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Supplemental Data

Biallelic Variants in *TTLL5*, Encoding a Tubulin Glutamylase, Cause Retinal Dystrophy

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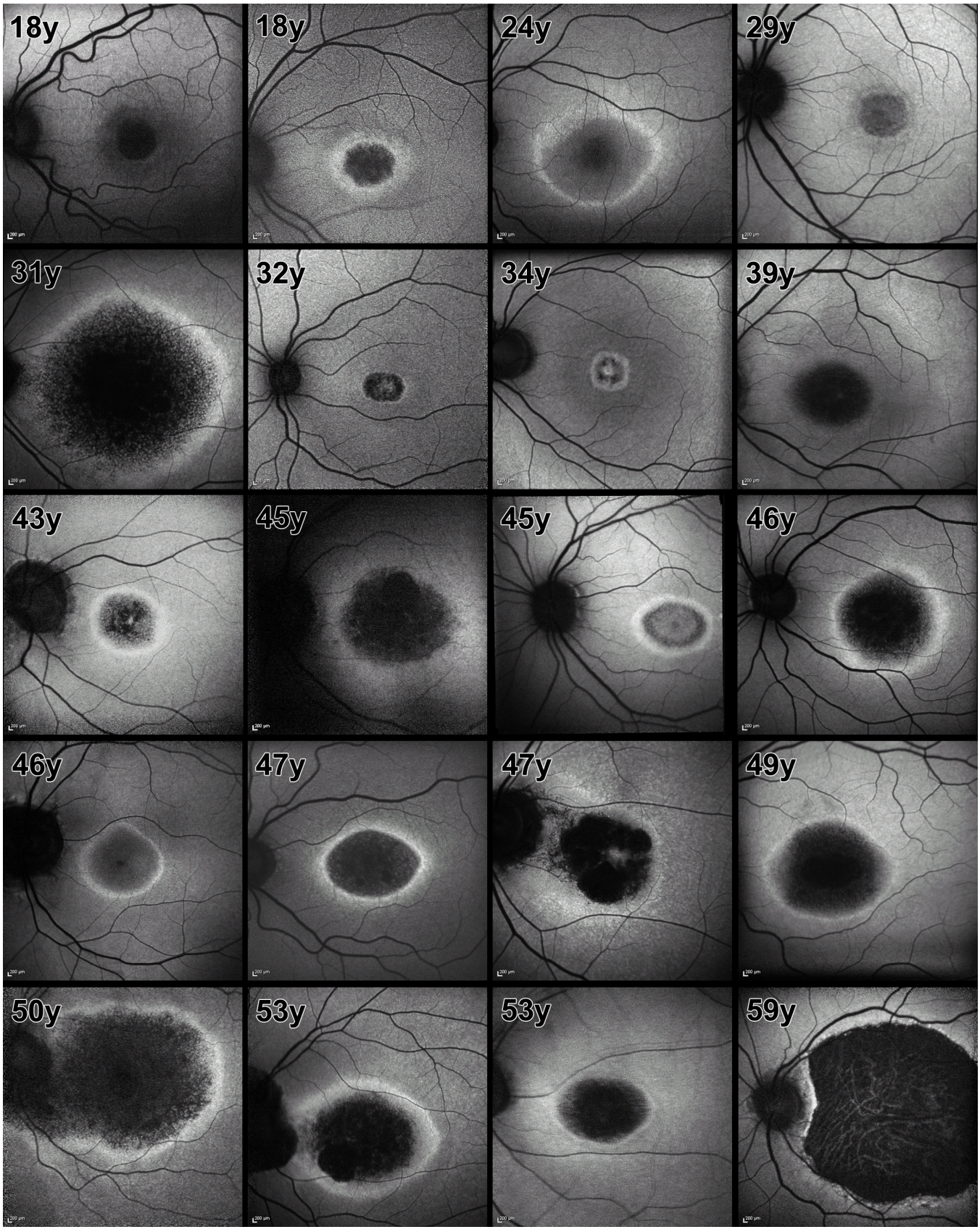
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Figure S1. Fundus autofluorescence (FAF) images of 20 individuals with: [i] a retinal dystrophy with early cone photoreceptor involvement, [ii] no previous genetic testing or an unknown molecular diagnosis after previous genetic screening, [iii] absence of fundoscopic features suggestive of *ABCA4*-retinopathy (yellow-white flecks and/or peripapillary sparing). Exome sequencing was performed in all these as well as eight additional cases with a similar phenotype (including subjects CD1 and CD2). FAF imaging uses naturally occurring fluorescence to map metabolic changes at the level of the retinal pigment epithelium. The FAF pattern observed in these 20 individuals is not unlike that seen in retinopathy due to dominant mutations in *GUCY2D* [MIM *600179], *PROM1* [MIM *604365], *RIMS1* [MIM *606629] and *CRX* [MIM *602225], and recessive mutations in *KCNV2* [MIM *607604]. Retinopathy due to mutations in *PRPH2* [MIM *179605], *ABCA4* [MIM *601691] and *RPGR* [MIM *312610] should also be in the differential although the presentation would be atypical for these.

