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Supplemental Material

Arsenic Metabolism in Mice Carrying a *BORCS7/AS3MT* Locus Humanized by Syntenic Replacement

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Figure S2. Expression of *BORCS7-AS3MT* read-through transcripts in tissues of the humanized (Hs/Hs) and wild type (WT/WT) mice and the WT/Hs heterozygotes. **A.** Read-through transcript expression in testes, adrenal glands, and liver of Hs/Hs mice (N=1/tissue). **B.** Separation of cDNA from testes of WT/WT, WT/Hs and Hs/Hs mice on a 1.6% agarose gel (N=1/genotype): (a) 100 bp fragment, consistent with the previously described read-through transcript; (b) 220 bp fragment of a read-through transcript that has not been previously reported. **C.** Schematic structures of the unspliced *BORCS7* isoforms (lavender), *AS3MT* (blue) and the previously reported (orange) (Lu X et al. 2015) and novel (red) *BORCS7-AS3MT* read-through transcripts. Introns are indicated by thin lines, untranslated exonic sequence by medium lines, and exonic coding sequence by thick lines. The position of the stop codon is indicated for the top two *BORCS7* transcripts. The PCR used for quantification and sequencing of the *BORCS7-AS3MT* junction of the read-through transcripts is indicated at the bottom of the figure (green).

Figure S3. Concentrations of inorganic arsenic (iAs), methyl-arsenic (MAs) and dimethyl-arsenic (DMAs) (µg As/L) in urine of humanized (Hs/Hs) and wild type (WT/WT) male (M) and female (F) mice collected during 24-h intervals after oral administration of a single dose of iAs (20 µg As/ kg body weight). Mean (x), median (—), 25th and 75th percentiles (box), maximum and minimum (whiskers), and individual values including outliers are shown (N=8 for Hs/Hs males, N=10 for Hs/Hs females, N=7 for WT/WT males, and N=11 for WT/WT females). MAs concentration was below limit od detection in 52 out of 54 urine samples collected from WT/WT mice during the 3 collection intervals; a value of 0 µg As/L was imputed for MAs concentrations in these samples. ^{a,b,c} Within each panel, statistically significant differences between strains and sexes are marked with different letters. (ANOVA with Student-Newman-Keuls post-test.).

Figure S4. Proportions of total arsenic (%tAs) represented by inorganic arsenic (%iAs), methyl-arsenic (%MAs) and dimethyl-arsenic (%DMAs) in urine of humanized (Hs/Hs) and wild type (WT/WT) male (M) and female (F) mice collected during 24-h intervals after oral administration of a single dose of iAs (20 µg As/kg body weight). Mean +SD (N=8 for Hs/Hs males, N=10 for Hs/Hs females, N=7 for WT/WT males, and N=11 for WT/WT females). MAs concentration was below limit od detection in 52 out of 54 urine samples collected from WT/WT mice during the 3 collection intervals; a value of 0 µg As/L was imputed for MAs Within each panel, statistically significant differences between strains and sexes are marked with different letters: ^{a,b,c} for differences in %iAs, ^{d,e,f} for differences in %MAs, g,hi for differences in %DMAs. (ANOVA with Student-Newman-Keuls post-test.).

Figure S5. Concentrations of inorganic arsenic (iAs), methyl-arsenic (MAs) and dimethyl-arsenic (DMAs) (µg As/L) in feces of humanized (Hs/Hs) and wild type (WT/WT) male (M) and female (F) mice collected during 24-h intervals after oral administration of a single dose of iAs (20 µg As/ kg body weight). Mean (x), median (—), 25th and 75th percentiles (box), maximum and minimum (whiskers), and individual values including outliers are shown (N=8 for Hs/Hs males, N=10 for Hs/Hs females, N=7 for WT/WT males, and N=11 for WT/WT females). DMAs concentration was below limit of detection in 48 out of 54 fecal samples collected during the 3 collection intervals from male and female Hs/Hs mice; a value of 0 µg As/kg was imputed for DMAs concentrations in these samples. ^{a,b} Within each panel, statistically significant differences between strains and sexes are marked with different letters. (ANOVA with Student-Newman-Keuls post-test.).

Figure S6. Proportions of total arsenic (%tAs) represented by inorganic arsenic (%iAs), methyl-arsenic (%MAs) and dimethyl-arsenic (%DMAs) in feces of humanized (Hs/Hs) and wild type (WT/WT) male (M) and female (F) mice collected during 24-h intervals after oral administration of a single dose of iAs (20 μg As/kg body weight). Mean +SD (N=8 for Hs/Hs males, N=10 for Hs/Hs females, N=7 for WT/WT males, and N=11 for WT/WT females). DMAs concentration was below limit of detection in 48 out of 54 fecal samples collected during the 3 collection intervals from male and female Hs/Hs mice; a value of 0 μg As/kg was imputed for DMAs concentrations in these samples. Within each panel, statistically significant differences between strains and sexes are marked with different letters: ^{a,b,c} for differences in %iAs, ^{d,e,f,g} for differences in %MAs, ^{h,i,j} for differences in %DMAs. (ANOVA with Student-Newman-Keuls post-test.).

Figure S7. Proportions of total arsenic (%tAs) represented by inorganic arsenic (%iAs), methyl-arsenic (%MAs) and dimethyl-arsenic (%DMAs) in urine of humanized (Hs/Hs) and wild type (WT/WT) male (M) and female (F) mice collected during 4-week exposure to iAs in drinking water (400 μg As/L). Mean +SD (N=8 for Hs/Hs males, N=10 for Hs/Hs females, N=7 for WT/WT males, and N=11 for WT/WT females). MAs concentration was below LOD in 70 out of 72 urine samples collected from WT/WT mice during the 4 collection intervals; a value of 0 μg As/L was imputed for MAs concentrations in these samples. Within each panel, statistically significant differences between strains and sexes are marked with different letters: ^{a,b,c} %iAs, ^{d,e,f} %MAs, ^{g,h} %DMAs. (ANOVA with Student-Newman-Keuls post-test.).

Figure S8. Concentrations of total arsenic (μg As/kg) in livers and kidneys of humanized (Hs/Hs) and wild type (WT/WT) male (M) and female (F) mice after 4-week exposure to iAs in drinking water (400 μg As/L). Total arsenic was calculated as sum of inorganic arsenic, methyl-arsenic and dimethyl-arsenic. Mean (x), median (—), 25th and 75th percentiles (box), maximum and minimum (whiskers), and individual values including outliers are shown (Mean+SD; N=8 for Hs/Hs males, N=10 for Hs/Hs females, N=7 for WT/WT males, and N=11 for WT/WT females). DMAs was below LOD in 16 out of 18 liver samples collected from Hs/Hs mice; a value of 0 μg As/kg was imputed for DMAs concentrations in these samples. ^{a,b,c} Within each panel, statistically significant differences between strains and sexes are marked with different letters. (ANOVA with Student-Newman-Keuls post-test.).

