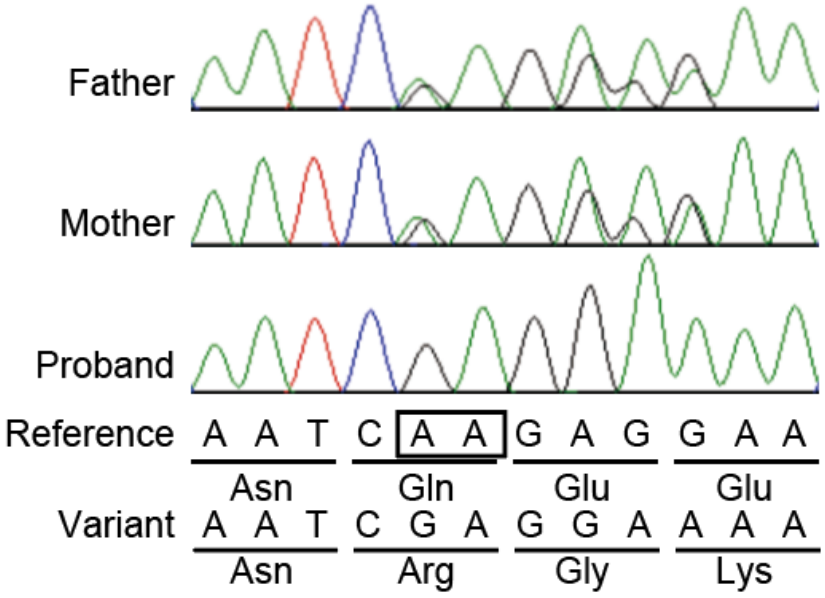
Supplementary information

Supplementary Figures



Supplementary Figure 1 Chromatograms of the frameshift *GON4L* variant in family 1

Chromatograms of the *GON4L* variant [NM_001282860.2:c.62_63del, p.(Gln21Argfs*12] in family 1. Boxed bases were deleted.

clustalw.aln

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CLUSTAL 2.1 multiple sequence alignment


NP_001269785.1_iso4     MLPCKKRRTTVTESLQHKGNQEENNVDLESAVKPESDQVKDLSSVSLSWDPSHGRVAGFE
NP_001269789.1_iso3     MLPCKKRRTTVTESLQHKGNQEENNVDLESAVKPESDQVKDLSSVSLSWDPSHGRVAGFE
NP_001269787.1_iso5     MLPCKKRRTTVTESLQHKGNQEENNVDLESAVKPESDQVKDLSSVSLSWDPSHGRVAGFE
NP_001269790.1_iso6     MLPCKKRRTTVTESLQHKGNQEENNVDLESAVKPESDQVKDLSSVSLSWDPSHGRVAGFE
NP_115668.4_iso2        MLPCKKRRTTVTESLQHKGNQEENNVDLESAVKPESDQVKDLSSVSLSWDPSHGRVAGFE
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NP_001269785.1_iso4     VQSLQDAGNQLGMEDTSLSSGMLTQNTNVPILEGVDVAISQGITLPSLESFHPLNIHIGK
NP_001269789.1_iso3     VQSLQDAGNQLGMEDTSLSSGMLTQNTNVPILEGVDVAISQGITLPSLESFHPLNIHIGK
NP_001269787.1_iso5     VQSLQDAGNQLGMEDTSLSSGMLTQNTNVPILEGVDVAISQGITLPSLESFHPLNIHIGK
NP_001269790.1_iso6     VQSLQDAGNQLGMEDTSLSSGMLTQNTNVPILEGVDVAISQGITLPSLESFHPLNIHIGK
NP_115668.4_iso2        VQSLQDAGNQLGMEDTSLSSGMLTQNTNVPILEGVDVAISQGITLPSLESFHPLNIHIGK
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NP_001269785.1_iso4     GKLHATGSKRGKKMTLRPGPVTQEDRCDHLTLKEPFSGEPSEEVKEEGGKPQMNSEGEIP
NP_001269789.1_iso3     GKLHATGSKRGKKMTLRPGPVTQEDRCDHLTLKEPFSGEPSEEVKEEGGKPQMNSEGEIP
NP_001269787.1_iso5     GKLHATGSKRGKKMTLRPGPVTQEDRCDHLTLKEPFSGEPSEEVKEEGGKPQMNSEGEIP
NP_001269790.1_iso6     GKLHATGSKRGKKMTLRPGPVTQEDRCDHLTLKEPFSGEPSEEVKEEGGKPQMNSEGEIP
NP_115668.4_iso2        GKLHATGSKRGKKMTLRPGPVTQEDRCDHLTLKEPFSGEPSEEVKEEGGKPQMNSEGEIP
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NP_001269785.1_iso4     SLPSGSQSAKPVSQPRKSTQPDVCASPQEKPLRTLFHQPEEEIEDGGLFIPMEEQDNEES
NP_001269789.1_iso3     SLPSGSQSAKPVSQPRKSTQPDVCASPQEKPLRTLFHQPEEEIEDGGLFIPMEEQDNEES
NP_001269787.1_iso5     SLPSGSQSAKPVSQPRKSTQPDVCASPQEKPLRTLFHQPEEEIEDGGLFIPMEEQDNEES
NP_001269790.1_iso6     SLPSGSQSAKPVSQPRKSTQPDVCASPQEKPLRTLFHQPEEEIEDGGLFIPMEEQDNEES
NP_115668.4_iso2        SLPSGSQSAKPVSQPRKSTQPDVCASPQEKPLRTLFHQPEEEIEDGGLFIPMEEQDNEES
                        ************************************************************

NP_001269785.1_iso4     EKRRKKKKGTKRKRDGRGQEGTLAYDLKLDDMLDRTLEDGAKQHNLTAVNVRNILHEVIT
NP_001269789.1_iso3     EKRRKKKKGTKRKRDGRGQEGTLAYDLKLDDMLDRTLEDGAKQHNLTAVNVRNILHEVIT
NP_001269787.1_iso5     EKRRKKKKGTKRKRDGRGQEGTLAYDLKLDDMLDRTLEDGAKQHNLTAVNVRNILHEVIT
NP_001269790.1_iso6     EKRRKKKKGTKRKRDGRGQEGTLAYDLKLDDMLDRTLEDGAKQHNLTAVNVRNILHEVIT
NP_115668.4_iso2        EKRRKKKKGTKRKRDGRGQEGTLAYDLKLDDMLDRTLEDGAKQHNLTAVNVRNILHEVIT
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NP_001269785.1_iso4     NEHVVAMMKAAISETEDMPMFEPKMTRSKLKEVVEKGVVIPTWNISPIKKANEIKPPQFV
NP_001269789.1_iso3     NEHVVAMMKAAISETEDMPMFEPKMTRSKLKEVVEKGVVIPTWNISPIKKANEIKPPQFV
NP_001269787.1_iso5     NEHVVAMMKAAISETEDMPMFEPKMTRSKLKEVVEKGVVIPTWNISPIKKANEIKPPQFV
NP_001269790.1_iso6     NEHVVAMMKAAISETEDMPMFEPKMTRSKLKEVVEKGVVIPTWNISPIKKANEIKPPQFV
NP_115668.4_iso2        NEHVVAMMKAAISETEDMPMFEPKMTRSKLKEVVEKGVVIPTWNISPIKKANEIKPPQFV
                        ************************************************************

NP_001269785.1_iso4     DIHLEEDDSSDEEYQPDDEEEDETAEESLLESDVESTASSPRGAKKSRLRQSSEMTETDE
NP_001269789.1_iso3     DIHLEEDDSSDEEYQPDDEEEDETAEESLLESDVESTASSPRGAKKSRLRQSSEMTETDE
NP_001269787.1_iso5     DIHLEEDDSSDEEYQPDDEEEDETAEESLLESDVESTASSPRGAKKSRLRQSSEMTETDE
NP_001269790.1_iso6     DIHLEEDDSSDEEYQPDDEEEDETAEESLLESDVESTASSPRGAKKSRLRQSSEMTETDE
NP_115668.4_iso2        DIHLEEDDSSDEEYQPDDEEEDETAEESLLESDVESTASSPRGAKKSRLRQSSEMTETDE
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NP_001269785.1_iso4     ESGILSEAEKVTTPAIRHISAEVVPMGPPPPPKPKQTRDSTFMEKLHAVDEELASSPVCM
NP_001269789.1_iso3     ESGILSEAEKVTTPAIRHISAEVVPMGPPPPPKPKQTRDSTFMEKLHAVDEELASSPVCM
NP_001269787.1_iso5     ESGILSEAEKVTTPAIRHISAEVVPMGPPPPPKPKQTRDSTFMEKLHAVDEELASSPVCM
NP_001269790.1_iso6     ESGILSEAEKVTTPAIRHISAEVVPMGPPPPPKPKQTRDSTFMEKLHAVDEELASSPVCM
NP_115668.4_iso2        ESGILSEAEKVTTPAIRHISAEVVPMGPPPPPKPKQTRDSTFMEKLHAVDEELASSPVCM
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NP_001269785.1_iso4     DSFQPMDDSLIAFRTRSKMPLKDVPLGQLEAELQAPDITPDMYDPNTADDEDWKMWLGGL
NP_001269789.1_iso3     DSFQPMDDSLIAFRTRSKMPLKDVPLGQLEAELQAPDITPDMYDPNTADDEDWKMWLGGL
NP_001269787.1_iso5     DSFQPMDDSLIAFRTRSKMPLKDVPLGQLEAELQAPDITPDMYDPNTADDEDWKMWLGGL
NP_001269790.1_iso6     DSFQPMDDSLIAFRTRSKMPLKDVPLGQLEAELQAPDITPDMYDPNTADDEDWKMWLGGL
NP_115668.4_iso2        DSFQPMDDSLIAFRTRSKMPLKDVPLGQLEAELQAPDITPDMYDPNTADDEDWKMWLGGL
                        ************************************************************