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Human           MPIVMARDLEETASSSEDEE-VISQED----HPCIMWTGG-CRRIPVLVFHADAILTKDN 54
Mouse           MPVVMARDLEETASSSEDED-LANQED----HPCIMWTGG-CRRIPVLVFHAEAILTKDN 54
Chicken         ----MARGLEESGSSSEEEEEEEDAGDGLLDHPCIRWTGGGCRRIPIFVFHADAILTNDS 56
Lizard          MPVGMARDLEETDSSSEEEEEVEGPGE----HPCITWTGG-FRRIPILVFHADAIITKDS 55
Pufferfish      ----------------------LCSHRD----NPCVAWCGL-SRSIPVLLFFPEAAVSKDG 34
Frog            ----MVPRGQQDEQSEEDDD--SKKGE----YSCILWAGG-SRKVPIVMFHAEAVLHKNL 49
                                      :     .*: * *   * :*:.:*..:* : ::

Human           NIRVIGERYHLSYKIVRTDSRLVRSILTAHGFHEVHPSSTDYNLMWTGSHLKPFLLRTLS 114
Mouse           NIRVIGERYHLSYKIVRTDSRLVRSILTAHGFHEVHPSSTDYNLMWTGSHLKPFLLRTLS 114
Chicken         YLRLIGERYHLSYKIVRTDSRLVRSILTAHGFHEVHPNSSDYNLMWTGSHLKPYLLRSLT 116
Lizard          YTRLIGERYRLAFKIVRTDSRLVRSILSAHGFREVHPSSNEYNLMWTGSHLKPYVLRSLT 115
Pufferfish      RISSTGERYHMAFKIVRTESRLVRGILANHGFREVHQNSNDFNLMWSGSHLKPYMLRNLQ 94
Frog            SLRAVGERYKLSYKIVRTDSRLVRSILSAHGFQEVNANSNDFNIMWTGSHVKPYIMRSLT 109
                     ****:::*****:*****.**: ***:**: .*.::*:**:***:**:::*.*

Human           EAQKVNHFPRSYELTRKDRLYKNIIRMQHTHGFKAFHILPQTFLLPAEYAEFCNSYSKDR 174
Mouse           EAQKVNHFPRSYELTRKDRLYKNIIRMQHTHGFKAFHILPQTFLLPAEYAEFCNSYSKDR 174
Chicken         DIQKVNHFPRSYELTRKDRLYKNVSRMQLSHGFKTFHILPQTFILPAEYQEFCSTYSKDR 176
Lizard          DIQKVNHFPRSYELTRKDRLYKNINRMQQTYGFKSFHVLPQTFILPAEYQEFCNSYAKDR 175
Pufferfish      DFQKVNHFPRSYELTRKDRLYKNIQRMQQAHGFKDFHIVPQTFVLPYEYQEFCNSFAKDR 154
Frog            NFQKVNHFPRSYELTRKDRLYKNVQRMQQSHGFKNFHLLPQTYLLPAEYQDFCTAFAKDR 169
                : ********************: *** ::*** **::***::** ** :**.:::***