References

Table S1: Haplotype for selected single nucleotide polymorphisms (SNPs) of human *BORCS7-AS3MT* segment included in the humanized locus of Hs/Hs mice

A. AS3MT SNPs previously associated with iAs metabolism

SNP	Allele	Frequency	AA
rs3740393	G	78.97%	-
rs3740390	C	84.29%	-
rs11191439	T	90.72%	Met
rs10748835	G	55.87%	-

B. GWAS schizophrenia-associated top eQTL (expression quantitative trait loci)

Gene	Top eQTL	Allele	Frequency
AS3MT	rs7085104	A	61.86%
BORCS7	rs11441374	-	82.33%

C. AS3MT VNTR

SNP	Allele	Frequency
rs45567337	3 copies	59.17%

The segment of DNA used to generate the humanized locus was derived from the tilepath bacterial artificial chromosome (BAC) encompassing the genes encoding for BLOC-1 Related Complex Subunit 7 (*BORCS7*) and arsenic (+3 oxidation state) methyltransferase (*AS3MT*), and therefore the sequence of the humanized locus matches the human reference allele (GRCh38/hg38 assembly). **A.** Haplotype based on SNPs previously reported to be associated with altered metabolism of inorganic arsenic (iAs). The haplotype carried by the reference allele corresponds to the previously described GCTG haplotype (Apata et al. 2017). **B.** Haplotype for SNPs carried by the humanized locus that have previously been associated with schizophrenia (Li et al. 2016). **C.** Haplotype for variable number tandem repeat (VNTR) in the *AS3MT* gene that has previously been associated with risk of schizophrenia (Li et al. 2016).

Table S2: Predesigned primers used in PCR reactions during the assembly of *Borcs5/As3mt* displacer and gene expression analyses

Primer #	Sequence
215317	TTCTCTGTCCTTCCTGTGCGACGGTTACGCCGCTCCATGAGCTTATCGCGACGCGTAAAGCTAGCCTGCCTCAAAAC
213218	TATTATGAACCCCATGGGCCAAGAGGACAAAAACTGCTGAGTGTATTTTCCTAAGCACTGTGGGCTAGGGTCTTGACTCG
215319	TAAAGCTAGCCTGCCTCAAAAC
215320	CAGCGCGTACGCCCATGGGGCGGTACCGGGAGGAGGAGGAAACTAGC
215323	ATGGCCCTTTCGTCTTCCTAGACCAGCCAGGACAGAAATG
215324	GGAAGGCAAGCAGTCTTCGGCCGCGTATTGGGCGCTCTTC
215325	ATACGCGGCCGAAGACTGCTTGCCTTCCTGTTGGGATTGT
215326	GAGAGAGAAGACCGCGGCCGCGTGGCCCCAGCTCTGGCTCGAACT
215330	AAATTGTAAGCGACGCGTTTGGGCACTAGAGGAAGAGGTGA
215332	GGCTGGTCTAGGAAGACGAAAGGGCCATCCTGCGCTCAGG
215336	CGCGCGTACGCCAGGCTGGCTGCTATCCGTGCAGAAGCCCTTGTA
215337	CACCACCCATGTGGTTCATCATCTCA
215338	TTGTAAGCGACGCGTGCCCAAAGTAGACCTCTGACCAGA
215339	CTACTTTGGGCACGCGTCGCTTACAATTTAGGTGGCACTTT
56719	CTTTGGCCGCCGCCCAGTCCTGCTCGCTTCGCTACTTGGAGCCACTATCGATGATCTTTTCTACGGGGTCTGACG
ScreenF	ATGCCCATGCTCTTCTCTTATGCT
176268	AAATTAAGGGCCAGCTCATTCCTC
common	TTTACCCCCAATTTCACTATGAAG
displaced	GCTCCATCTGCTAAATCTACATCC
endo	TGGGAGAATTATTGATTCGACATC
d2d3-F	GCCGAGGAGACAATATTATGGCT
d2d3-R	TGGTCATGTCTATTCCAGTCACGT
full-F	CGAGGAGACATGGCTGCAC
full-R	GTGGTGACACAGCCGTTGG

Table S3: The pFloxxerX plasmid used during the assembly of *Borcs5/As3mt* displacer to derive the vector backbone carrying a ColE1 origin of replication and a spectinomycin gene.

