Model 2: adjusted for age, sex and smaller apo(a) isoform** | | | | | | | | | |
| KORA F3 | All   | Wild type            | 2,135       | reference   | 38.25     | 35.53, 40.98  | 3.19E-148 | 19.83       | 17.50, 22.17  | 1.24E-59 |
|         |       | rs41272110 only      | 117         | 38.25     | 35.53, 40.98  | 3.19E-148 | 19.83      | 17.50, 22.17  | 1.24E-59 |
|         |       | 4925G>A only         | 9           | 10.31     | 0.72, 19.91   | 0.035    | -8.35      | -16.49, -0.21 | 0.045    |
|         |       | Double carriers      | 678         | -0.5      | -1.77, 0.77   | 0.441    | -18.48     | -19.64, -17.32 | 2.25E-184 |
| LMW     | Wild type | reference            | 424         | reference   | 20.08     | 13.31, 26.84  | 9.30E-09 | 22.09       | 14.94, 29.25  | 2.36E-09 |
|         | rs41272110 only | 47          | 20.08     | 13.31, 26.84 | 9.30E-09 | 22.09      | 14.94, 29.25  | 2.36E-09 |
|         | 4925G>A only   | 3           | NA        | NA         | NA        | NA        | NA        | NA          | NA      |
|                | Wild type | 1,708 | reference |
|----------------|-----------|-------|-----------|
| rs41272110 only | 70        | 14.69 | 8.87, 20.51 | 8.02E-07 | 11.58 | 9.38, 13.78 | 1.94E-24 |
| 4925G>A only   | 6         | 5.15  | 1.69, 8.60  | 0.00351  | 1.03  | -6.29, 8.36 | 0.782   |
| Double carriers | 472       | 1.9   | 1.07, 2.73  | 8.22E-06 | -2.46 | -3.54, -1.38 | 8.10E-06 |

| KORA F4        | Wild type | 2,130 | reference |
|----------------|-----------|-------|-----------|
| rs41272110 only | 119       | 24.27 | 21.57, 26.97 | 4.30E-06 | 13.17 | 10.66, 15.68 | 1.99E-24 |
| 4925G>A only   | 8         | -5.56 | -15.71, 4.59 | 0.283   | -20.31 | -29.68, -10.93 | 2.26E-05 |
| Double carriers | 634       | -2.27 | -3.57, -0.97 | 0.0006  | -18.99 | -20.26, -17.72 | 6.39E-166 |

| LMW            | Wild type | 468 | reference |
|----------------|-----------|-----|-----------|
| rs41272110 only | 44        | 7.29 | -1.11, 15.69 | 0.0893  | 10.69  | 2.41, 18.97 | 0.012   |
| 4925G>A only   | 1         | NA  | NA         | NA      | NA    | NA         | NA      |
| Double carriers | 198       | -37.41 | -41.90, -32.91 | 5.55E-51 | -34.66 | -39.09, -30.23 | 5.01E-46 |

| HMW            | Wild type | 1,662 | reference |
|----------------|-----------|-------|-----------|
| rs41272110 only | 75        | 16.59 | 14.27, 18.91 | 1.00E-42 | 13.44 | 11.21, 15.66 | 1.82E-31 |
| 4925G>A only   | 7         | -0.63 | -8.08, 6.82  | 0.869   | -5.15  | -12.24, 1.94 | 0.154   |
| Double carriers | 436       | 0.06 | -1.00, 1.11  | 0.918   | -3.84  | -4.97, -2.71 | 3.31E-11 |
**Supplementary Table VII.** Quantile regression analysis of rs41272110 and 4925G>A on Lp(a) concentration in Caucasians from UK Biobank with available Lp(a) concentration, rs41272110 genotype carrier status and 4925G>A exome data (n=173,878). Model adjusted for age and sex.

| Variant        | carrier [n] | β [nmol/L] | 95% CI [nmol/L] | p-value  |
|----------------|-------------|------------|-----------------|----------|
| rs41272110     | 47,028      | -0.03      | -0.38, 0.32     | 0.860    |
| 4925G>A        | 30,693      | -3.77      | -4.08, -3.45    | 1.20e-119|

**Joint model analysis (one variant adjusted for the other)**

| Variant        | carrier [n] | β [nmol/L] | 95% CI [nmol/L] | p-value  |
|----------------|-------------|------------|-----------------|----------|
| rs41272110     | 47,028      | +7.95      | 7.25, 8.64      | 7.55e-112|
| 4925G>A        | 30,693      | -10.45     | -11.13, -9.78   | 3.79e-202|

**Different genotype combinations**

| Variant        | carrier [n] | β [nmol/L] | 95% CI [nmol/L] | p-value  |
|----------------|-------------|------------|-----------------|----------|
| rs41272110 only | 17,006     | +9.44      | 8.48, 10.40     | 1.63e-82 |
| 4925G>A only   | 604         | -2.51      | -3.23, -1.79    | 7.90e-12 |
| Double carriers | 30,022     | -2.59      | -2.91, -2.27    | 9.76e-56 |
**Supplementary Table VIII.** Sensitivity analysis in UK Biobank: Quantile regression analysis of rs41272110 and 4925G>A on Lp(a) concentration in Caucasians with available Lp(a) concentration, rs41272110 genotype carrier status, 4925G>A exome data and no genetic kinship to other participants found (n=120,228). Model adjusted for age, sex and the first 30 principal components.

| Variant          | carrier [n] | β [nmol/L] | 95% CI [nmol/L] | p-value  |
|------------------|-------------|------------|-----------------|----------|
| rs41272110       | 32,637      | -0.17      | -0.57, 0.22     | 0.406    |
| 4925G>A          | 20,998      | -3.88      | -4.25, -3.52    | 1.47e-97 |

**Joint model analysis (one variant adjusted for the other)**

| Variant          | carrier [n] | β [nmol/L] | 95% CI [nmol/L] | p-value  |
|------------------|-------------|------------|-----------------|----------|
| rs41272110       | 32,637      | +7.80      | 6.96, 8.64      | 7.19e-74 |
| 4925G>A          | 20,998      | -10.50     | -11.32, -9.68   | 3.90e-138|

**Different genotype combinations**

| Variant          | carrier [n] | β [nmol/L] | 95% CI [nmol/L] | p-value  |
|------------------|-------------|------------|-----------------|----------|
| rs41272110 only  | 12,034      | +9.10      | 8.03, 10.18     | 7.04e-62 |
| 4925G>A only     | 395         | -3.10      | -4.93, -1.27    | 8.87e-04 |
| Double carriers  | 20,603      | -2.74      | -3.11, -2.37    | 3.50e-47 |
**Supplementary Table IX.** Median Lp(a) concentration and IQR of the different genotype combinations in UK Biobank. Populations were stratified into four genotype combination categories: individuals carrying only rs41272110, individuals carrying only 4925G>A, individuals carrying both variants (double carriers) and individuals carrying neither of both (wild type).

| study  | genotype combination | n    | n (%) with Lp(a) concentration >120 nmol/L | median Lp(a) [nmol/L] | IQR [nmol/L] |
|--------|----------------------|------|------------------------------------------|----------------------|--------------|
| UK Biobank | Wild type            | 126,246 | 22,588 (18.0)                      | 18.70               | 6.10, 80.30  |
|         | rs41272110 only      | 17,006  | 4,134 (24.3)                       | 28.40               | 11.90, 116.60|
|         | 4925G>A only         | 604      | 63 (10.4)                          | 15.70               | 10.12, 39.12 |
|         | Double carriers      | 30,022   | 2814 (9.4)                         | 16.08               | 9.60, 36.70  |
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