Human           GPWIVKPVASSRGRGVYLINNPNQISLEENILVSRYINNPLLIDDFKFDVRLYVLVTSYD 234
Mouse           GPWIVKPVASSRGRGVYLINNPNQISLEENILVSRYINNPLLIDDFKFDVRLYVLVTSYD 234
Chicken         GPWIVKPVASSRGRGVYLINNPNQIVLEDNILVSRYINNPLLIDDFKFDVRLYVLVTSYD 236
Lizard          GPWIVKPVASSRGRGVYLINSPNQISLEENILVSRYINNPLLIDDFKFDVRLYVLVTSYD 235
Pufferfish      GPWIIKPVASSRGRGIYLVSNPTQISVDDNILVSRYINNPLLIDEFKFDVRLYVLVTSYD 214
Frog            GPWIVKPVASSRGRGVYLINSPSLISMEDNILVSRYIGNPLLIDGFKFDVRLYVLITSYD 229
                ****:**********:**:..*. * :::********.****** **********:****

Human           PLVIYLYEEGLARFATVRYDQGAKNIRNQFMHLTNYSVNKKSGDYVSCDDPEVEDYGNKW 294
Mouse           PLVIYLYEEGLARFATVRYDQGSKNIRNQFMHLTNYSVNKKSGDYVSCDDPEVEDYGNKW 294
Chicken         PLVIYLYEEGLARFATVRYDQASKNIKNQFMHLTNYSVNKKSGDYVSCDDPEVEDYGNKW 296
Lizard          PLLVYLYEEGLARFATVRYDQGAKNIKNQFMHLTNYSVNKKSGDYVSCDDPEVEDYGNKW 295
Pufferfish      PLLIYVYEEGLARFATVKYDQTSKNIKNTFMHLTNYSVNKKSSDYVSCDDPEVEDYGNKW 274
Frog            PLVIYLYEEGLTRFATAKYDRAAKNIKNQFMHLTNYSVNKKSGDYVSCDDPDVEDYGNKW 289
                **::*:*****:****.:**: :***:* *************.********:********

Human           SMSAMLRYLKQEGRDTTALMAHVEDLIIKTIISAELAIATACKTFVPHRSSCFELYGFDV 354
Mouse           SMSAMLRYLKQEGKDTTALMAHVEDLIIKTIISAELAIATACKTFVPHRSSCFELYGFDV 354
Chicken         SMSAMLRYLKQEGRDTAALMASVEDLIIKTVVSAELAIATACKTFLSHRGSCFELYGFDV 356
Lizard          SMSAMLRYLKQEGKDTTALMASVEDLIIKTILSAELAIASACKAFVPHRGVCFELYGFDV 355
Pufferfish      SMSAVLRYLKQEGKDTTLLMRQVEDLIIKAIMGAEQQIATACKTFVPHKTNCFELYGFDV 334
Frog            SMSAMLRYLKQDGKDTAALMSQVEDLIIKTIVSAELPIASACKSLITHRGNCFGMRGLSI 349
                ****:******:*:**: **  *******:::.**  **:***:::.*:  ** : *:.:

Human           LIDSTLKPWLLEVNLS-----PSLACDAPLDLKIKASMISDMFTVVGFVCQDPAQRASTR 409
Mouse           LIDNTLKPWLLEVNLS-----PSLACDAPLDLKIKASMISDMFTVVGFVCQDPAQRTSNR 409
Chicken         LIDDTLKPWLLEVNLS-----PSLACDAPLDLKIKASMLSDMFTLVGFVCQDPGQRSS-R 410
Lizard          LIDSTLKPWLLEVNLS-----PSLACDAP-DLKIKASMISDMFTLVGFVCQDPGQRLN-R 408
Pufferfish      LIDANLKPWLLEVNLS-----PSLACDAPLDLKIKASMIADMFSLVGFVCQDPLSRQS-R 388
Frog            CLRGVLRPTMLTIFFQIFEGIPSLYIDAPLDLKVKASMISDMFTLVGVECQDPQQRFG-- 407
                 :   *:* :* : :.     ***  *** ***:****::***::**. **** .* .