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10-JUN-2020
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                     /type="Custom cloned insert"
     insert          complement(2351..2744)
                     /source="pShuffler-lacZ"
                     /type="Custom cloned insert"
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                     /note="lacZ alpha PCR"
     misc_feature    2544..2744
                     /dnas_title="lacZ"
                     /note="lacZ"
     misc_feature    complement(2582..2598)
                     /note="m13 -20"
     misc_feature    2580..2738
                     /note="lacZ aa 6-58"
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                     /pair=""
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     misc_feature    2527..2572
                     /note="lacZ alpha upper"
     misc_feature    2416..2537
                     /note="lacZpro"
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                     /pair=""
                     /primer="GTGTGAAATTGTTATCCGCTCAC"
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                     /note="lacZ pro lower"
     misc_feature    2351..2526
                     /note="lacZ promoter PCR"
     misc_feature    2351..2371
                     /dnas_title="lacZ pro upper"
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     PCR_primer      2351..2371
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                     /primer="GCGCGTTGGCCGATTCATTAA"
                     /current=0
     misc_feature    2334..2371
                     /dnas_title="#14 lacZ upper"
                     /note="lacZ upper"
     insert          complement(2351..2744)
                     /source="Floxxer5 segmented"
                     /type="Custom cloned insert"
     insert          join(273..273,288..1161)
                     /source="Floxxer3 segmented"
                     /type="Custom cloned insert"
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                /note="Floxer backbone"
misc_feature    1086..1109
                /note="56719/56201"
misc_feature    complement(1091..1113)
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misc_feature    1086..1161
                /note="Red/ET amp PCR"
misc_feature    complement(1099..1161)
                /note="TN3"
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insert          288..1161
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misc_feature    complement(1138..1161)
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misc_feature    273..309
                /dnas_title="#15 colE1 lower"
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PCR_primer      288..309
                /pair=""
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insert          2334..2350
                /source="Floxxer5 segmented"
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insert          274..287
                /source="Floxxer3 segmented"
                /type="Custom cloned insert"