NP_001269785.1_iso4     MNDDVGNEDEADDDDDPEYNFLEDLDEPDTEDFRTDRAVRITKKEVNELMEELFETFQDE
NP_001269789.1_iso3     MNDDVGNEDEADDDDDPEYNFLEDLDEPDTEDFRTDRAVRITKKEVNELMEELFETFQDE
NP_001269787.1_iso5     MNDDVGNEDEADDDDDPEYNFLEDLDEPDTEDFRTDRAVRITKKEVNELMEELFETFQDE
NP_001269790.1_iso6     MNDDVGNEDEADDDDDPEYNFLEDLDEPDTEDFRTDRAVRITKKEVNELMEELFETFQDE
NP_115668.4_iso2        MNDDVGNEDEADDDDDPEYNFLEDLDEPDTEDFRTDRAVRITKKEVNELMEELFETFQDE
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NP_001269785.1_iso4     MGFSNMEDDGPEEEECVAEPRPNFNTPQALRFEEPLANLLNEQHRTVKELFEQLKMKKSS
NP_001269789.1_iso3     MGFSNMEDDGPEEEECVAEPRPNFNTPQALRFEEPLANLLNEQHRTVKELFEQLKMKKSS
NP_001269787.1_iso5     MGFSNMEDDGPEEEECVAEPRPNFNTPQALRFEEPLANLLNEQHRTVKELFEQLKMKKSS
NP_001269790.1_iso6     MGFSNMEDDGPEEEECVAEPRPNFNTPQALRFEEPLANLLNEQHRTVKELFEQLKMKKSS
NP_115668.4_iso2        MGFSNMEDDGPEEEECVAEPRPNFNTPQALRFEEPLANLLNEQHRTVKELFEQLKMKKSS
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NP_001269785.1_iso4     AKQLQEVEKVKPQSEKVHQTLILDPAQRKRLQQQMQQHVQLLTQIHLLATCNPNLNPEAT
NP_001269789.1_iso3     AKQLQEVEKVKPQSEKVHQTLILDPAQRKRLQQQMQQHVQLLTQIHLLATCNPNLNPEAT
NP_001269787.1_iso5     AKQLQEVEKVKPQSEKVHQTLILDPAQRKRLQQQMQQHVQLLTQIHLLATCNPNLNPEAT
NP_001269790.1_iso6     AKQLQEVEKVKPQSEKVHQTLILDPAQRKRLQQQMQQHVQLLTQIHLLATCNPNLNPEAT
NP_115668.4_iso2        AKQLQEVEKVKPQSEKVHQTLILDPAQRKRLQQQMQQHVQLLTQIHLLATCNPNLNPEAT
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NP_001269785.1_iso4     TTRIFLKELGTFAQSSIALHHQYNPKFQTLFQPCNLMGAMQLIEDFSTHVSIDCSPHKTV
NP_001269789.1_iso3     TTRIFLKELGTFAQSSIALHHQYNPKFQTLFQPCNLMGAMQLIEDFSTHVSIDCSPHKTV
NP_001269787.1_iso5     TTRIFLKELGTFAQSSIALHHQYNPKFQTLFQPCNLMGAMQLIEDFSTHVSIDCSPHKTV
NP_001269790.1_iso6     TTRIFLKELGTFAQSSIALHHQYNPKFQTLFQPCNLMGAMQLIEDFSTHVSIDCSPHKTV
NP_115668.4_iso2        TTRIFLKELGTFAQSSIALHHQYNPKFQTLFQPCNLMGAMQLIEDFSTHVSIDCSPHKTV
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NP_001269785.1_iso4     KKTANEFPCLPKQVAWILATSKVFMYPELLPVCSLKAKNPQDKIVFTKAEDNLLALGLKH
NP_001269789.1_iso3     KKTANEFPCLPKQVAWILATSKVFMYPELLPVCSLKAKNPQDKIVFTKAEDNLLALGLKH
NP_001269787.1_iso5     KKTANEFPCLPKQVAWILATSKVFMYPELLPVCSLKAKNPQDKIVFTKAEDNLLALGLKH
NP_001269790.1_iso6     KKTANEFPCLPKQVAWILATSKVFMYPELLPVCSLKAKNPQDKIVFTKAEDNLLALGLKH
NP_115668.4_iso2        KKTANEFPCLPKQVAWILATSKVFMYPELLPVCSLKAKNPQDKIVFTKAEDNLLALGLKH
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NP_001269785.1_iso4     FEGTEFPNPLISKYLLTCKTAHQLTVRIKNLNMNRAPDNIIKFYKKTKQLPVLGKCCEEI
NP_001269789.1_iso3     FEGTEFPNPLISKYLLTCKTAHQLTVRIKNLNMNRAPDNIIKFYKKTKQLPVLGKCCEEI
NP_001269787.1_iso5     FEGTEFPNPLISKYLLTCKTAHQLTVRIKNLNMNRAPDNIIKFYKKTKQLPVLGKCCEEI
NP_001269790.1_iso6     FEGTEFPNPLISKYLLTCKTAHQLTVRIKNLNMNRAPDNIIKFYKKTKQLPVLGKCCEEI
NP_115668.4_iso2        FEGTEFPNPLISKYLLTCKTAHQLTVRIKNLNMNRAPDNIIKFYKKTKQLPVLGKCCEEI
                        ************************************************************

NP_001269785.1_iso4     QPHQWKPPIEREEHRLPFWLKASLPSIQEELRHMADGAREVGNMTGTTEINSDRSLEKDN
NP_001269789.1_iso3     QPHQWKPPIEREEHRLPFWLKASLPSIQEELRHMADGAREVGNMTGTTEINSDRSLEKDN
NP_001269787.1_iso5     QPHQWKPPIEREEHRLPFWLKASLPSIQEELRHMADGAREVGNMTGTTEINSDRSLEKDN
NP_001269790.1_iso6     QPHQWKPPIEREEHRLPFWLKASLPSIQEELRHMADGAREVGNMTGTTEINSDRSLEKDN
NP_115668.4_iso2        QPHQWKPPIEREEHRLPFWLKASLPSIQEELRHMADGAREVGNMTGTTEINSDRSLEKDN
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NP_001269785.1_iso4     LELGSESRYPLLLPKGVVLKLKPVATRFPRKAWRQKRSSVLKPLLIQPSPSLQPSFNPGK
NP_001269789.1_iso3     LELGSESRYPLLLPKGVVLKLKPVATRFPRKAWRQKRSSVLKPLLIQPSPSLQPSFNPGK
NP_001269787.1_iso5     LELGSESRYPLLLPKGVVLKLKPVATRFPRKAWRQKRSSVLKPLLIQPSPSLQPSFNPGK
NP_001269790.1_iso6     LELGSESRYPLLLPKGVVLKLKPVATRFPRKAWRQKRSSVLKPLLIQPSPSLQPSFNPGK
NP_115668.4_iso2        LELGSESRYPLLLPKGVVLKLKPVATRFPRKAWRQKRSSVLKPLLIQPSPSLQPSFNPGK
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NP_001269785.1_iso4     TPARSTHSEAPPSKMVLRIPHPIQPATVLQTVPGVPPLGVSGGESFESPAALPAVPPEAR
NP_001269789.1_iso3     TPARSTHSEAPPSKMVLRIPHPIQPATVLQTVPGVPPLGVSGGESFESPAALPAVPPEAR
NP_001269787.1_iso5     TPARSTHSEAPPSKMVLRIPHPIQPATVLQTVPGVPPLGVSGGESFESPAALPAVPPEAR
NP_001269790.1_iso6     TPARSTHSEAPPSKMVLRIPHPIQPATVLQTVPGVPPLGVSGGESFESPAALPAVPPEAR
NP_115668.4_iso2        TPARSTHSEAPPSKMVLRIPHPIQPATVLQTVPGVPPLGVSGGESFESPAALPAVPPEAR
                        ************************************************************

NP_001269785.1_iso4     TSFPLSESQTLLSSAPVPKVMLPSLAPSKFRKPYVRRRPSKRRGVKASPCMKPAPVIHHP
NP_001269789.1_iso3     TSFPLSESQTLLSSAPVPKVMLPSLAPSKFRKPYVRRRPSKRRGVKASPCMKPAPVIHHP
NP_001269787.1_iso5     TSFPLSESQTLLSSAPVPKVMLPSLAPSKFRKPYVRRRPSKRRGVKASPCMKPAPVIHHP
NP_001269790.1_iso6     TSFPLSESQTLLSSAPVPKVMLPSLAPSKFRKPYVRRRPSKRRGVKASPCMKPAPVIHHP
NP_115668.4_iso2        TSFPLSESQTLLSSAPVPKVMLPSLAPSKFRKPYVRRRPSKRRGVKASPCMKPAPVIHHP
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NP_001269785.1_iso4     ASVIFTVPATTVKIVSLGGGCNMIQPVNAAVAQSPQTIPITTLLVNPTSFPCPLNQSLVA
NP_001269789.1_iso3     ASVIFTVPATTVKIVSLGGGCNMIQPVNAAVAQSPQTIPITTLLVNPTSFPCPLNQSLVA
NP_001269787.1_iso5     ASVIFTVPATTVKIVSLGGGCNMIQPVNAAVAQSPQTIPITTLLVNPTSFPCPLNQSLVA
NP_001269790.1_iso6     ASVIFTVPATTVKIVSLGGGCNMIQPVNAAVAQSPQTIPITTLLVNPTSFPCPLNQSLVA
NP_115668.4_iso2        ASVIFTVPATTVKIVSLGGGCNMIQPVNAAVAQSPQTIPITTLLVNPTSFPCPLNQSLVA
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NP_001269785.1_iso4      SSVSPLIVSGNSVNLPIPSTPEDKAHVNVDIACAVADGENAFQGLEPKLEPQELSPLSAT
NP_001269789.1_iso3      SSVSPLIVSGNSVNLPIPSTPEDKAHVNVDIACAVADGENAFQGLEPKLEPQELSPLSAT
NP_001269787.1_iso5      SSVSPLIVSGNSVNLPIPSTPEDKAHVNVDIACAVADGENAFQGLEPKLEPQELSPLSAT
NP_001269790.1_iso6      SSVSPLIVSGNSVNLPIPSTPEDKAHVNVDIACAVADGENAFQGLEPKLEPQELSPLSAT
NP_115668.4_iso2         SSVSPLIVSGNSVNLPIPSTPEDKAHVNVDIACAVADGENAFQGLEPKLEPQELSPLSAT
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NP_001269785.1_iso4      VFPKVEHSPGPPLADAECQEGLSENSACRWTVVKTEEGRQALEPLPQGIQESLNNPTPGD
NP_001269789.1_iso3      VFPKVEHSPGPPLADAECQEGLSENSACRWTVVKTEEGRQALEPLPQGIQESLNNPTPGD
NP_001269787.1_iso5      VFPKVEHSPGPPLADAECQEGLSENSACRWTVVKTEEGRQALEPLPQGIQESLNNPTPGD
NP_001269790.1_iso6      VFPKVEHSPGPPLADAECQEGLSENSACRWTVVKTEEGRQALEPLPQGIQESLNNPTPGD
NP_115668.4_iso2         VFPKVEHSPGPPLADAECQEGLSENSACRWTVVKTEEGRQALEPLPQGIQESLNNPTPGD
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NP_001269785.1_iso4      LEEIVKMEPEEAREEISGSPERDICDDIKVEHAVELDTGAPSEELSSAGEVTKQTVLQKE
NP_001269789.1_iso3      LEEIVKMEPEEAREEISGSPERDICDDIKVEHAVELDTGAPSEELSSAGEVTKQTVLQKE
NP_001269787.1_iso5      LEEIVKMEPEEAREEISGSPERDICDDIKVEHAVELDTGAPSEELSSAGEVTKQTVLQKE
NP_001269790.1_iso6      LEEIVKMEPEEAREEISGSPERDICDDIKVEHAVELDTGAPSEELSSAGEVTKQTVLQKE
NP_115668.4_iso2         LEEIVKMEPEEAREEISGSPERDICDDIKVEHAVELDTGAPSEELSSAGEVTKQTVLQKE
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NP_001269785.1_iso4      EERSQPTKTPSSSQEPPDEGTSGTDVNKGSSKNALSSMDPEVRLSSPPGKPEDSSSVDGQ
NP_001269789.1_iso3      EERSQPTKTPSSSQEPPDEGTSGTDVNKGSSKNALSSMDPEVRLSSPPGKPEDSSSVDGQ
NP_001269787.1_iso5      EERSQPTKTPSSSQEPPDEGTSGTDVNKGSSKNALSSMDPEVRLSSPPGKPEDSSSVDGQ
NP_001269790.1_iso6      EERSQPTKTPSSSQEPPDEGTSGTDVNKGSSKNALSSMDPEVRLSSPPGKPEDSSSVDGQ
NP_115668.4_iso2         EERSQPTKTPSSSQEPPDEGTSGTDVNKGSSKNALSSMDPEVRLSSPPGKPEDSSSVDGQ
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NP_001269785.1_iso4      SVGTPVGPETGGEKNGPEEEEEEDFDDLTQDEEDEMSSASEESVLSVPELQETMEKLTWL
NP_001269789.1_iso3      SVGTPVGPETGGEKNGPEEEEEEDFDDLTQDEEDEMSSASEESVLSVPELQETMEKLTWL
NP_001269787.1_iso5      SVGTPVGPETGGEKNGPEEEEEEDFDDLTQDEEDEMSSASEESVLSVPELQETMEKLTWL
NP_001269790.1_iso6      SVGTPVGPETGGEKNGPEEEEEEDFDDLTQDEEDEMSSASEESVLSVPELQVRAGEYSQV
NP_115668.4_iso2         SVGTPVGPETGGEKNGPEEEEEEDFDDLTQDEEDEMSSASEESVLSVPELQVRAGEYSQV
                         ************************************************    : : :

NP_001269785.1_iso4      ASERRMSQEGESEEENSQEENSEPEEEEEEEAEGMESLQKEDEMTDEAVGDSAEKPPTFA
NP_001269789.1_iso3      ASERRMSQEGESEEENSQEENSEPEEEEEEEAEGMESLQKEDEMTDEAVGDSAEKPPTFA
NP_001269787.1_iso5      ASERRMSQEGESEEENSQEENSEPEEEEEEEAEGMESLQKEDEMTDEAVGDSAEKPPTFA
NP_001269790.1_iso6      FRG-------------------------------------------------------
NP_115668.4_iso2         FRG-------------------------------------------------------