Human           PIYPTFESSRRNPFQKPQR--------------CRPLSASDAEMKNLVGSAREKGPGKLG 455
Mouse           SIYPSFESSRRNPFQKPQR--------------TRPLSASDAEMKNLVASAREKVPGKLG 455
Chicken         TVYHSSESVRRNPYQKLQRPASAQSQPTNTRMRTRPLSASDVEMKNLMSSGREKATGRQG 470
Lizard          TSFYSS-EARRNPYQKPQRPVSAQSRSTNAKLRSRPLSASDAEMKNLMSSAKEKIPGRHV 467
Pufferfish      SERVTLEPSLKHPAAQRTQ------------VLERPLSEPTAAKNGRVAGSKDKLAVKQ- 435
Frog            ---RASSSLYDKRTQKSTH--------------QRPLSANDIDT-GLQVGNREK-AVRRT 448
                    :     :   :  :              ****       .   . ::* . :
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Human           GSVLGLSMEEIKVLRRVKEENDRRGGFIRIFPTSETWEIYGSYLEHKTSMNYMLATRLFQ 515
Mouse           GSVLGLSMEEIKVLRRVKEENDRRGGFIRIFPTSETWEIYGSYLEHKTSMNYMLATRLFQ 515
Chicken         SSVLGLSMEEIKVLRRVRDENERRGGFIRIFPTPLTWDLYGSFLEYKTSMNYMLATRLFQ 530
Lizard          GSMLGLSMEEIKVLRRVKDEYERRGGFIRIFPTPITWDTYGSFLEHKTTMNYMLATRLFQ 527
Pufferfish      ESTLSLTAEEIKVLRRIQEEYERRGGFIRIFPTAETWELYGEYLESKTSMNYTVANRLFH 495
Frog            SCLLGLSIEELKILRRVQDEYERRGGFVRIFPRHNTWQLYGSFLEYKTSLNYMLVTHLFP 508
                 . *.*: **:*:***:::* :*****:****   **: **.:** **::** :..:**

Human           DR-------------MTADGAPELKIESLNSKAKLHAALYERKLLSLEVRKRRRRSSRLR 562
Mouse           DRGNPRRSLLTGRARVSTEGAPELKVESMNSKAKLHAALYERKLLSLEVRKRRRRSGRLR 575
Chicken         DRDKMKGDLITG----RSREDLSGRLDTNLEAVDSHSLFYERKLVSLELRKRRRCRTKAR 586
Lizard          DPCNAE----------PSRE-LG--LDVVDCNAQLHAALYERKLLSLEVRKRRRRHGKLR 574
Pufferfish      GRLGMGNKSLHK--FMERGNVSGNVQLQVESFHDCHVIQYERKLLTLETHKRRRHRLTSR 553
Frog            NR------------------AAGNDHCEKNWDPRMHAAFYERKLVSLHLR-RARHRGLTR 549
                .                                 *   *****::*. : * *     *

Human           AMRPKYPVITQPAEMNVKTETESEEEEEVALDNEDEEQEASQEESAGFLRENQAKYTPSL 622
Mouse           AMRPKYPVIAQPAEMNIKTETESEEEEEVGLDNDDEEQEASQEESAGSLGENQAKYTPSL 635
Chicken         AAQTRSSGTSQPTKLSLT-DTEGEEEEEAAD--EDEE----QDGTLGSLSNSQLKSKPKL 639
Lizard          PRRSRLSGALQSTDFALKSEMECEEEEETTE--EDEEPEIPQNETADCLKNMKVKSKPQL 632
Pufferfish      SAAGKRK-SGSSQNLFQKCLSESKTSLTLSG----------SQEAEECAQEEREEVKAVL 602
Frog            KTGLSHAPQCSDHEQSSKEQEEQEEEEELDEN------------------------HEL 584
                          .  .   .   * : .                               *

Human           TALVENTPKENSM-KVREWNNKGGHCCKLETQELEPK-----FNLMQILQDNGNLSKMQA 676
Mouse           TVIVENSPRDNAM-KVAEWTNKGEPCCKIEAQEPESK-----FNLMQILQDNGNLSKVQA 689
Chicken         SELVKTASKERLT-EKLDKKTRNGGEPFLEKSDSKSQ-----FNLLQILKKDGNLSKVQA 693
Lizard          SEQVEPSHQGKLTKNQLEQKPKSEELPCESKLDTVPKSVELPFNLLQVLHENKNLSKVQA 692
Pufferfish      EPLSKRALEAELS-KQMAASLKRCQAEALSSSEAAAHNGGHKVSLLDVLQQGWDLSKVQA 661
Frog            EVVQEKVSSPDSS-KIIIPPPR--------------------ISLMDILRKGADLSKVQA 623
                    :        :     :                    ..*:::*:.. :***:**