insert          1..272
                /source="FloxxerX"
                /type="Custom cloned insert"
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                /primer="AAAGGGCGAAAAACCGTCTATCAG"
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misc_feature    complement(243..272)
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insert          complement(1..272)
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misc_feature         1..213
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misc_feature         complement(243..272)
                     /note="#05 lacZ lower"
insert               complement(join(0..270,3..272))
                     /dnas_title="Floxxer5 segmented"
                     /source="Floxxer5 segmented"
insert               join(1..1,1..1,1..270)
                     /dnas_title="Floxxer3 segmented"
                     /source="Floxxer3 segmented"
insert               1162..2333
                     /source="FloxxerX"
                     /type="Custom cloned insert"
insert               1166..2333
                     /source="spectinomycin PCR"
                     /type="Custom cloned insert"
misc_feature         complement(1184..2194)
                     /note="spectinomycin resistance"
misc_feature         complement(1184..2328)
                     /note="spectinomycin cassette"
PCR_primer           1166..1188
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insert               complement(1166..2333)
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misc_feature         1166..1188
                     /note="spec lower"
PCR_primer           complement(2311..2333)
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misc_feature         1162..1188
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misc_feature         complement(2311..2333)
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                     /current=0
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     misc_feature    complement(320..343)
                     /note="FloxxerX seq R"
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CGCCACGTTC
      121 GCCGGCTTTC CCCGTCAAGC TCTAAATCGG GGGCTCCCTT TAGGGTTCCG
ATTTAGTGCT
      181 TTACGGCACC TCGACCCCAA AAAACTTGAT TAGGGTGATG GTTCACGTAG
TGGGCCATCG
      241 CCCTGATAGA CGGTTTTTCG CCCTTTgaat tcgcggccac cttggccggc
cgcGTATTGG
      301 GCGCTCTTCC GCTTCCTCGC TCACTGACTC GCTGCGCTCG GTCGTTCGGC
TGCGGCGAGC
      361 GGTATCAGCT CACTCAAAGG CGGTAATACG GTTATCCACA GAATCAGGGG
ATAACGCAGG
      421 AAAGAACATG TGAGCAAAAG GCCAGCAAAA GGCCAGGAAC CGTAAAAAGG
CCGCGTTGCT
      481 GGCGTTTTTC CATAGGCTCC GCCCCCCTGA CGAGCATCAC AAAAATCGAC
GCTCAAGTCA
      541 GAGGTGGCGA AACCCGACAG GACTATAAAG ATACCAGGCG TTTCCCCCTG
GAAGCTCCCT
      601 CGTGCGCTCT CCTGTTCCGA CCCTGCCGCT TACCGGATAC CTGTCCGCCT
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      661 GGGAAGCGTG GCGCTTTCTC ATAGCTCACG CTGTAGGTAT CTCAGTTCGG
TGTAGGTCGT
      721 TCGCTCCAAG CTGGGCTGTG TGCACGAACC CCCCGTTCAG CCCGACCGCT
GCGCCTTATC