NP_001269785.1_iso4      SPETAPEVETSRTPPGESIKAAGKGRNNHRARNKRGSRARASKDTSKLLLLYDEDILERD
NP_001269789.1_iso3      SPETAPEVETSRTPPGESIKAAGKGRNNHRARNKRGSRARASKDTSKLLLLYDEDILERD
NP_001269787.1_iso5      SPETAPEVETSRTPPGESIKAAGKGRNNHRARNKRGSRARASKDTSKLLLLYDEDILERD
NP_001269790.1_iso6      -------------------------------------------------------------
NP_115668.4_iso2         -------------------------------------------------------------

NP_001269785.1_iso4      PLREQKDLAFAQAYLTRVREALQHIPGKYEDFLQVIYEFESSTQRRTAVDLYKSLQILLQ
NP_001269789.1_iso3      PLREQKDLAFAQAYLTRVREALQHIPGKYEDFLQVIYEFESSTQRRTAVDLYKSLQILLQ
NP_001269787.1_iso5      PLREQKDLAFAQAYLTRVREALQHIPGKYEDFLQVIYEFESSTQRRTAVDLYKSLQILLQ
NP_001269790.1_iso6      -------------------------------------------------------------
NP_115668.4_iso2         -------------------------------------------------------------

NP_001269785.1_iso4      DWPQLLKDFAAFLLPEQALACGLFEEQQAFEKSRKFLRQLEICFAENPSHHQKIIKVLQG
NP_001269789.1_iso3      DWPQLLKDFAAFLLPEQALACGLFEEQQAFEKSRKFLRQLEICFAENPSHHQKIIKVLQG
NP_001269787.1_iso5      DWPQLLKDFAAFLLPEQALACGLFEEQQAFEKSRKFLRQLEICFAENPSHHQKIIKVLQG
NP_001269790.1_iso6      ----------------------------------------------LSNMYHLLICHLLAC
NP_115668.4_iso2         ----------------------------------------------LSNMYHLLICHLLAC
                                                                        .  :*  * ::*

NP_001269785.1_iso4      CADCLPQEITELKTQMWQLLKGHDHLQDEFSIFFDHLRPAASRMGDFEEINWTEEKEYEF
NP_001269789.1_iso3      CADCLPQEITELKTQMWQLLKGHDHLQDEFSIFFDHLRPAASRMGDFEEINWTEEKEYEF
NP_001269787.1_iso5      CADCLPQEITELKTQMWQLLKGHDHLQDEFSIFFDHLRPAASRMGDFEEINWTEEKEYEF
NP_001269790.1_iso6      CTMDSPKIICI-----------------------------------------------
NP_115668.4_iso2         CTMDSPKIICI-----------------------------------------------
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NP_001269785.1_iso4     DGFEEVALPDVEEEEEPPKIPTASKNKRKKEIGVQNHDKETEWPDGAKDCACSCHEGGPD
NP_001269789.1_iso3     DGFEEVALPDVEEEEEPPKIPTASKNKRKKEIGVQNHDKETEWPDGAKDCACSCHEGGPD
NP_001269787.1_iso5     DGFEEVALPDVEEEEEPPKIPTASKNKRKKEIGVQNHDKETEWPDGAKDCACSCHEGGPD
NP_001269790.1_iso6     ------------------------------------------------------------
NP_115668.4_iso2        ------------------------------------------------------------

NP_001269785.1_iso4     SKLKKSKRRSCSHCSSKVCDSKSYKSKEPHELVGSSPHREASPMPGAKEAGQGKDMMEEE
NP_001269789.1_iso3     SKLKKSKRRSCSHCSSKVCDSKSYKSKEPHELVGSSPHREASPMPGAKEAGQGKDMMEEE
NP_001269787.1_iso5     SKLKKSKRRSCSHCSSKVCDSKSYKSKEPHELVGSSPHREASPMPGAKEAGQGKDMMEEE
NP_001269790.1_iso6     ------------------------------------------------------------
NP_115668.4_iso2        ------------------------------------------------------------

NP_001269785.1_iso4     APEERESTEATQSRTVRTTRKGEMPVSAGLAVGSTLPSPREVTVTERLLLDGPPPHSPET
NP_001269789.1_iso3     APEERESTEATQSRTVRTTRKGEMPVSAGLAVGSTLPSPREVTVTERLLLDGPPPHSPET
NP_001269787.1_iso5     APEERESTEATQSRTVRTTRKGEMPVSG-LAVGSTLPSPREVTVTERLLLDGPPPHSPET
NP_001269790.1_iso6     ------------------------------------------------------------
NP_115668.4_iso2        ------------------------------------------------------------

NP_001269785.1_iso4     PQFPPTTGAVLYTVKRNQVGPEVRSCPKASPRLQKEREGQKAVSESEALMLVWDASETEK
NP_001269789.1_iso3     PQFPPTTGAVLYTVKRNQVGPEVRSCPKASPRLQKEREGQKAVSESEALMLVWDASETEK
NP_001269787.1_iso5     PQFPPTTGAVLYTVKRNQVGPEVRSCPKASPRLQKEREGQKAVSESEALMLVWDASETEK
NP_001269790.1_iso6     ------------------------------------------------------------
NP_115668.4_iso2        ------------------------------------------------------------

NP_001269785.1_iso4     LPGTVEPPASFLSPVSSKTRDAGRRHVSGKPDTQERWLPSSRARVKTRDRTCPVHESPSG
NP_001269789.1_iso3     LPGTVEPPASFLSPVSSKTRDAGRRHVSGKPDTQERWLPSSRARVKTRDRTCPVHESPSG
NP_001269787.1_iso5     LPGTVEPPASFLSPVSSKTRDAGRRHVSGKPDTQERWLPSSRARVKTRDRTCPVHESPSG
NP_001269790.1_iso6     ------------------------------------------------------------
NP_115668.4_iso2        ------------------------------------------------------------

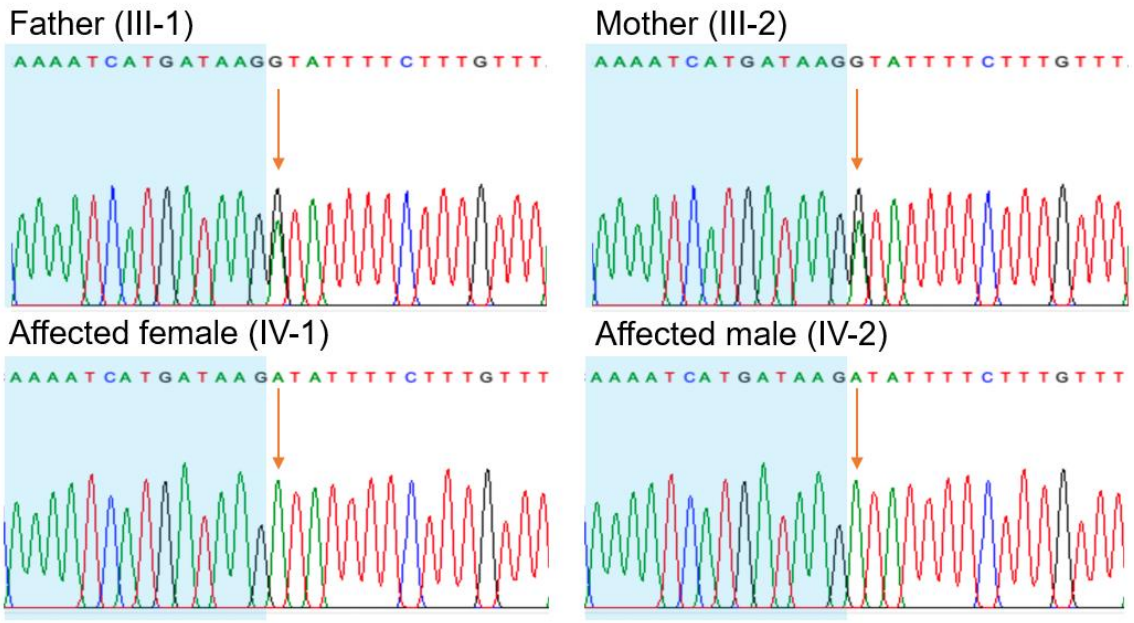
NP_001269785.1_iso4     IDTSETSPKAPRGGLAKDSGTQAKGPEGEQQPKAAEATVCANNSKVSSTGEKVVLWTREA
NP_001269789.1_iso3     IDTSETSPKAPRGGLAKDSGTQAKGPEGEQQPKAAEATVCANNSKVSSTGEKVVLWTREA
NP_001269787.1_iso5     IDTSETSPKAPRGGLAKDSGTQAKGPEGEQQPKAAEATVCANNSKVSSTGEKVVLWTREA
NP_001269790.1_iso6     ------------------------------------------------------------
NP_115668.4_iso2        ------------------------------------------------------------

NP_001269785.1_iso4     DRVILTMCQEQGAQPQTFNIISQQLGNKTPAEVSHRFRELMQLFHTACEASSEDEDDATS
NP_001269789.1_iso3     DRVILTMCQEQGAQPQTFNIISQQLGNKTPAEVSHRFRELMQLFHTACEASSEDEDDATS
NP_001269787.1_iso5     DRVILTMCQEQGAQPQTFNIISQQLGNKTPAEVSHRFRELMQLFHTACEASSEDEDDATS
NP_001269790.1_iso6     ------------------------------------------------------------
NP_115668.4_iso2        ------------------------------------------------------------

NP_001269785.1_iso4     TSNADQLSDHGDLLSEEELDE
NP_001269789.1_iso3     TSNADQLSDHGDLLSEEELDE
NP_001269787.1_iso5     TSNADQLSDHGDLLSEEELDE
NP_001269790.1_iso6     ----------------------
NP_115668.4_iso2        ----------------------
```

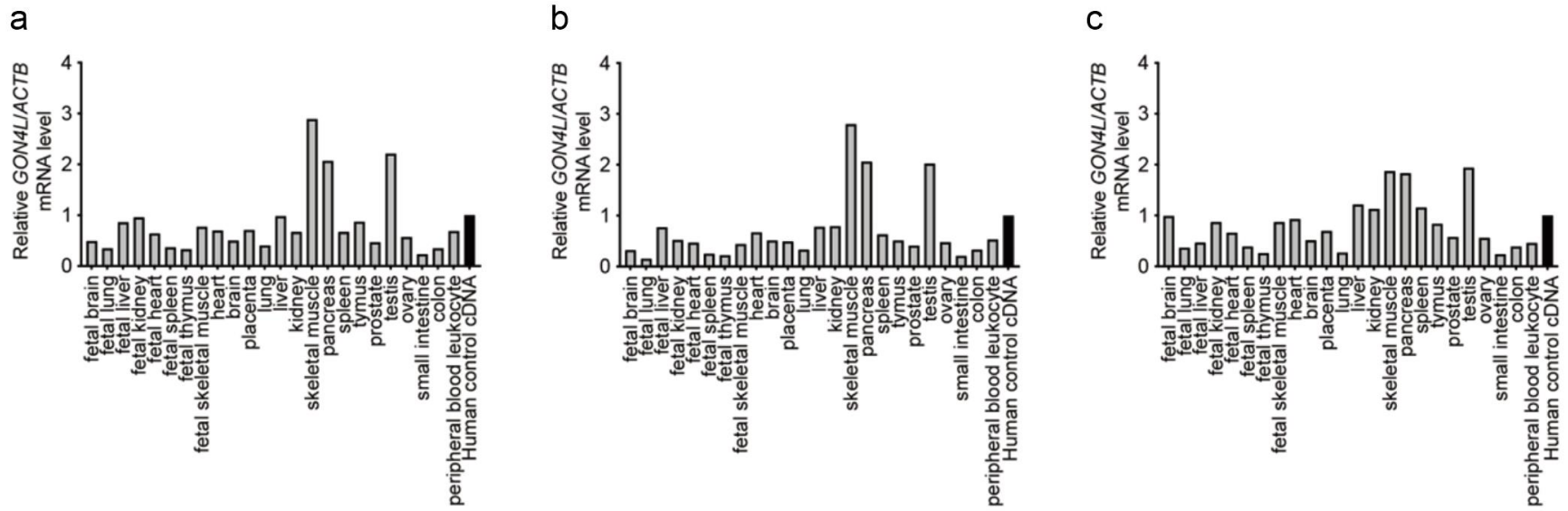
Supplementary Figure 2 GON4L protein alignment by CLUSTALW

Five GON4L protein sequences encoded by each isoform were aligned using CLUSTALW (https://www.genome.jp/tools-bin/clustalw): NP_001269785.1 encoded by NM_001282856.2 (transcript variant 4), NP_001269789.1 encoded by NM_001282860.2 (transcript variant 3), NP_001269787.1 encoded by NM_001282858.2 (transcript variant 5), NP_001269790.1 encoded by NM_001282861.2 (transcript variant 6), and NP_115668.4 encoded by NM_032292.6 (transcript variant 2).



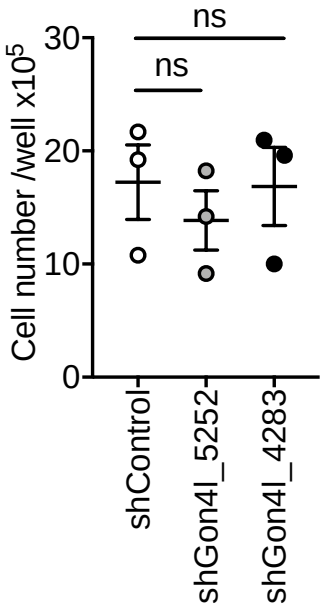
Supplementary Figure 3 Chromatograms of the *GON4L* variant in family 2

The variant (NM_001282860.2:c.5517+1G>A) is indicated by orange arrows. The exonic regions are highlighted by light-blue shading.



Supplementary Figure 4 Human *GON4L* expression

GON4L expression in human fetal and adult tissues assessed by TaqMan assays. Panels a and b show the relative expression covering short and long isoforms (A: Hs00228595_m1, B: Hs01685033_mH), and Panel c shows the expression specific for long isoforms (Hs00250331_m1). Expression levels were normalized against *ACTB* and levels relative to the control are shown.



Supplementary Figure 5 Growth of *Gon4l*-knockdown PC12 cells

Numbers of live cells after culture for 5 days are shown. Dots represent data from each of three independent experiments and bars represent the mean with standard error of the mean (SEM). ns, not significant. One-way ANOVA followed by Tukey's multiple comparison test was used for statistical analysis.

CLUSTAL 2.1 Multiple Sequence Alignments

Sequence 1: gon4la_XP_003200651.2 1602 aa
Sequence 2: gon4lb_NP_001188464.1 2055 aa
Sequence 3: GON4L_NP_001269789 2241 aa

Sequences (1:2) Aligned. Score: 29.588
Sequences (1:3) Aligned. Score: 28.0275
Sequences (2:3) Aligned. Score: 29.0511