Human           RIAFSAYLQHVQIRLMKDSGGQTFSASWAAKEDEQMELVVRFLKRASNNLQHSLRMVLPS 736
Mouse           RLAFSAYLQHVQIRLTKDSGGQTLSPSWAAKEDEQMELVVRFLKRASSNLQHSLRMVLPS 749
Chicken         RRAFSAYLQHVQLRLMKDVGDQFQNAAWAAKEDEQMELVVHFLKRAASNLQQSLRMLLPS 753
Lizard          RKAFSAYLHRVQLRLMKEAGDQVHNPAWAAKEDEQMELVVRFLKRAASNLQQSLRMLLPS 752
Pufferfish      RKAFSSYLQRVQQRLLAESR-TDAIPAWPDKDNDQMDLVIRFLKRAASNLQQDIQVAFPS 720
Frog            RNAFSCYLQRVQNRLQTERNPERVQP----KEEEQIELVMRFLQRGAANLKRSLPLNLPG 679
                * ***.**::** **  :       .    *:::*::**::**:*.: **::.: : :*.

Human           RRLALLERRRILAHQLGDFIIVYNKETEQMAEKKSKKKVE-------EEEEDGVNMENFQ 789
Mouse           RRLALLERRRILAHQLGDFIGVYNKETEQMAEKKSKKKLE-------EEEEDGVNAESFQ 802
Chicken         RHLGLNDRRRILAHQLGEFIICYNKETEQMIQKRSKKKQE-------EEEE-GVNPEGFQ 805
Lizard          RRLALFDRRRILAHQLGEFIICYNRETDQMAQKKLKQKQE-------EEEEEGVDPEGFH 805
Pufferfish      RQLPLQDRRRILSHQLGEFIHCYDQVFALPAKQQFKQETENIVKKQVSDGGLCVNAGVFQ 780
Frog            QSVPYLERRHLLAKLLGDFVALYNQETQQMQNSEETQSNE----------ECGVNPDDFE 729
                : :   :**::*:: **:*:  *::      :.. .:. *            *:   *.

Human           EFIRQASEAELEEVLTFYTQKNKSASVFLGTHSKISKNNNN--YSDSGAKGDHPETIMEE 847
Mouse           EFIRQASEAELEEVLTFYTQKNKSASVFLGTHSKSSKNSSS--YSDSGAKGDHPET-IQE 859
Chicken         NFITRASERDLEEVLTFYTQKNKSASVFLGTNSGTTKPRNTSNQSENQPQGDHPEVMKNT 865
Lizard          EFVIKASESDLEEVLTFYTHKNKSASVFLGTNPGTSKHSNS--QLENRGK----EVVKEN 859
Pufferfish      EYISAASEAELEEVLTFYTQKNKSSTVFLGAQGKSVRPKSCR-FSDAEAAVRQPSDRQEA 839
Frog            AFVADASENELEEVLTFYTQKNKSASVFLGTPNNADRRETG---KPPGGPQNRLTCERSV 786
                 ::  *** :*********:****::****:     :  .                .