      781 CGGTAACTAT CGTCTTGAGT CCAACCCGGT AAGACACGAC TTATCGCCAC
TGGCAGCAGC
      841 CACTGGTAAC AGGATTAGCA GAGCGAGGTA TGTAGGCGGT GCTACAGAGT
TCTTGAAGTG
      901 GTGGCCTAAC TACGGCTACA CTAGAAGAAC AGTATTTGGT ATCTGCGCTC
TGCTGAAGCC
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CCGCTGGTAG
     1021 CGGTGGTTTT TTTGTTTGCA AGCAGCAGAT TACGCGCAGA AAAAAAGGAT
CTCAAGAAGA
     1081 TCCTTTGATC TTTTCTACGG GGTCTGACGC TCAGTGGAAC GAAAACTCAC
GTTAAGGGAT
     1141 TTTGGTCATG AGATTATCAA AagttTCATG GGTGGCTCGA GGGTTATTTG
CCGACTACCT
     1201 TGGTGATCTC GCCTTTCACG TAGTGGACAA ATTCTTCCAA CTGATCTGCG
CGCGAGGCCA
     1261 AGCGATCTTC TTCTTGTCCA AGATAAGCCT GTCTAGCTTC AAGTATGACG
GGCTGATACT
     1321 GGGCCGGCAG GCGCTCCATT GCCCAGTCGG CAGCGACATC CTTCGGCGCG
ATTTTGCCGG
     1381 TTACTGCGCT GTACCAAATG CGGGACAACG TAAGCACTAC ATTTCGCTCA
TCGCCAGCCC
     1441 AGTCGGGCGG CGAGTTCCAT AGCGTTAAGG TTTCATTTAG CGCCTCAAAT
AGATCCTGTT
     1501 CAGGAACCGG ATCAAAGAGT TCCTCCGCCG CTGGACCTAC CAAGGCAACG
CTATGTTCTC
     1561 TTGCTTTTGT CAGCAAGATA GCCAGATCAA TGTCGATCGT GGCTGGCTCG
AAGATACCTG
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GGATAACGCC
     1681 ACGGAATGAT GTCGTCGTGC ACAACAATGG TGACTTCTAC AGCGCGGAGA
ATCTCGCTCT
     1741 CTCCAGGGGA AGCCGAAGTT TCCAAAAGGT CGTTGATCAA AGCTCGCCGC
GTTGTTTCAT
     1801 CAAGCCTTAC GGTCACCGTA ACCAGCAAAT CAATATCACT GTGTGGCTTC
AGGCCGCCAT
     1861 CCACTGCGGA GCCGTACAAA TGTACGGCCA GCAACGTCGG TTCGAGATGG
CGCTCGATGA
     1921 CGCCAACTAC CTCTGATAGT TGAGTCGATA CTTCGGCGAT CACCGCTTCC
CTCATGATGT
     1981 TTAACTTTGT TTTAGGGCGA CTGCCCTGCT GCGTAACATC GTTGCTGCTC
CATAACATCA
     2041 AACATCGACC CACGGCGTAA CGCGCTTGCT GCTTGGATGC CCGAGGCATA
GACTGTACCC
     2101 CAAAAAAACA GTCATAACAA GCCATGAAAA CCGCCACTGC GCCGTTACCA
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     2161 CGGTCAAGGT TCTGGACCAG TTGCGTGAGC GCATACGCTA CTTGCATTAC
AGCTTACGAA
     2221 CCGAACAGGC TTATGTCCAC TGGGTTCGTG CCTTCATCCG TTTCCACGGT
GTGCGTCACC
     2281 CGGCAACCTT GGGCAGCAGC GAAGTCGAGG CATTTCTGTC CTGGCTGGTC
TAGgcccggc
     2341 cccagtggcc GCGCGTTGGC CGATTCATTA ATGCAGCTGG CACGACAGGT
TTCCCGACTG
     2401 GAAAGCGGGC AGTGAGCGCA ACGCAATTAA TGTGAGTTAG CTCACTCATT
AGGCACCCCA
     2461 GGCTTTACAC TTTATGCTTC CGGCTCGTAT GTTGTGTGGA ATTGTGAGCG
GATAACAATT
     2521 TCACACAGGA AACAGCTCCT AGGATGAATT CGCCCTATAG TGAGTCGTAT
TACGCGCGCT
     2581 CACTGGCCGT CGTTTTACAA CGTCGTGACT GGGAAAACCC TGGCGTTACC
CAACTTAATC
     2641 GCCTTGCAGC ACATCCCCCT TTCGCCAGCT GGCGTAATAG CGAAGAGGCC
CGCACCGATC
     2701 GCCCTTCCCA ACAGTTGCGC AGCCTGAATG GCGAATGGGA CGCG
//
```

Table S4: The pSfiI-JT15-neoJTZ17-SfiI vector used during the assembly of *Borcs5/As3mt* displacer as a source of the neomycin resistance gene.

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LOCUS       pSfiI-JT15-neo-J        4880 bp    DNA     circular
10-JUN-2020
Created: Monday, May 30, 2011 4:40 PM
FEATURES             Location/Qualifiers
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                     /note="pgk-k/n"
     misc_feature    complement(699..732)
                     /note="loxP JT15 (LE1)"
     misc_feature    complement(2624..2657)