```
CLUSTAL 2.1 multiple sequence alignment


gon4lb_NP_001188464.1      --------------------------------------------------
gon4la_XP_003200651.2      --------------------------------------------------
GON4L_NP_001269789         MLPCKKRRTTVTESLQHKGNQEENNVDLESAVKPESDQVKDLSSVSLSWD


gon4lb_NP_001188464.1      --------------------------------------------------
gon4la_XP_003200651.2      --------------------------------------------------
GON4L_NP_001269789         PSHGRVAGFEVQSLQDAGNQLGMEDTSLSSGMLTQNTNVPILEGVDVAIS


gon4lb_NP_001188464.1      ----------------MGWKRKSSSPEPQPNLVKLPKRESLSRSPSSWKR
gon4la_XP_003200651.2      --------------MDQTRKRRLNNRKPGLSQCKVARAEEPEDISESRDV
GON4L_NP_001269789         QGITLPSLESFHPLNIHIGKGKLHATGSKRGKKMTLRPGPVTQEDRCDHL
                                         * :     .  .     :         . .


gon4lb_NP_001188464.1      KASTPSKTKSWTSIQSLSPDRHVDQCNGQEKMSSAGHVEDDSDCIQSSTP
gon4la_XP_003200651.2      NVTEPAGSN----------------------FSSIRASSPQSDSTSQEQH
GON4L_NP_001269789         TLKEPFSGEPSEEVKEEGGKPQMNSEGEIPSLPSGSQSAKPVSQPRKSTQ
                           . . *   :                     :.*        .   ..


gon4lb_NP_001188464.1      VSSPLRSEEDAELGLVITVDEDRCEGEEWLKKRNGVNIKKNGINQTEGEI
gon4la_XP_003200651.2      AACTQTSEDDAENNLIITFDKE-QAGTRGMGRRKGLRRKKDAINEVEAQQ
GON4L_NP_001269789         PDVCASPQEKPLRTLFHQPEEEIEDGGLFIPMEEQDNEESEKRRKKKKGT
                                 .::..   *.   :::   *   :  .:  . :.:  .: :
```

```
gon4lb_NP_001188464.1      PQKEDGDVEKTMEQLSEEDENEEELRKLDRDLTLKSKKLNLSSINVRNII
gon4la_XP_003200651.2      NEVED-----------EIQPEVEIDRELDRELENKSRQHNLTSANVRSII
GON4L_NP_001269789         KRKRDGR-----GQEGTLAYDLKLDDMLDRTLEDGAKQHNLTAVNVRNIL
                            . .*              : :    *** *   ::: **:: ***.*:

gon4lb_NP_001188464.1      HEVVTNEHVVAMMKAAIKETQDMPMFEPKMTRSKLKEAVEKGVGMGNWNI
gon4la_XP_003200651.2      HEVITNEHVVAMMKAAISETEPIPVFEPKMTRSKLKEVVEKGVVIPTWNI
GON4L_NP_001269789         HEVITNEHVVAMMKAAISETEDMPMFEPKMTRSKLKEVVEKGVVIPTWNI
                           ***:*************.**: :*:************.***** : .***

gon4lb_NP_001188464.1      SPIKKANDIKP-PQFVDIPLQEEEDSSDEEYCPDEDEEDETAEETFLESD
gon4la_XP_003200651.2      SPIKKPTEAKKGPQFVDIPLEEE-DSSDEEYRPDEEEEDETAEETLLESD
GON4L_NP_001269789         SPIKKANEIKP-PQFVDIHLEED-DSSDEEYQPDDEEEDETAEESLLESD
                           *****..: *  ****** *:*: ******* **::********::****

gon4lb_NP_001188464.1      VESTSSSPRGIR-------RFPSQTPPHCDDASNSPRLKPRLARHLRVEA
gon4la_XP_003200651.2      LENSSSSPRVSR-------VQRSHSE--SEDGASRSRLNLCRSRHLTVAA
GON4L_NP_001269789         VESTASSPRGAKKSRLRQSSEMTETDEESGILSEAEKVTTPAIRHISAEV
                           :*.::****  :          :.:   .   :.  ::.    **: . .

gon4lb_NP_001188464.1      VPMGPPAPPPQSCGLSRSLKTLDPFIEKLHAVDKELELSPLCMEPYQALS
gon4la_XP_003200651.2      TPMGPPPPPDTSR-----APPECSFLEKLHAVDEELAFGTDCMDSYQSLG
GON4L_NP_001269789         VPMGPPPPPKPKQ------TRDSTFMEKLHAVDEELASSPVCMDSFQPMD
                           .*****.**  .           .*:*******:**  .. **:.:*.:.

gon4lb_NP_001188464.1      SGGAGEPDDSLVACRTRSKRPLRDVPLDQLEAELRAPDITPDMYDNVSTP
gon4la_XP_003200651.2      G---ASGEESLISFRTRSKRPLRDVPLGRLEAELRAPDITPDMYEFGSAP
GON4L_NP_001269789         D--------SLIAFRTRSKMPLKDVPLGQLEAELQAPDITPDMYDPN-TA
                           .        **:: ***** **:****.:*****:*********:   :.

gon4lb_NP_001188464.1      EDREWTQWLQGLMTSHLDNDEEADEDDDPEYNFLDDLDEPDLEDYRNDRA
gon4la_XP_003200651.2      EDREWTQWLQGLMISDMDNDEEGDDEDDPEYNFLADIDEPDVEDYRNDKA
GON4L_NP_001269789         DDEDWKMWLGGLMNDDVGNEDEADDDDDPEYNFLEDLDEPDTEDFRTDRA
                           :*.:*. ** *** ..:.*::*.*::******** *:**** **:*.*:*
```

```
gon4lb_NP_001188464.1      VRITKKEVNELMEELFETFHDELAANEPDDEGHDEDEEREEEANDTPQFN
gon4la_XP_003200651.2      VRITKKEVNDLMEELFDAFQDELGGQ--DDEGHEEEEEKEEEESPLQEPP
GON4L_NP_001269789         VRITKKEVNELMEELFETFQDEMGFSNMEDDGPEEEECVAEP----RPNF
                           *********:******::*:**:. .  :*:* :*:*   *

gon4lb_NP_001188464.1      -VPQAIRFEEPLAHMLTACRRTVREQLDALQQRRENQ-VRTTQHASGPGM
gon4la_XP_003200651.2      GILENIQYEDPLADVLKQRYRTVREQLAAVRKRKALLESKGVSVPPACPQ
GON4L_NP_001269789         NTPQALRFEEPLANLLNEQHRTVKELFEQLKMK--KSSAKQLQEVEKVKP
                              : :::*:***.:*.   ***:* :  :: :      :  .

gon4lb_NP_001188464.1      VFVQPSCPLVVTPAQRIQLQQQIQQHVQLLTQVSMLCDPVGALQTEAQTT
gon4la_XP_003200651.2      RSSSPITSMTLNAAQRLQLQQQIQQHVQLLTQVNMLSSTVKGLETEASTS
GON4L_NP_001269789         QSEKVHQTLILDPAQRKRLQQQMQQHVQLLTQIHLLATCNPNLNPEATTT
                              .   .: : .*** :****:*********: :*.     *:.** *:

gon4lb_NP_001188464.1      KHFLGELLSFAERAEEER-SAVNLGFKSVFRVCNLLSSINLLEEVKQSPS
gon4la_XP_003200651.2      RQFLLELQMFGQRGEHNCGRAEHGFFTSIFNACNLQGAVSLLEELDQS--
GON4L_NP_001269789         RIFLKELGTFAQSS-IALHHQYNPKFQTLFQPCNLMGAMQLIEDFSTHVS
                           : ** **  *.: .        :  * ::*. *** .::.*:*:..

gon4lb_NP_001188464.1      LSCLPPKPNRHHSVHSYPLLPAGLAWLFATRSVFLYPELLPHCSLDPALH
gon4la_XP_003200651.2      ---LKGDPAVLSPCLPGCQFPASLAWLMATRSVFLYPELLPTIQLR----
GON4L_NP_001269789         -IDCSPHKTVKKTANEFPCLPKQVAWILATSKVFMYPELLPVCSLKAK--
                                 .     .      :*  :**::** .**:******  .*

gon4lb_NP_001188464.1      PSRSKHYYSKGEDGLLVLGLKHFAQTEFPYQLISRYLIRPKRQEQLRMRV
gon4la_XP_003200651.2      PSKFKGPFTSAEDCLVVLGHKHLRGTLHPLQMTCRYLLATRSFISVKSHI
GON4L_NP_001269789         NPQDKIVFTKAEDNLLALGLKHFEGTEFPNPLISKYLLTCKTAHQLTVRI
                            .: *  ::..** *:.** **:  * .*  : .:**:  :   .:  ::

gon4lb_NP_001188464.1      KDMVSPKYPHNIIKYYCQNHVVPPLPVVCKPVVHGEERPPVEREQEVMPN
gon4la_XP_003200651.2      RDACQKPFPS-VIKTYFMAGKCPSMPLASKRVSPCDQRPPVEREQSLMPD
GON4L_NP_001269789         KNLNMNRAPDNIIKFYKKTKQLPVLGKCCEEIQPHQWKPPIEREEHRLPF
                           ::      *  :** *      * :   .: :   : :**:***:  :*
```

```
gon4lb_NP_001188464.1      WLKKSLPLIQKSICQSDLTMTST-----TKSASLPFPKETRYPQFLPKGL
gon4la_XP_003200651.2      WLSKNLKCIYKHVRTYNQASGNP-----QTTEATDPAGPGPHFCFPPGMR
GON4L_NP_001269789         WLKASLPSIQEELRHMADGAREVGNMTGTTEINSDRSLEKDNLELGSESR
                           **. .*  * : :       .      .     .      : .