Human           VKIKPP-------------KQQQTTEIHSDKLSRFTTSAEKEAKLVYSNSS----SGPTA 890
Mouse           VKIKQP-------------KQQQATEIHADKLSRFTTSSGKEAKLVYTNCSSFC-SPAAV 905
Chicken         KGDQAKSSVADLPVEGRVRVCKARVKSTLPEKS--TFSLNAEVKLPRCCPPSAASSASGA 923
Lizard          VAEELK--------DDQLKETRLSSNIHFPKQAGVTSSPEDENAPQLSFLSATSSSVPDA 911
Pufferfish      VTTQPEIQAP-------QHRSSFPATIDSADIQQHRRSASSATLPLYCLPP----PPPPP 888
Frog            VMSSAP----------------SQPSVSKPGYSQGCNVSDGPIIITNSAVN--------- 821
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Human           TLQKIPNTHLSS-VTTSDLSPGPCHHSSLSQIP--SAIPSMPHQP-TILLNTVSASASPC 946
Mouse           LLQRLPSSHLSSVITTSALSAGPGHHASLSQIP--PAVPSLPHQP-ALLLSPVPDNAPPS 962
Chicken         TFRRSTSSQLPSQPTASGNPQVPGHCSLPTPPSGLRLIHSSSSLPSSQSQSTATDCSSVF 983
Lizard          ILPQSISPQLPSHTAASDNAQLPDHLSGFSLSSGSRLIPSSS------FQNAAMDSWSST 965
Pufferfish      QLPSYAQSLAKSQFCYSERPPDPPAYASSAVVS------------------QPLGVSWTP 930
Frog            GLPESCSQRNSSTHVLSNDASLCSTIVGSNGIH--------------------VSPAKLT 861
                 :    .    *    *  .

Human           LHPGAQNIPSPTGLPRCRSGSHTIGPFSSFQSAAHIYSQKLSRPSSAKAG--SCYLNKHH 1004
Mouse           IHSGTQNVS-PAGLPRCRSGSYTIGPFSSFQSAAHIYSQKLSRPSSAKAAG-SCHPHKHH 1020
Chicken         TNPVSSEASSLAGLHRC-SGSYTIGPLSSFQRAAQIYSQRLSRSPSAKAGLRHRSPSGQR 1042
Lizard          TKNVPQLSSNNAGLHRCQSGSFTASPFSSFQSAMQIYSQRLTRPSSAKAGSRSHSPSRQR 1025
Pufferfish      VSTGKNPPNQVLRRIQSFTSSMSCGGASSLPRTMQLYSQKLSRPTSTIHS-FSCSPHESP 989
Frog            VTPGSWAKS------GSRPHSSSLGTFSSFQSAAQIYSQKLRRPSSTRSECNHVSVHCNY 915
                              . . * : .  **:  : ::***:* *..*:

Human           SGIAKTQKEGEDASLYSKRYNQSMVTAELQRLAEKQAARQYSPSSHINLLTQQVTNLNLA 1064
Mouse           SGIAKTQKEGEDVSLN-RRYNQSLVTAELQRLAEKQAARQYSPASHISLLTQQVTNLNLA 1079
Chicken         VSSIMMNKGTEDAPSLGKRYSPSMVAAELQQLAEKQAACQYSPPSHISLLTQQLTSLNLA 1102
Lizard          SAFARVTKDGEEC----KRFSHGVIAEELHRLAEKQATRQYCPPSHINLLTQQLTNLNLM 1081
Pufferfish      RGATPTFKELHPRPEP-TQSNQQAFLSALQKLADKQAARRYASSSHINLLTHHLTQMNLA 1048
Frog            PSLCANCTALNIP------EARNAFSCYLQRVQNRLQTERNPERVQPKEEEQILTSMNIK 969
                 .     .  .             .   *::: ::  : :     : .   : :*.:*:

Human           TGIINRSSASAPPTLRPIISPSG--PTWSTQSDPQAPENHSSSPGSRSLQTGGFAWEGEV 1122
Mouse           SSVINRSSASTPPTLRPVISPSG--PTWSIQPDLHASETHSSPPGSRSLQTGGFAWEGEV 1137
Chicken         SGAVSKGNAAVPPSYRSALNRKG--PLCTVQSDTLTDDRRCISSAVRAPESDRFAWEGEM 1160
Lizard          NGAVSRVNTTS--SYRPSLNPGG--SFWAFQTNTVIISNHDKPMQEMALETDRFAWEGDA 1137
Pufferfish      NRMLSRDGFALNPPVQRTAAPAAQRPEWAGQLMLYGDRVHVCLPTNRPQKDRDDAFKGQT 1108
Frog            DGAFGSGSFRH----CSAKSFCG---------RAVHAGTETVESITRDIQRRRSAWESDQ 1016
                   ..  .             .                .        :    *::.:

Human           ENNVYSQATGVVPQHKYHP-TAGSYQLQFALQQLEQQKLQSRQLLDQSRARHQAIFGSQT 1181
Mouse           ENNAYSKTTGVVPQHKYHP-TAGSYQLHFALQQLEQQKLQSRQLLDQSRARHQAIFGSQT 1196
Chicken         ENNVYGKVTRSPLAHP-------NYQLNLAVQQLQQQKLQSRQLLEQSQARHQALFASYS 1213
Lizard          ENSLHSKLIGSQPLHPKASSSTGSYQLHFALQQLQQQKLQSRQLLDQSRARHQALFANFP 1197
Pufferfish      QS-PYSLLTPMTPQQIKPP-APGSDQLQSAIKKLQQQSLRSRQFLDQSHRGQQALF---- 1162
Frog            ESGTFSFSSDVPLQHQ-------PDQMQYSAKGGQHPDSAIISLPNQTCTLLPTPPVSHK 1069
                :.  ..        :          *:: : :  :: .    .: :*:     :

Human           LPNSNLWTMNNGAGCRISSATASGQKPTTLPQKVVPPPSSCASLVPKPPPNHEQ-VLRRA 1240
Mouse           LPNSSLWTMNNGPGCRISSATTGGQKPNTLPQKVVAPPNS-STLVSKPASNHKQ-VLRKP 1254
Chicken         QSSTSHVPMSPGSGAHKTSSATSSIQKAASLHKVMPSQCTPSQLVPKPPANHRQAVVRKT 1273
Lizard          TSSISSITLSSGSGARRTSSAISSSQKASTLHKVMSSQSASSHLIPKPPASHRQTVIRKV 1257
Pufferfish      ------------------------------------------------------------
Frog            QSAARTLSATR--------------------------------LVRVAPVEQHG----TP 1093


Human           TSQKAS-KGSSAEGQLNGLQSSLN-PAAFVPITSSTDPAHTKI----------------- 1281
Mouse           ASQRAS-KGSSAEGQLNGLQSSLN-PAAFMPITNSTGSLEAPQVIFARSKPLPTQSGALA 1312
Chicken         AAQRIS-KVSSVERQLNGFQNSLRGAASCELGSNSTASACREGLALNTRRNPESCFQVWG 1332
Lizard          ASQRISNRAISMEGQMNGFQNSLDSATSCEPLTNSTGEAKIKK----------------- 1300
Pufferfish      ------------------------------------------------------------
Frog            TSTIVSDFGTPSQGSMEATQIIFARARPSAPKIDIKGQRK-------------------- 1133


Human           ----------------
Mouse           TVIGQRKSKSVKSGTI 1328
Chicken         KGKKQQ---------- 1338
Lizard          ----------------
Pufferfish      ----------------
Frog            ----------------
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Figure S2. Amino acid sequence alignment of TTLL5 orthologs from all branches of the vertebrate animal kingdom. Conservation of the p.Glu543 residue (highlighted in purple) that is mutated in subjects CD3, CD4 and CD5 is observed despite some sequence divergence elsewhere. The alignment was performed with ClustalW2 (EMBL-EBI, Hinxton, UK) using appropriate Ensembl transcripts

Table S1. Clinical and genetic findings from the 28 cases that were selected for exome sequencing