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                     /note="m13R"
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                     /current=1
     misc_feature    1475..1987
                     /note="new neo  probe 2012"
     misc_feature    2549..2572
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     misc_feature    2455..2482
                     /note="51657"
     misc_feature    2316..2338
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     misc_feature    2403..2426
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AATAGACCGA
      121 GATAGGGTTG AGTGTTGTTC CAGTTTGGAA CAAGAGTCCA CTATTAAAGA
ACGTGGACTC
      181 CAACGTCAAA GGGCGAAAAA CCGTCTATCA GGGCGATGGC CCACTACGTG
AACCATCACC
      241 CTAATCAAGT TTTTTGGGGT CGAGGTGCCG TAAAGCACTA AATCGGAACC
CTAAAGGGAG
      301 CCCCCGATTT AGAGCTTGAC GGGGAAAGCC GGCGAACGTG GCGAGAAAGG
AAGGGAAGAA
      361 AGCGAAAGGA GCGGGCGCTA GGGCGCTGGC AAGTGTAGCG GTCACGCTGC
GCGTAACCAC
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TCAGGCTGCG
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TGGCGAAAGG
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CACGACGTTG
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TGGGTACCGG
      661 GCCCCCCCTC GAGCAATTGG CCGGCCCGGC CGAATTGGAA TTATTCGTAT
AGCATACATT
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GTAGGGGAGG
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CTTGGCGCTA
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GGGGCGGGCT
     1141 CAGGGGCGGG CTCAGGGGCG GGCGGGCGCC CGAAGGTCCT CCCGAGGCCC
GGCATTCTGC
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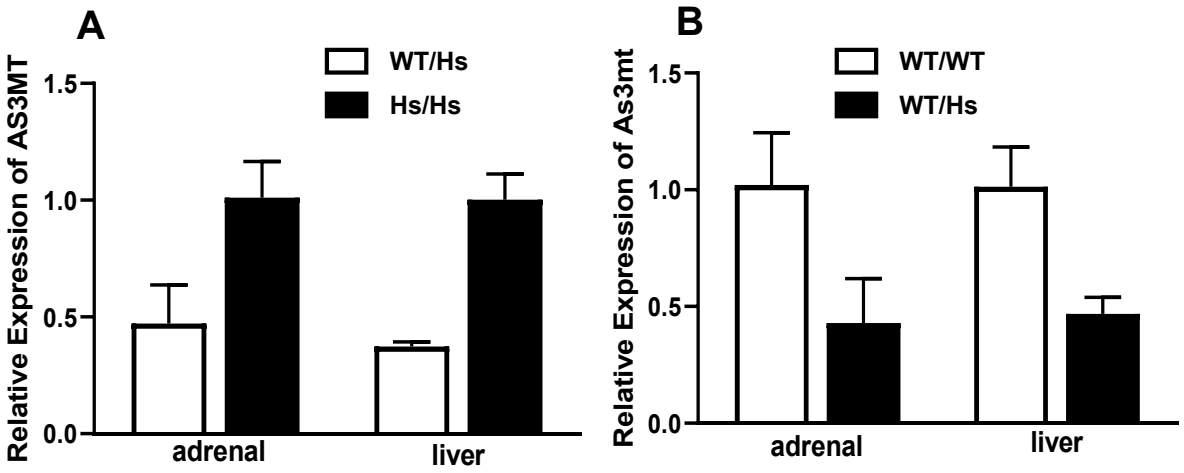

Figure S1: Comparison of *AS3MT* and *As3mt* expression levels in adrenals and liver of the humanized (Hs/Hs) and wild type (WT/WT) mice and the WT/Hs heterozygotes: **A.** Relative expression of the human *AS3MT*; **B.** Relative expression of the mouse *As3mt*. 2 µg RNA was reverse transcribed and quantitative PCR was run using *AS3MT* (Hs00960526_q1), *As3mt* (Mm00491075_m1), and 18S gene expression assays (Applied Biosystems) and qPCRBIO Probe Blue Mix (low ROX, Genesee Scientific). For each tissue, expression level in the mice homozygous for the gene was assigned a value of 1 (Mean +SE, N=6 for adrenals, N=3 for liver).

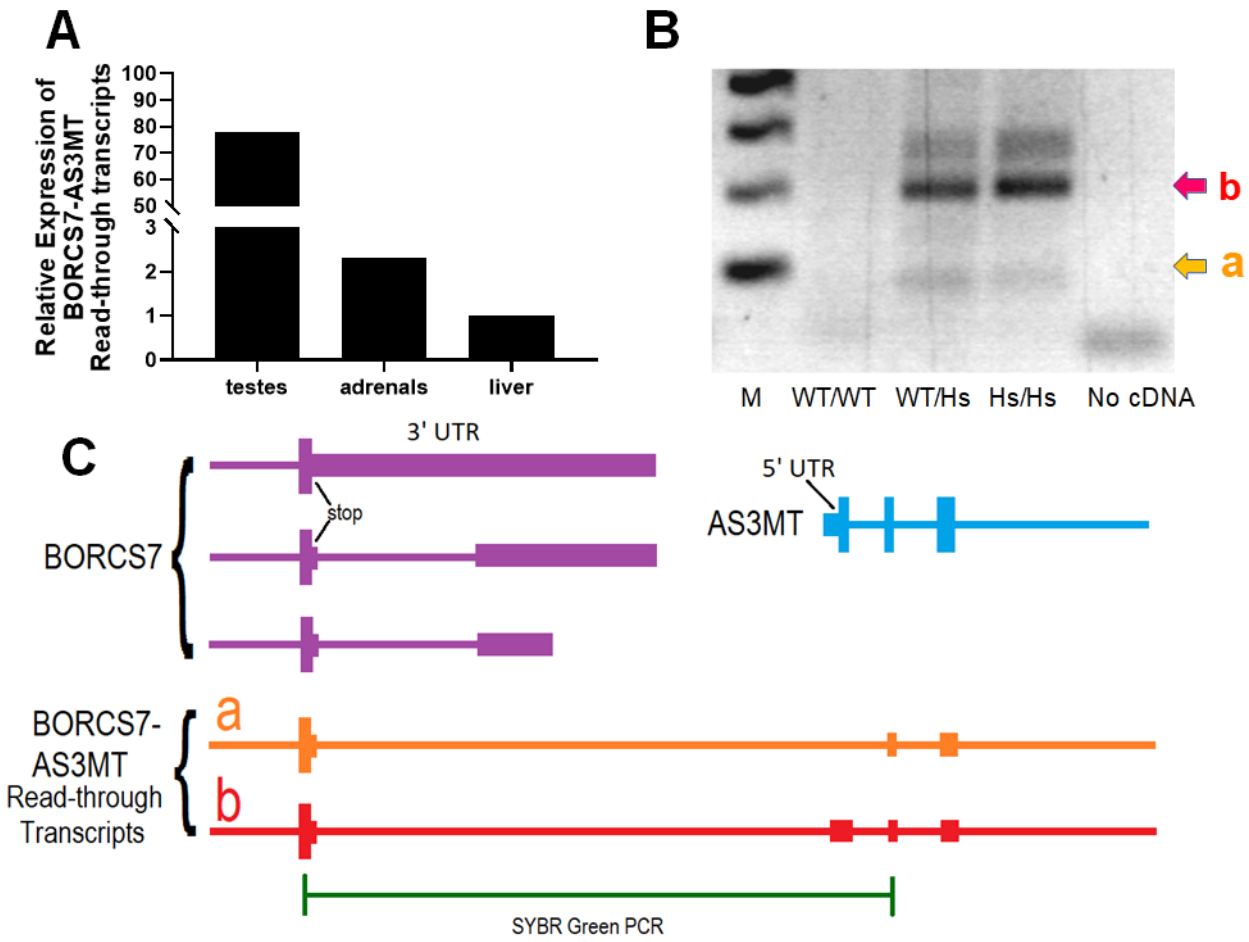

Figure S2: Expression of *BORCS7-AS3MT* read-through transcripts in tissues of the humanized (Hs/Hs) and wild type (WT/WT) mice and the WT/Hs heterozygotes. **A.** Read-through transcript expression in testes, adrenal glands, and liver of Hs/Hs mice (N=1/tissue). **B.** Separation of cDNA from testes of WT/WT, WT/Hs and Hs/Hs mice on a 1.6% agarose gel (N=1/genotype): (a) 100 bp fragment, consistent with the previously described read-through transcript; (b) 220 bp fragment of a read-through transcript that has not been previously reported. **C.** Schematic structures of the unspliced *BORCS7* isoforms (lavender), *AS3MT* (blue) and the previously reported (orange) (Lu X et al. 2015) and novel (red) *BORCS7-AS3MT* read-through transcripts. Introns are indicated by thin lines, untranslated exonic sequence by medium lines, and exonic coding sequence by thick lines. The position of the stop codon is indicated for the top two *BORCS7* transcripts. The PCR used for quantification and sequencing of the *BORCS7-AS3MT* junction of the read-through transcripts is indicated at the bottom of the figure (green).