gon4lb_NP_001188464.1      SLRLHPSQVASRPSQPKSRILRAFTNRTLAPLAKAPSCPTGTGHLLTNIS
gon4la_XP_003200651.2      YPLSLPEDLAQTLEASALSAFKKKKDKTDKSAKPLKPPPSAEKLELVLN-
GON4L_NP_001269789         YPLLLPKGVVLKLKPVATRFPRKAWRQKRSSVLKPLLIQPSPSLQPSFNP
                                *. :.   .      :    :.  .       ..

gon4lb_NP_001188464.1      TPVLLLAQAPSTPINGVFPLVHPSLTPAHGTVPLNASYPINFHYLSPELG
gon4la_XP_003200651.2      --------------------------------------------------
GON4L_NP_001269789         GKTPARSTHSEAPPSKMVLRIPHPIQPATVLQTVPGVPPLG---VSGGES

gon4lb_NP_001188464.1      ASNPAHLPANLPPSVVQKPQCDVPLLSTGTVKTHGVQQQTSDKHKKRTMP
gon4la_XP_003200651.2      -----QLPAILPKTLS-----------------------------------
GON4L_NP_001269789         FESPAALPAVPPEARTSFPLSE-------------------------SQT
                                ***  * :

gon4lb_NP_001188464.1      RKLAPLRPAPQLPRLLPLSSGSIGNISNPGIIIDQQISLNVPHNLQSDNV
gon4la_XP_003200651.2      --LSRPQPNPCLPGNRAITGPFILSRVPP---------------VGSKQA
GON4L_NP_001269789         LLSSAPVPKVMLPSLAPSKFRKPYVRRRPS------------KRRGVKAS
                              :   *   **   . .        *                .

gon4lb_NP_001188464.1      IVIKAHENVNTHRTVPSLSPDLVVQLVPQTQVAENTTSSLPRKTTPRSDV
gon4la_XP_003200651.2      RAIATSPNISTTFKPSSSTSAPVKNAVETPMGISCSAAQRDIIITLPAAV
GON4L_NP_001269789         PCMKPAPVIHHPASVIFTVPATTVKIVSLGGGCNMIQPVNAAVAQSPQTI
                             : .   :    .     . . : *      .   .          :

gon4lb_NP_001188464.1      SQTAKDIPSVQSSGENGQRTVFSPQTAAPAAVDSSQFVLVQTVSPTGPPQ
gon4la_XP_003200651.2      TPELKSYPSG------------------HITVNQTQIVTSNVVEPAVPR-
GON4L_NP_001269789         PITTLLVNPTSFPCPLNQSLVASSVSPLIVSGNSVNLPIPSTPEDKAHVN
                           .      .                   : :. ::   .. .
```

```
gon4lb_NP_001188464.1      FLLLPQDSLVLNQPASLPSEGTLQNLSQQ----TSHLDISTTSTALKNSE
gon4la_XP_003200651.2      -----------------ASNLIISFQPPQ----VANTFICPTPIINTNVQ
GON4L_NP_001269789         VDIACAVADGENAFQGLEPKLEPQELSPLSATVFPKVEHSPGPPLADAEC
                                           .:   .  .       .:   .. .

gon4lb_NP_001188464.1      KTEVHLNNPTTSLPVSREEDGERQEVDEEMVGDRWEEEMASALFGSPLLA
gon4la_XP_003200651.2      MPQNHISQRCGTLPKLLPKVSGGLAQVCPKPVNRFVLLPSGNVFANSSFG
GON4L_NP_001269789         QEGLSENSACRWTVVKTEEGRQALEPLPQGIQESLNNPTPGDLEEIVKME
                                 ..          :             :      .. :     :

gon4lb_NP_001188464.1      LSESSCSPDSSPDASMDSGSDAMVRVEMEDGELPSVHSASATQETPDVHK
gon4la_XP_003200651.2      HQRAGQEQTLKQSSALKCKHVKLMRQQTSQDSLHSADRLKGDQSQMSFIQ
GON4L_NP_001269789         PEEAREEISGSPERDICDDIKVEHAVELDTGAPSEELSSAGEVTKQTVLQ
                            ..:  .   . .  :          : . .   .     .      . :

gon4lb_NP_001188464.1      HSSGDEKEQQSSGGEKQNSGNEEGRAEESESRKDEAQDEDKGGEKNEDGE
gon4la_XP_003200651.2      ETPNDGFEETAEAELNDDDDDDDGGIVENEEEERGKIDSIEMSLTLSESS
GON4L_NP_001269789         KEEERSQPTKTPSSSQEPPDEGTSGTDVNKGSSKNALSSMDPEVRLSSPP
                           .         : .  ::  .:  .    .:  .    .. .     ..

gon4lb_NP_001188464.1      GDGKRDEGGSGDKGREEKDGDGEKDGDGERDEEEEDFDDLTQDEDEEEVM
gon4la_XP_003200651.2      GSPMPSIDGE----------DAEMEMEKPEEQKEKEQEGCNRLFGDEETG
GON4L_NP_001269789         GKPEDSSSVDGQSVGTPVGPETGGEKNGPEEEEEEDFDDLTQDEEDE--M
                           *.   . . .          :   : :  .:::*:: :. .:   :*

gon4lb_NP_001188464.1      SSASEESVLSVPELQETMEKLTWLASERRLCREGDSEEDNSPTSPTSPTS
gon4la_XP_003200651.2      GADNVSGVRLVPELQETMEKFLHLATKTVSEKEGRS--------------
GON4L_NP_001269789         SSASEESVLSVPELQETMEKLTWLASERRMSQEGESEEENSQEENSEPEE
                           .: . ..*  **********:  **::    :** *

gon4lb_NP_001188464.1      PNSQNSPASQNSQEENSEDEDDGAMKGDELEAGEGEGEKLPEGDAPAGDD
gon4la_XP_003200651.2      --------------------------------------------------
GON4L_NP_001269789         EEEEEAEGMESLQKEDEMTDEAVG-------DSAEKPPTFASPETAPEVE
```

```
gon4lb_NP_001188464.1      PPQISEKVGGRGRGRGRPPPRSLKRGRRQERGSKDASKLLLLYDDHILDN
gon4la_XP_003200651.2      ----------------------NIKSKHQPSGSYWTQTERKTVLHNDASDH
GON4L_NP_001269789         TSRTPPGESIKAAGKGRNNHRARNKRGSRARASKDTSKLLLLYDEDILER
                                                :       .    ::   : .:.  :.

gon4lb_NP_001188464.1      DPMRESKDMAYAQAYLNRVREALQDVPGKVEEFLGLLYEFDQAGESHSVI
gon4la_XP_003200651.2      DPYRDAKDIAFAQAYLEKVYEVLHQVPGKVDEFLCILSDFVKNPESHTSL
GON4L_NP_001269789         DPLREQKDLAFAQAYLTRVREALQHIPGKYEDFLQVIYEFESSTQRRTAV
                           ** *: **:*:***** :* *.*:.:*** ::** :: :* .  : :: :

gon4lb_NP_001188464.1      ELFAQLKQLLKDWPELLKDFAAFLLPEQALECGLFEEQQAFERSRRFLRQ
gon4la_XP_003200651.2      QLLMRLKPILEDWPELLQDFAAFLHPDQARECGLLAEQQAFERSRGFLRQ
GON4L_NP_001269789         DLYKSLQILLQDWPQLLKDFAAFLLPEQALACGLFEEQQAFEKSRKFLRQ
                           :*   *: :*:***:**:****** *:**  ***: ******:** ****

gon4lb_NP_001188464.1      LEISFGENPSHYQKIVRALQSGSPLSPAGIEELKTQMATLLKGHTHLQGE
gon4la_XP_003200651.2      LESTFGEQSYLYRKVVHILQGDQSQGLADLKEIKAEMALLLRDHTDLLEE
GON4L_NP_001269789         LEICFAENPSHHQKIIKVLQGCADCLPQEITELKTQMWQLLKGHDHLQDE
                           **  *.*:.  ::*::: **.        : *:*::*  **:.* .*  *

gon4lb_NP_001188464.1      FWMFFDEMRPPPARPGQFEEAVWPEDVATGTDGEAGVSVTSRGGVWGGFE
gon4la_XP_003200651.2      FWEYFKQIYP-----------------------------------------
GON4L_NP_001269789         FSIFFDHLRPAASRMGDFEEINWTEEKEYEFDG---------------FE
                           *  :*..: *

gon4lb_NP_001188464.1      EVTLPDLDEDEESHKIRQISSRSKRRKE----LHTYKDCDWPEKDCSCSC
gon4la_XP_003200651.2      -----QVQENVETNQVLE------------------------EKQPSQPS
GON4L_NP_001269789         EVALPDVEEEEEPPKIPTASKNKRKKEIGVQNHDKETEWPDGAKDCACSC
                                ::::*: *. ::                          *: : ..

gon4lb_NP_001188464.1      HDSVHDAKHRRHKRKGCLRCQSNKAANGSKVLKGRDSAFSSADAQSERGG
gon4la_XP_003200651.2      RNMLADKKLETDKTSIKHRRKTNKHAQMAEMRRNK--------VKNSSAM
GON4L_NP_001269789         HEGGPDSKLKKSKRRSCSHCSSKVCDSKSYKSKEPHELVGSSPHREASPM
                           ::   * * .  *     : .::   . :   :          :.
```

```
gon4lb_NP_001188464.1      EEKEEERVLGEDGEAEKELKDETGSGANS----------------------
gon4la_XP_003200651.2      LDKDSEASLGDS-----------------------------------------
GON4L_NP_001269789         PGAKEAGQGKDMMEEEAPEERESTEATQSRTVRTTRKGEMPVSAGLAVGS
                              ..     :

gon4lb_NP_001188464.1      -------------------------------------------------
gon4la_XP_003200651.2      -------------------------------------------------
GON4L_NP_001269789         TLPSPREVTVTERLLLDGPPPHSPETPQFPPTTGAVLYTVKRNQVGPEVR


gon4lb_NP_001188464.1      -------------------------------------------------
gon4la_XP_003200651.2      -------------------------------------------------
GON4L_NP_001269789         SCPKASPRLQKEREGQKAVSESEALMLVWDASETEKLPGTVEPPASFLSP


gon4lb_NP_001188464.1      ---------PHHDGEGSVWEREERATSSIPEEQNTHNQDDEEKTEEKNHH
gon4la_XP_003200651.2      -------------------------------------------------
GON4L_NP_001269789         VSSKTRDAGRRHVSGKPDTQERWLPSSRARVKTRDRTCPVHESPSGIDTS

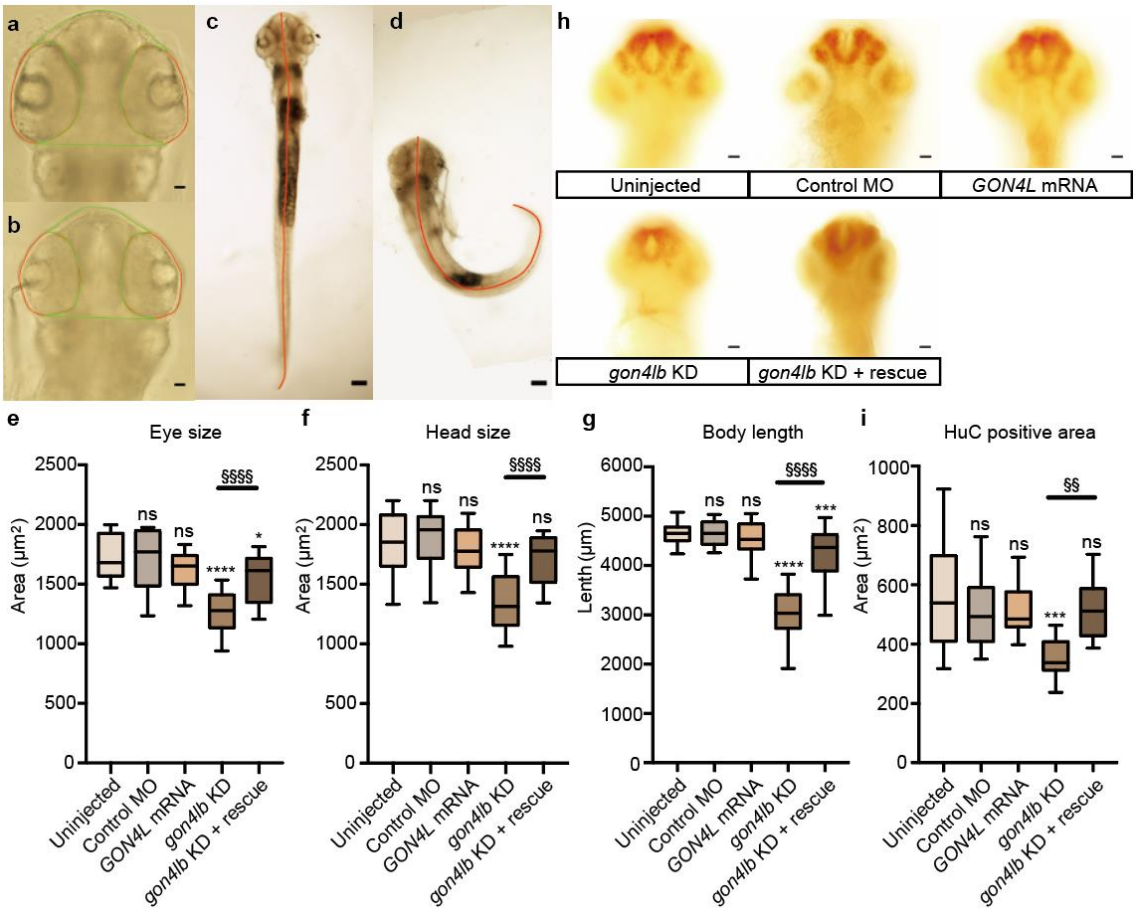

gon4lb_NP_001188464.1      ASPEKHSRDEEDSAESGQTEAAQQSSLSPALDAPVCAKNISLTPTGERVI
gon4la_XP_003200651.2      ------------------------QQSLFNATGSSVCAKNISHTSAGKKVV
GON4L_NP_001269789         ETSPKAPRGGLAKDSGTQAKGPEGEQQPKAAEATVCANNSKVSSTGEKVV
                                                ..   *  :.***:* . :.:*::*:

gon4lb_NP_001188464.1      LWTREADRVILTTCQQQGASQSTFQAVSEQLGNKTASEVSRRFRDLMRLF
gon4la_XP_003200651.2      LWTREADRVILTTCQQRGAKQTTFHAIAAQLGNKTASEVSERFQDLIKLF
GON4L_NP_001269789         LWTREADRVILTMCQEQGAQPQTFNIISQQLGNKTPAEVSHRFRELMQLF
                           ************ **::**.  **: :: ******.:***.**::*::**

gon4lb_NP_001188464.1      HTSASQASSEDEAAEQQSATDEEQD------------
gon4la_XP_003200651.2      HKSSKLHHTPDNWTQ----------------------
GON4L_NP_001269789         HTACEASSEDEDDATSTSNADQLSDHGDLLSEEELDE
                           *.:..     :: :
```

Supplementary Figure 6 Protein sequence alignment of GON4L and Gon4la/b

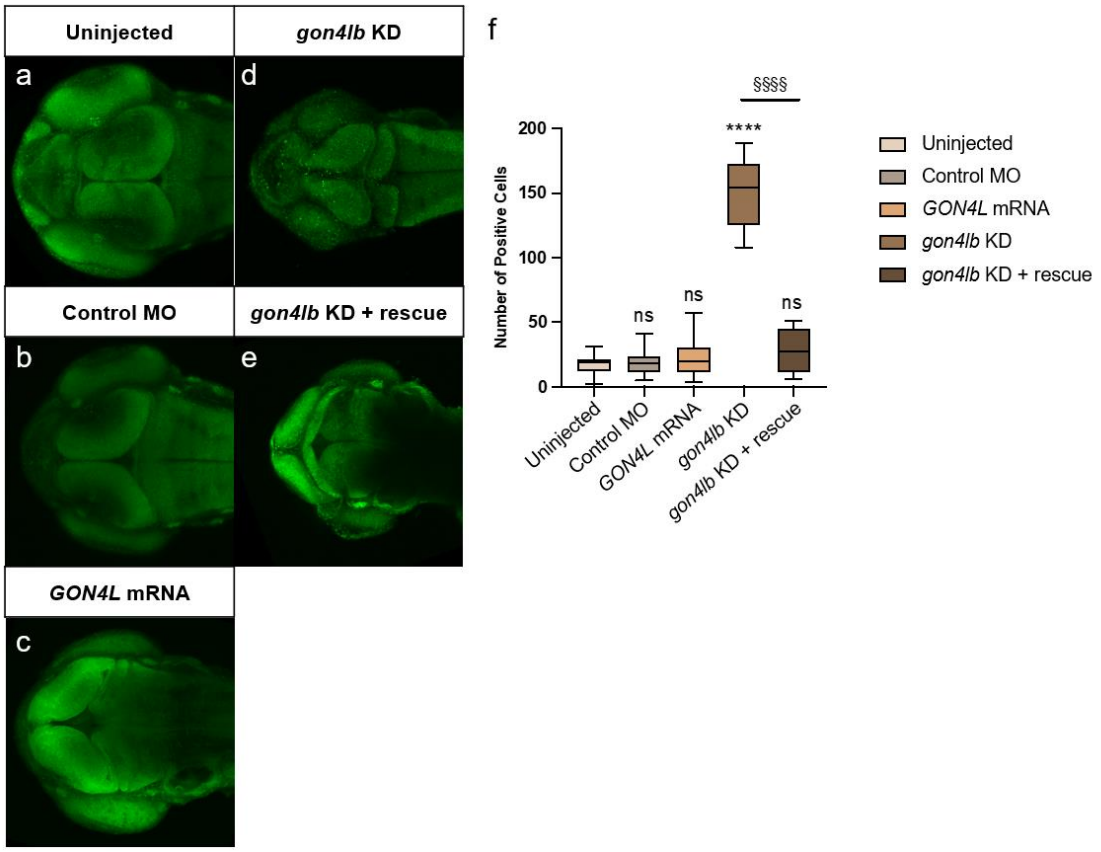
This alignment was analyzed with Clustal W (https://www.genome.jp/tools-bin/clustalw).



Supplementary Figure 7 *gon4lb* antisense morpholino oligo knockdown and rescue in zebrafish embryos at 50 hpf

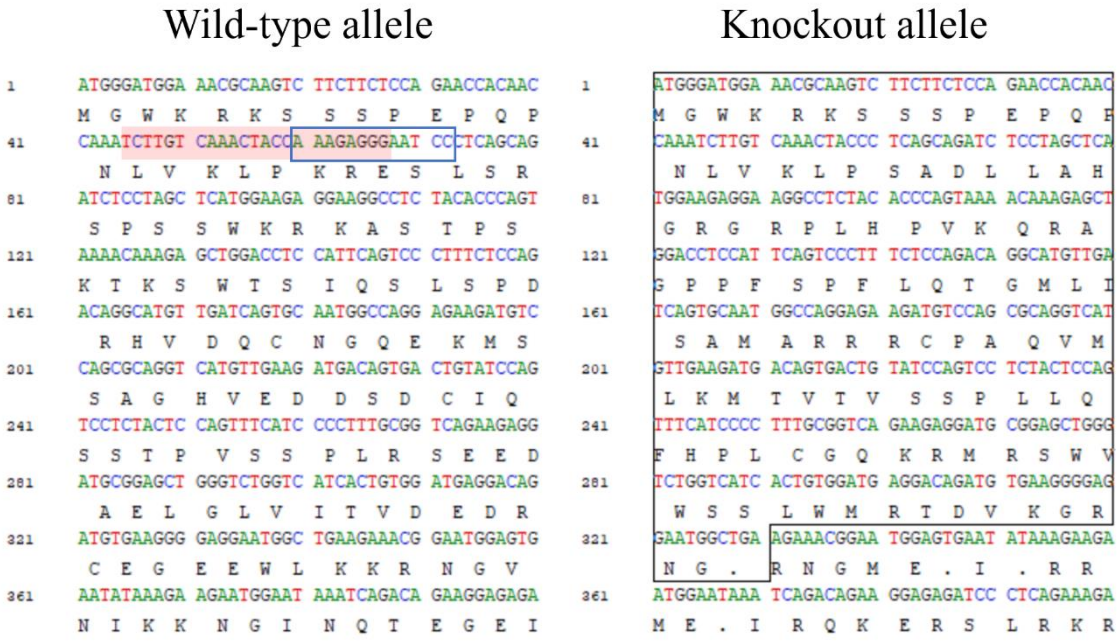
(a–d) Representative images of eye size, head size, and body length of 50-hpf zebrafish embryos injected with a standard control morpholino oligo (a, c) or a *gon4lb* morpholino oligo (b, d). The green and red lines in panels a and b delineate the contour of the head and eye, respectively, and red lines in panels c and d indicate the position for measuring the body axis. For head and eye size, uninjected wild-type: n=28, control MO: n=16, human *GON4L* mRNA: n=16, *gon4lb* MO: n=26, and *gon4lb* + human *GON4L* mRNA (rescue): n=20. For body length, uninjected wild-type: n=33, control MO: n = 28, human *GON4L* mRNA: n = 34, *gon4lb* MO: n = 30, and *gon4lb* MO + rescue: n=28. All images presented in a-d are dorsal views, with the anterior surface at the top. (e-g) Quantitative data showing eye size (e), head size (f), and body length (g). *gon4lb*-knockdown morphants showed reductions in eye size (26%), head size (26%), and body length (35%) compared with uninjected embryos, while embryos injected with the standard control MO did not display any abnormal changes. Co-injection of human *GON4L* mRNA and *gon4lb* MO into embryos restored eye size, head size, and body length. (h) Representative images

of wholemount zebrafish embryos immunostained with a HuC/HuD monoclonal antibody at 50 hpf. Images presented in h are ventral views, with the anterior side at the top. (i) Quantitative data showing the HuC/HuD-positive area of 50-hpf embryos (uninjected wild-type: n=29, control MO: n=18, human *GON4L* mRNA: n=20, *gon4lb* MO: n=16, and *gon4lb* MO + rescue: n=16). This phenotype was rescued by injection of human *GON4L* mRNA (a 30% recovery compared with the *gon4lb* MO group, $p = 0.003$). Furthermore, injection of human *GON4L* mRNA into zebrafish embryos did not result in any specific changes in brain area compared with uninjected embryos. Scale bar: 50 µm (a, b, h), 200 µm (c, d). Data are shown as the mean ± SEM; *$p \leq 0.05$, §§$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$, §§§§$p \leq 0.0001$ using one-way ANOVA with post hoc Tukey's test.



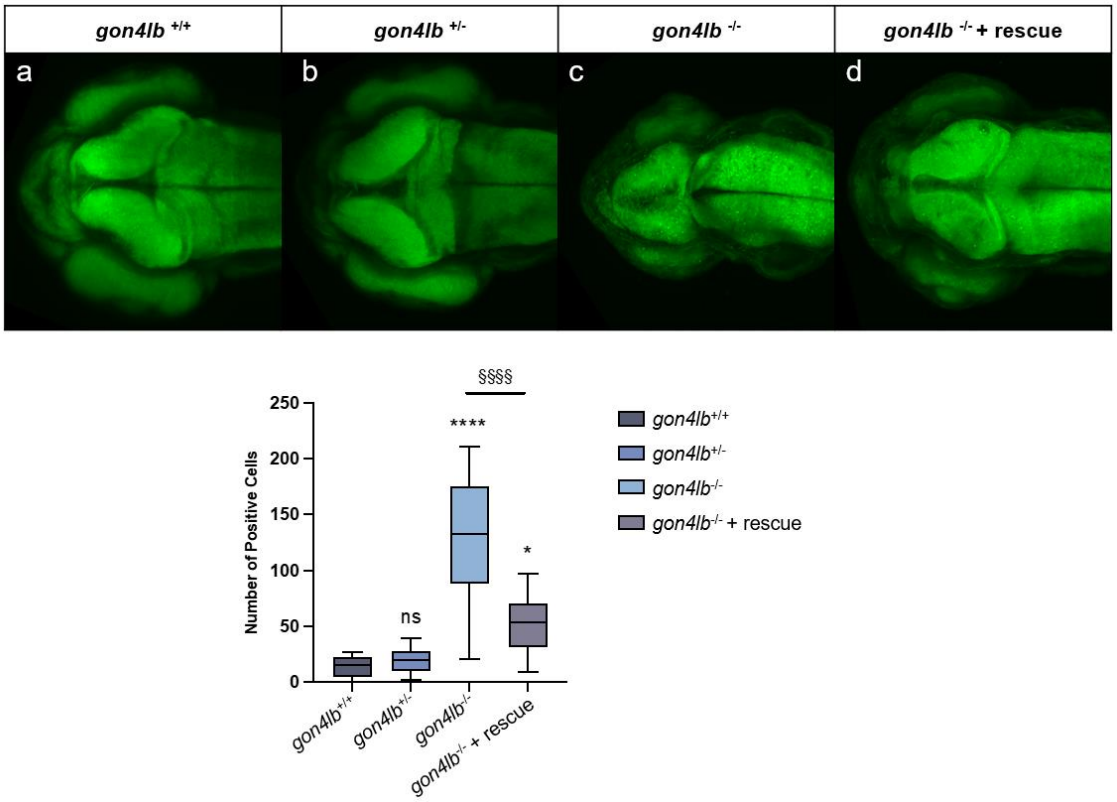
Supplementary Figure 8 Antisense morpholino oligo knockdown of *gon4lb* causes cell death in the brain and eye of zebrafish embryos at 50-hpf.