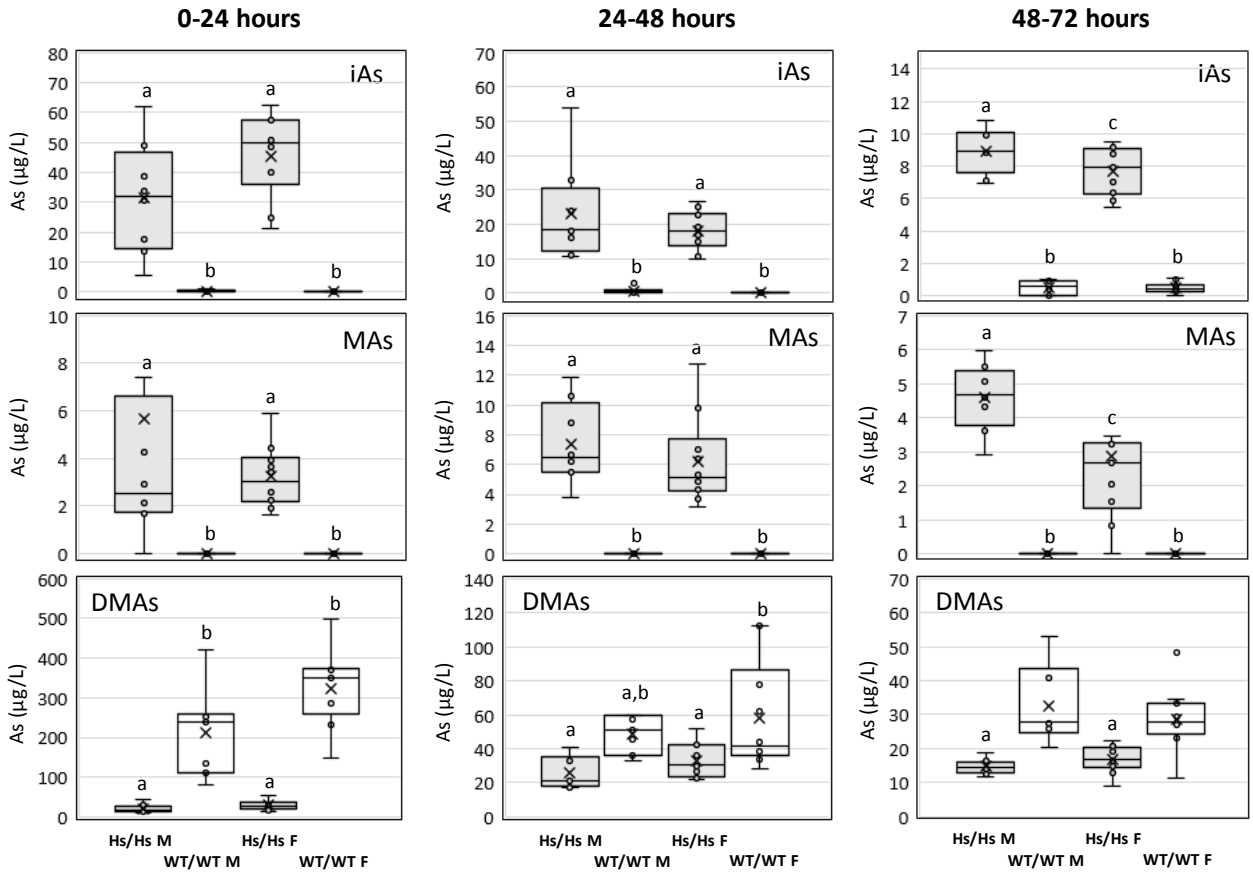

Figure S3: Concentrations of inorganic arsenic (iAs), methyl-arsenic (MAs) and dimethyl-arsenic (DMAs) (µg As/L) in urine of humanized (Hs/Hs) and wild type (WT/WT) male (M) and female (F) mice collected during 24-h intervals after oral administration of a single dose of iAs (20 µg As/kg body weight). Mean (x), median (—), 25th and 75th percentiles (box), maximum and minimum (whiskers), and individual values including outliers are shown (N=8 for Hs/Hs males, N=10 for Hs/Hs females, N=7 for WT/WT males, and N=11 for WT/WT females). MAs concentration was below limit od detection in 52 out of 54 urine samples collected from WT/WT mice during the 3 collection intervals; a value of 0 µg As/L was imputed for MAs concentrations in these samples. [a,b,c] Within each panel, statistically significant differences between strains and sexes are marked with different letters. (ANOVA with Student-Newman-Keuls post-test.)

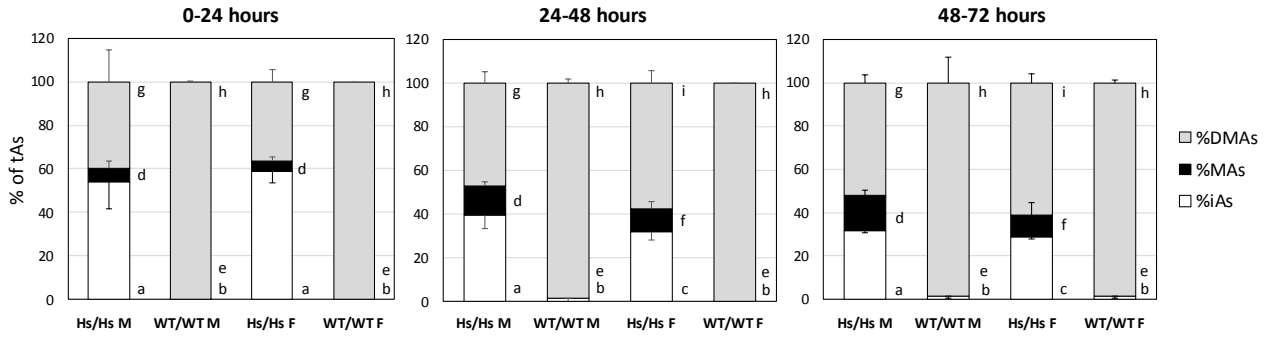

Figure S4: Proportions of total arsenic (%tAs) represented by inorganic arsenic (%iAs), methyl-arsenic (%MAs) and dimethyl-arsenic (%DMAs) in urine of humanized (Hs/Hs) and wild type (WT/WT) male (M) and female (F) mice collected during 24-h intervals after oral administration of a single dose of iAs (20 µg As/kg body weight). Mean +SD (N=8 for Hs/Hs males, N=10 for Hs/Hs females, N=7 for WT/WT males, and N=11 for WT/WT females). MAs concentration was below limit od detection in 52 out of 54 urine samples collected from WT/WT mice during the 3 collection intervals; a value of 0 µg As/L was imputed for MAs Within each panel, statistically significant differences between strains and sexes are marked with different letters: ^{a,b,c} for differences in %iAs, ^{d,e,f} for differences in %MAs, ^{g,hi} for differences in %DMAs. (ANOVA with Student-Newman-Keuls post-test.)

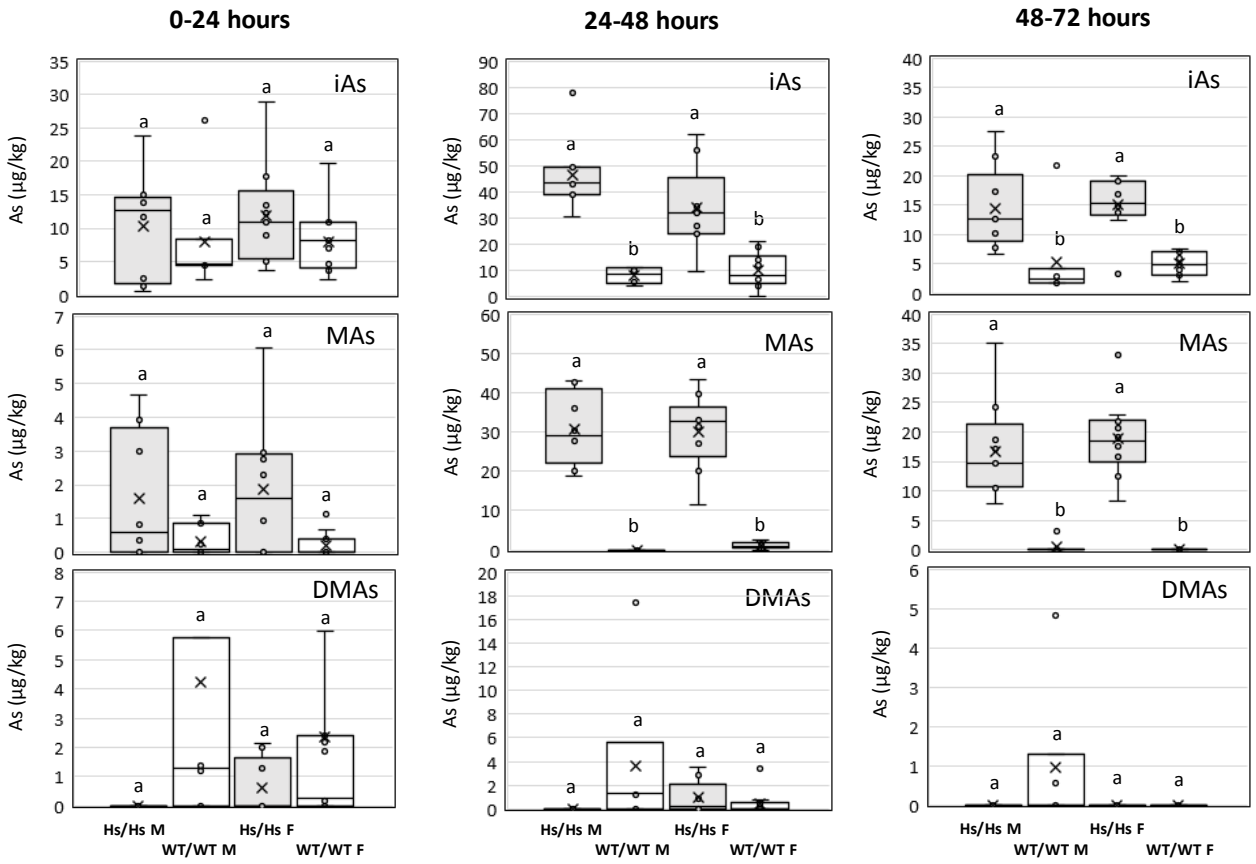

Figure S5: Concentrations of inorganic arsenic (iAs), methyl-arsenic (MAs) and dimethyl-arsenic (DMAs) (µg As/L) in feces of humanized (Hs/Hs) and wild type (WT/WT) male (M) and female (F) mice collected during 24-h intervals after oral administration of a single dose of iAs (20 µg As/kg body weight). Mean (x), median (—), 25th and 75th percentiles (box), maximum and minimum (whiskers), and individual values including outliers are shown (N=8 for Hs/Hs males, N=10 for Hs/Hs females, N=7 for WT/WT males, and N=11 for WT/WT females). DMAs concentration was below limit of detection in 48 out of 54 fecal samples collected during the 3 collection intervals from male and female Hs/Hs mice; a value of 0 µg As/kg was imputed for DMAs concentrations in these samples. [a,b] Within each panel, statistically significant differences between strains and sexes are marked with different letters. (ANOVA with Student-Newman-Keuls post-test.)