(a–e) Representative images of 50-hpf zebrafish embryos stained with Acridine Orange, where (a) is uninjected wild-type, (b) is injected with control morpholino oligo (MO), (c) is injected with human *GON4L* mRNA, (d) is injected with *gon4lb* MO, and (e) is co-injected with *gon4lb* MO and human *GON4L* mRNA for rescue. All images are dorsal views with the anterior aspect to the left. (f) Quantitative data of the number of Acridine Orange-positive cells in the head region of 50-hpf zebrafish embryos. Sample numbers are as follows: uninjected wild-type (n = 10), control MO (n = 10), human *GON4L* mRNA (n = 12), *gon4lb* MO (n = 11), and *gon4lb*+human *GON4L* mRNA (n=11). Data are shown as the mean ± SEM; ****$p \leq 0.0001$; §§§§$p \leq 0.0001$ using one-way analysis of variance (ANOVA) with post hoc Tukey's test.



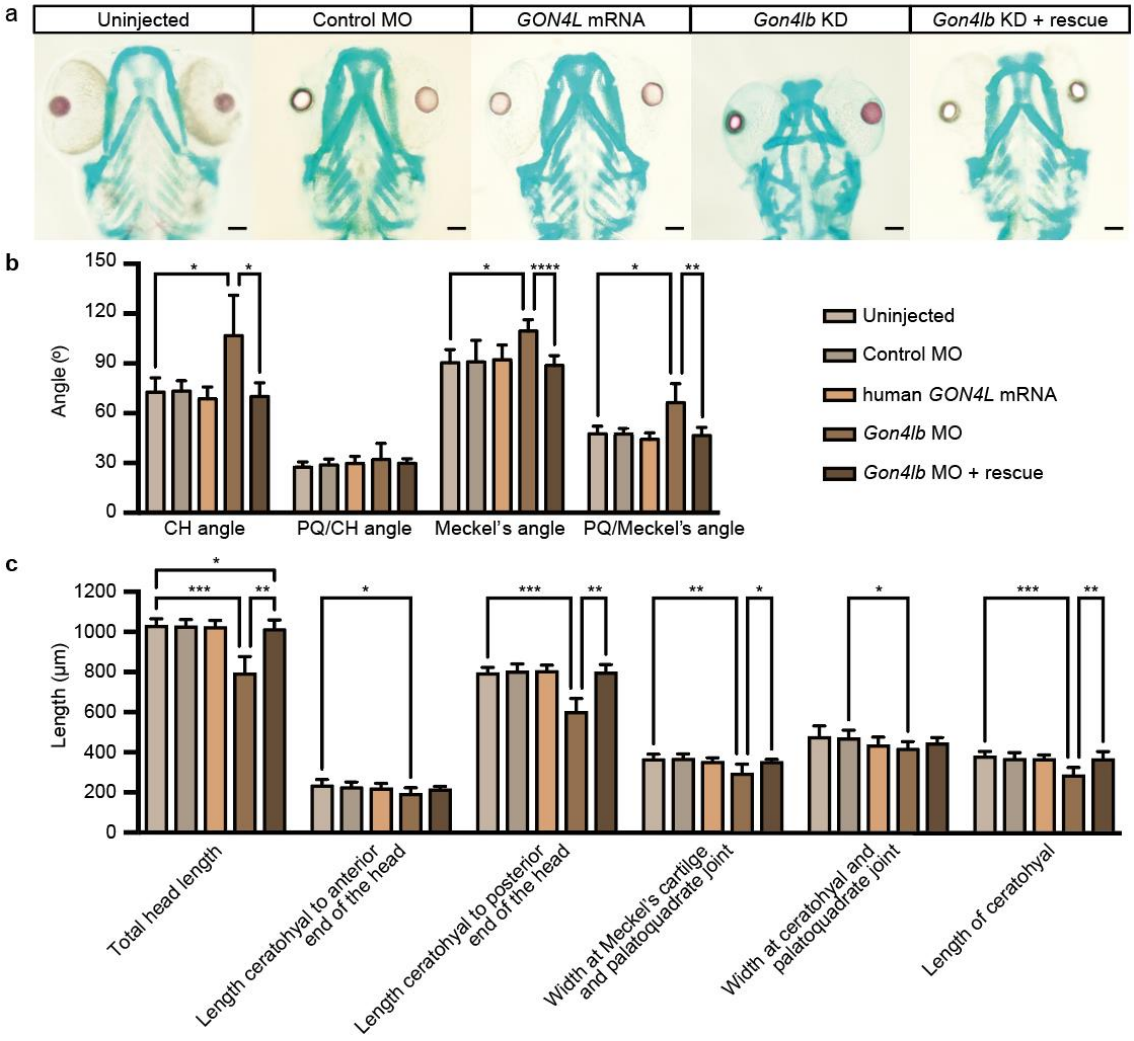
Supplementary Figure 9 Predicted mRNA and protein sequences of the zebrafish *gon4lb*-knockout allele

Left and right panels show wild-type and knockout sequences and encoded amino acid residues of the first part of the cDNA sequence of zebrafish *gon4lb* (NM_001201535). The red heighted region is the CRISPR/Cas9 knockout target region. The blue box indicates the 13 bp deletion (c.60_72del). The premature stop codon in the knockout allele is represented as a dot within a boxed region in the right panel.



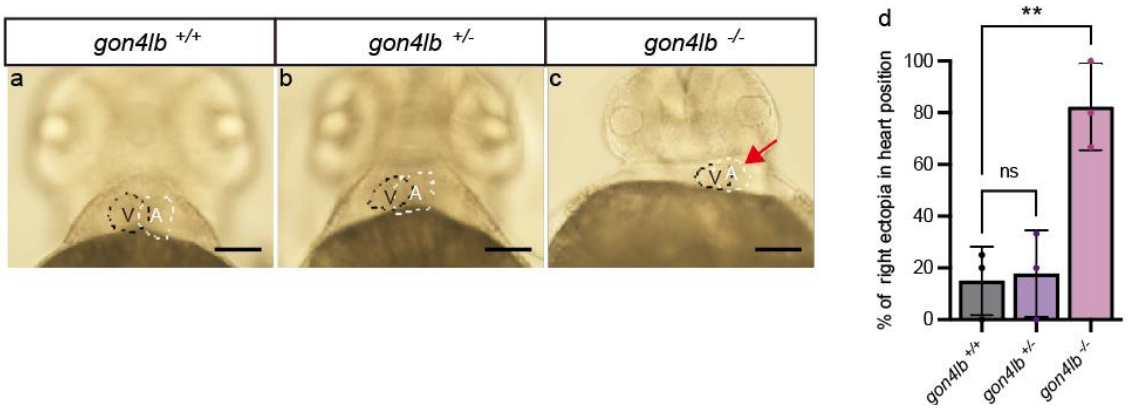
Supplementary Figure 10 *gon4lb*$^{-/-}$ zebrafish embryos show increased cell death in the brain and eye, which is rescued by human *GON4L* mRNA co-injection.

(a–d) Representative images of 50-hpf zebrafish embryos from the *gon4lb*-knockout line stained with Acridine Orange: (a) *gon4lb*$^{+/+}$, (b) *gon4lb*$^{+/-}$, (c) *gon4lb*$^{-/-}$, and (d) *gon4lb*$^{-/-}$ embryos injected with human *GON4L* mRNA. All images are dorsal views with the anterior aspect to the left. (e) Quantitative data show the number of Acridine Orange-positive cells in the head region of 50-hpf zebrafish embryos from the *gon4lb*-knockout line. Sample numbers are as follows: *gon4lb*$^{+/+}$ (n = 10), *gon4lb*$^{+/-}$ (n = 11), *gon4lb*$^{-/-}$ (n = 11), and *gon4lb*$^{-/-}$ embryos injected with human *GON4L* mRNA (n=13). Data are shown as the mean ± SEM; *p ≤ 0.05; ****p ≤ 0.0001, §§§§p ≤ 0.0001 using one-way ANOVA with post hoc Tukey's test.



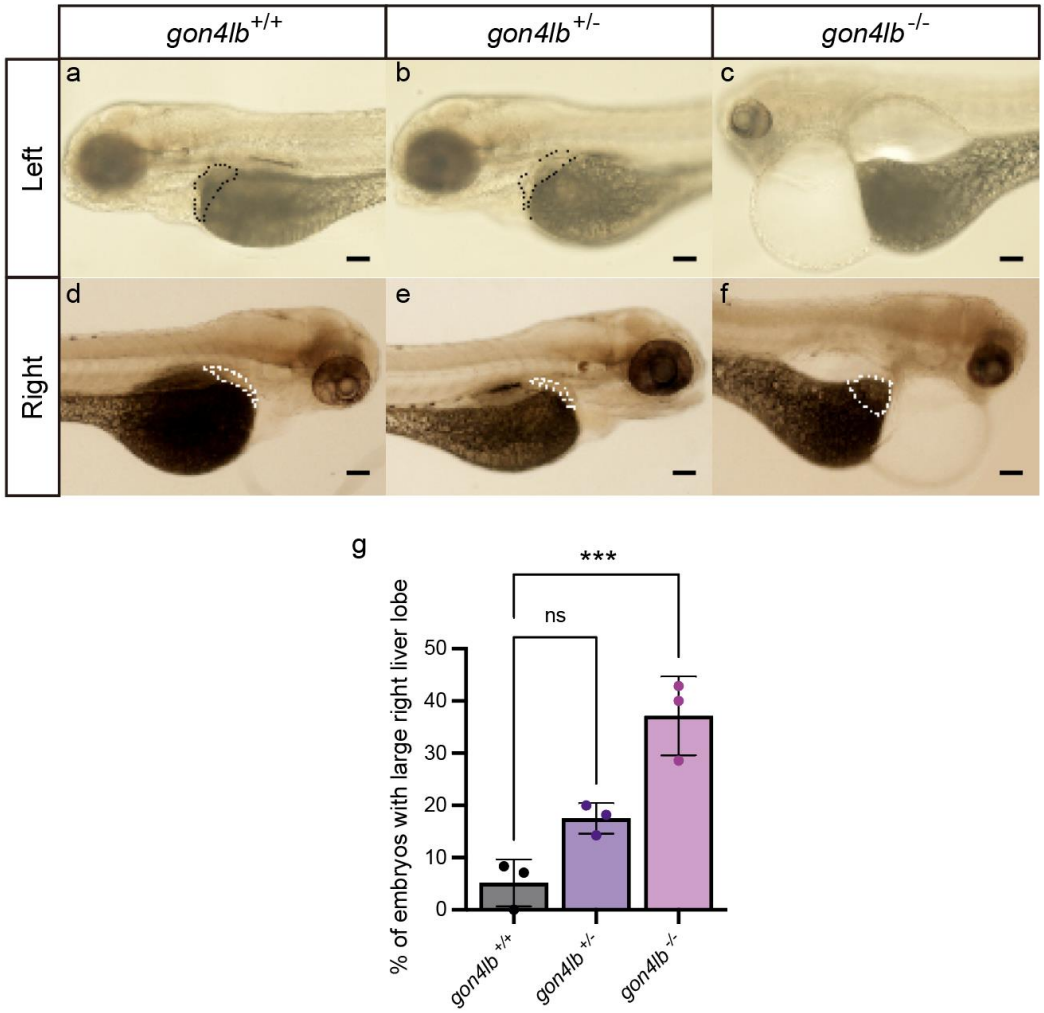
Supplementary Figure 11 *gon4lb* antisense MO knockdown causes abnormal craniofacial development

(a) Representative images of head cartilage from 5-dpf zebrafish embryos stained with Alcian blue and Alizarin Red (10 embryos each). All images are ventral views, with the anterior aspect at the top. Scale bar: 100 µm. (b,c) Quantitative data show the angle of four different mineralized craniofacial bone elements (b) and the length of six different mineralized craniofacial bone elements (c) from 5-dpf zebrafish embryos. Data are shown as the mean ± SEM; *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001; ****p ≤ 0.0001 using two-way ANOVA with Tukey's multiple comparisons test (α = 0.05).



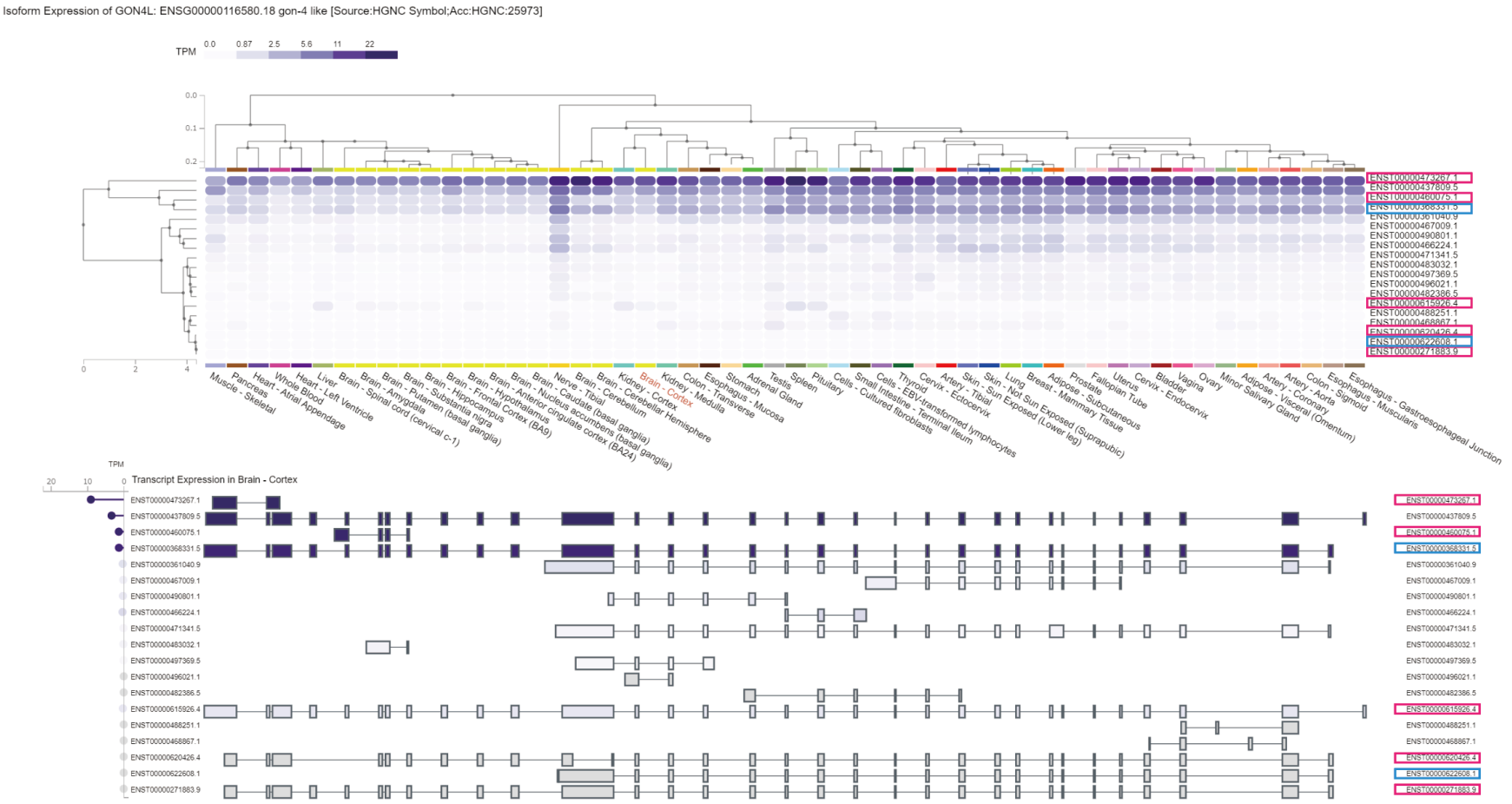
Supplementary Figure 12 Left-right heart displacement induced by *gon4lb* gene knockout

(a-c) Representative images of heart positioning in zebrafish embryos at 48 hpf under light microscopy. Most embryos of *gon4lb*$^{+/+}$(a) and *gon4lb*$^{+/-}$(b) genotypes exhibit normal left-sided heart positioning. A subset of *gon4lb*$^{-/-}$(c) embryos display abnormal right-sided heart positioning as indicated by a red arrow. The boundaries of the atrium and ventricle are outlined with white and black dashed lines, respectively. All images are ventral views with anterior at the top. Scale bar: 100 μm. Abbreviations: (A) atrium, (V) ventricle. (d) Percentage of embryos exhibiting left-right heart displacement anomalies at 48 hpf. Sample sizes are *gon4lb*$^{+/+}$ (n=14), *gon4lb*$^{+/-}$ (n=13), *gon4lb*$^{-/-}$ (n=15). Data are presented as mean ± SEM; ns, not significant; **p < 0.01; analyzed using one-way analysis of variance (ANOVA) with Tukey's post hoc test.



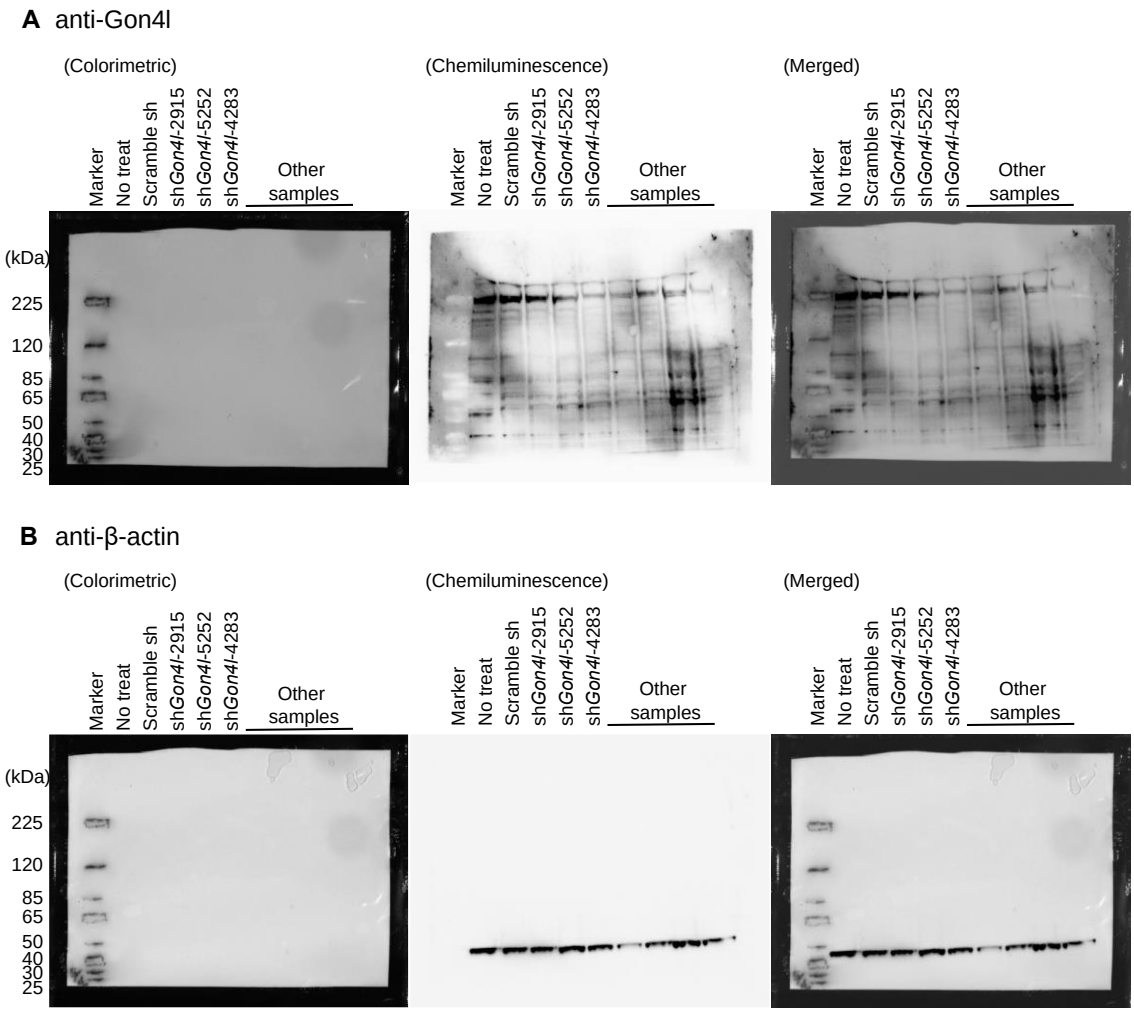
Supplementary Figure 13 Left-right liver displacement induced by *gon4lb* gene knockout

(a-f) Representative images of liver positioning in zebrafish embryos at 5 dpf under light microscopy, shown in left lateral views (a-c) and right lateral views (d-f). In most embryos of *gon4lb*$^{+/+}$ (a and d) and *gon4lb*$^{+/-}$ (b and e) genotypes, the left lobe of the liver is significantly larger than the right lobe; however, in a subset of *gon4lb*$^{-/-}$ (c and f) embryos, the right liver lobe is observed to be larger than or equal to the left lobe. The liver boundaries are delineated by black and white dashed lines in left (a-c) and right (d-f) lateral views. Liver is not observed in left lateral view of panel c. All images are lateral views, with anterior to the left in (a-c) and anterior to the right in (d-f). Scale bar: 100 μm. (G) Percentage of embryos displaying abnormal right lobe equal to or larger than the left lobe at 5 dpf. Sample sizes are *gon4lb*$^{+/+}$ (n=31), *gon4lb*$^{+/-}$ (n=26), *gon4lb*$^{-/-}$ (n=19). Data are presented as mean ± SEM; ns, not significant; ***$p < 0.001$; analyzed using one-way analysis of variance (ANOVA) with Tukey's post hoc test.



Supplementary Figure 14 Human *GON4L* expression in GTEx portal

Isoform-specific expression of human *GON4L* in all tissues (upper panel) and brain cortex (lower panel) is shown. Isoforms were annotated using Ensembl. The isoforms boxed with pink and blue lines correspond to long and short isoforms based on the coding protein length, respectively. Among them, ENST00000368331.5 is equivalent to one of three long isoforms NM_001262860.2.



Supplementary Figure 15 Uncropped blots of Western blotting showing *Gon4l*-knockdown efficiencies in PC12 cells

Uncropped blots from Figure. 3C. Representative blot images were shown (three independent experiments). Colorimetric and chemiluminescent images were detected and merged with a ChemiDoc Touch imaging system (BioRad).

Supplementary Table 1 *GON4L*-related facial characteristics and other features

	Patient 1	Patient 2	Patient 3	Sum
Facial asymmetry*	-	+	+	3
Long face	+	+	+	3
High forehead	+	+	+	3
Thick eyebrows	-	+	+	2
Downslanted palpebral fissures	+	+	+	3
Strabismus	NA	+	+	2
Broad nasal root	-	+	+	2
Broad nose	-	+	+	2
Beaked tip	+	+	-	2
Bulbous tip	-	-	+	1
Deviated nasal septum	-	+	+	2
Prominent cheek	-	+ (left)	+ (right)	2
Short philtrum	-	+	-	1
Long and prominent philtrum	-	-	+	1
Broad chin	-	+	-	1
Pointed chin	+	-	+	2
Low-set ears	-	+	+	2
Folded helix	-	+	+	2
Situs inversus totalis	-	+	+	2

NA: Not assessed

*except for eyes