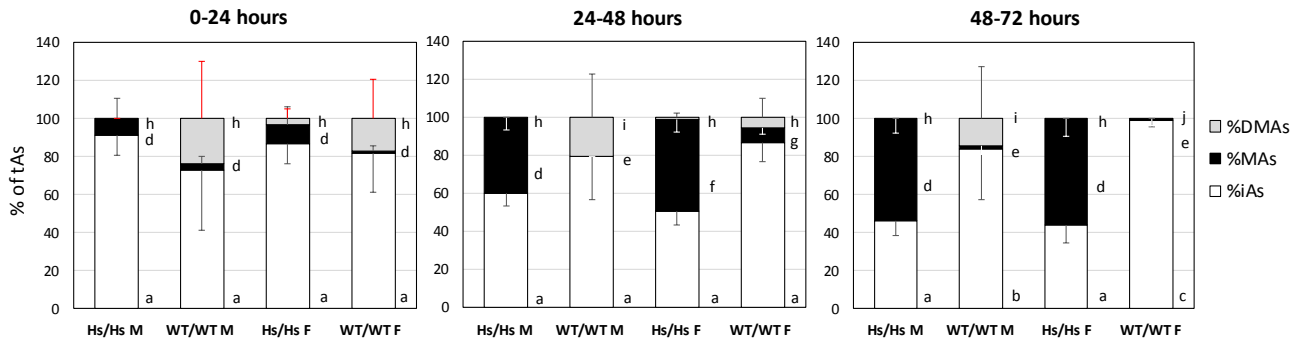

Figure S6: Proportions of total arsenic (%tAs) represented by inorganic arsenic (%iAs), methyl-arsenic (%MAs) and dimethyl-arsenic (%DMAs) in feces of humanized (Hs/Hs) and wild type (WT/WT) male (M) and female (F) mice collected during 24-h intervals after oral administration of a single dose of iAs (20 µg As/kg body weight). Mean +SD (N=8 for Hs/Hs males, N=10 for Hs/Hs females, N=7 for WT/WT males, and N=11 for WT/WT females). DMAs concentration was below limit of detection in 48 out of 54 fecal samples collected during the 3 collection intervals from male and female Hs/Hs mice; a value of 0 µg As/kg was imputed for DMAs concentrations in these samples. Within each panel, statistically significant differences between strains and sexes are marked with different letters: ^{a,b,c} for differences in %iAs, ^{d,e,f,g} for differences in %MAs, ^{h,i,j} for differences in %DMAs. (ANOVA with Student-Newman-Keuls post-test.)

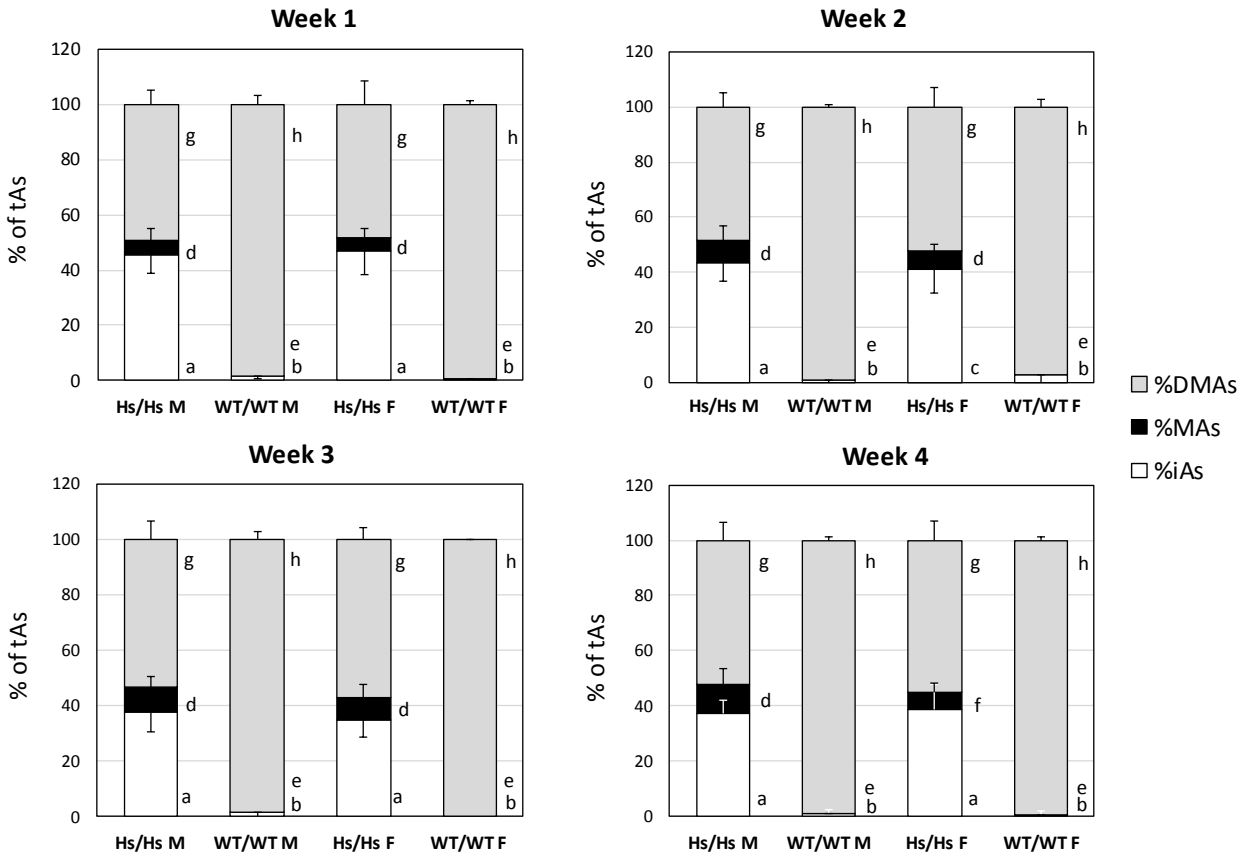

Figure S7: Proportions of total arsenic (%tAs) represented by inorganic arsenic (%iAs), methyl-arsenic (%MAs) and dimethyl-arsenic (%DMAs) in urine of humanized (Hs/Hs) and wild type (WT/WT) male (M) and female (F) mice collected during 4-week exposure to iAs in drinking water (400 µg As/L). Mean +SD (N=8 for Hs/Hs males, N=10 for Hs/Hs females, N=7 for WT/WT males, and N=11 for WT/WT females). MAs concentration was below LOD in 70 out of 72 urine samples collected from WT/WT mice during the 4 collection intervals; a value of 0 µg As/L was imputed for MAs concentrations in these samples. Within each panel, statistically significant differences between strains and sexes are marked with different letters: ^{a,b,c} %iAs, ^{d,e,f} %MAs, ^{g,h} %DMAs. (ANOVA with Student-Newman-Keuls post-test.)

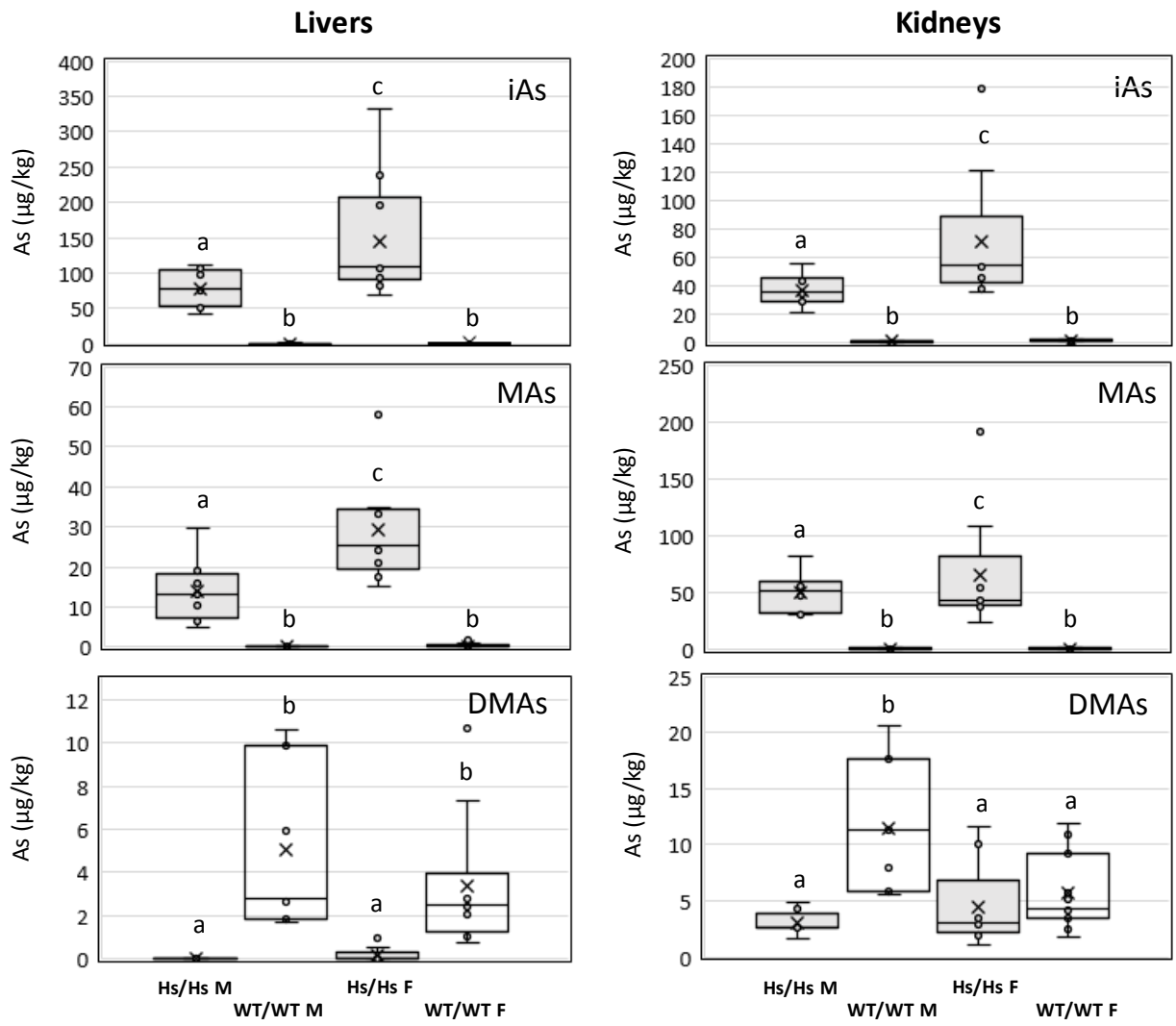

Figure S8: Concentrations of total arsenic (µg As/kg) in livers and kidneys of humanized (Hs/Hs) and wild type (WT/WT) male (M) and female (F) mice after 4-week exposure to iAs in drinking water (400 µg As/L). Total arsenic was calculated as sum of inorganic arsenic, methyl-arsenic and dimethyl-arsenic. Mean (x), median (—), 25th and 75th percentiles (box), maximum and minimum (whiskers), and individual values including outliers are shown (Mean+SD; N=8 for Hs/Hs males, N=10 for Hs/Hs females, N=7 for WT/WT males, and N=11 for WT/WT females). DMAs was below LOD in 16 out of 18 liver samples collected from Hs/Hs mice; a value of 0 µg As/kg was imputed for DMAs concentrations in these samples. ^{a,b,c} Within each panel, statistically significant differences between strains and sexes are marked with different letters. (ANOVA with Student-Newman-Keuls post-test.)

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