Family ID	Age tested, sex	Likely disease-causing gene (exome sequencing result)	Electrophysiological diagnosis	Genetic testing prior exome sequencing	Family history
gc18728 (CD1)	38,M	*TTLL5* p.[(Glu529fs)];[(Glu529fs)].	CD	*ABCA4* microarray.	No other affected; consanguinity.
gc19552 (CD2)	45,M	*TTLL5* p.[(Leu134fs)(;)(Trp1118*)].	CD	*ABCA4* microarray.	No other affected.
gc17090	18,F	Not known.	Not available (clinically MD).	None.	Sister affected.
gc15017	18,M	*ABCA4* p.[(Gly1961Glu)(;)(Asp295fs)].	MD	None.	Brother affected.
gc19458	24,F	*CRX* p.[(Arg43Cys)];[=].	MD	None.	No other affected.
gc17004	29,F	Not known.	MD	*ABCA4* microarray.	No other affected.
gc17898	31,F	*PROM1* p.[(Arg373Cys)];[=].	CRD	*ABCA4* microarray; *PRPH2* all exons.	Children & paternal uncle affected; consanguinity.
gc15235	32,F	Not known.	MD	*ABCA4* microarray; *PRPH2* all exons.	Two affected siblings.
gc19146	34,M	Not known.	CRD	*ABCA4* microarray.	No other affected.
gc17967	39,M	Not known.	CRD	None.	No other affected; consanguinity.
gc17988	43,M	*RPGR* p.[(Glu1060fs)];[0].	CRD	*GUCA1A* all exons.	No other affected.
gc4728	45,M	Not known.	MD	ABCA4 microarray.	No other affected.
gc16362	45,M	*ABCA4* p.[(Arg1843Gly)];[?].	MD	None.	No other affected.
gc19964	46,M	Not known.	MD	*PRPH2* all exons.	No other affected.
gc19080	46,M	*RPGR* p.[(Lys1106fs)];[0].	CD	None.	No other affected.
gc16258	47,M	Not known.	MD	ABCA4 microarray.	No other affected.
gc5342	47,F	Not known.	MD	None.	No other affected.
gc17836	49,M	Not known.	CD	None.	Sister affected; consanguinity.
gc19457	50,M	Not known.	RCD	None.	No other affected.
gc18729	53,M	*ABCA4* p.[(Gly1961Glu)];[?].	CD	*ADAM9* all exons; *RPGR* exon ORF15.	No other affected.
gc16711	53,M	*CRX* p.[(Arg91Lys)];[=].	CRD	*RS1* all exons.	No other affected.
gc16174	59,M	Not known.	MD	*ABCA4* microarray; *PRPH2* all exons.	No other affected.
gc18250	18,M	*CDH3* p.[(Asp523fs)][(Asp523fs)].	MD	None.	No other affected; consanguinity.
gc17784	19,M	*ABCA4* p.[(Asp1734Thr)];[?].	RCD	*RS1* all exons; genotyping array.	No other affected; consanguinity.
gc19018	50,F	Not known.	CRD	*RIMS1* exons 14-15; *GUCY2D* exon 13; *PRPH2* all exons.	Affected sister, father & paternal grandfather.
gc18280	56,F	*CRX* p.[(Tyr258*)];[=].	MD	*PRPH2* all exons.	Affected sister & son.
gc16966	63,M	Not known.	MD	*ABCA4* microarray; *PRPH2* all exons.	No other affected.
gc4055	74,M	Not known.	CD	All exons of *PRPH2*, *PROM1* & *RS1*.	Father affected.

CD, cone dystrophy; CRD, cone-rod dystrophy; RCD, rod-cone dystrophy; MD, macular dystrophy; *ABCA4* microarray, *ABCA4* APEX microarray (ABCR400 or ABCR600 chip, Asper Ophthalmics, Tartu, Estonia). All genes except *ABCA4* were screened using Sanger sequencing. Individuals with family IDs gc17898, gc19457, gc16711, gc19018 and gc18280 were excluded from the case-control analysis based on ancestry.

Table S2. Top five most significant autosomal genes: the total count of non-synonymous and splice altering rare variants was compared between probands with retinal dystrophy and internal controls

	Chromosome	Number of non-synonymous and splice altering variants cases[a] (n = 23)	Number of non-synonymous and splice altering variants in UCL-exomes controls[b] (n = 1,465)	Sequence Kernel Association Test (SKAT) P-value	Binomial P-value
TTLL5	14	9	50	0.00069	4.46e-7
KRTAP10-8	21	5	11	0.0036	1.54e-6
TPR	1	9	67	2.12e-4	2.73e-5
RTTN	18	7	37	1.21e-4	3.08e-5
MUC16	19	21	351	6.25e-4	4.09e-5

[a]Case group: 28 probands with [i] a retinal dystrophy with early cone photoreceptor involvement, [ii] an unknown molecular diagnosis after previous genetic screening or no previous genetic testing, [iii] absence of fundoscopic and fundus autofluorescence imaging features suggestive of *ABCA4*-retinopathy. Five of these 28 cases were excluded based on ancestry (Figure 2A).

[b]UCL-exomes control group: 1,750 individuals analyzed with using the same sequence variant calling strategy as the 28 retinal dystrophy cases. After [i] inferring ancestry based on the exome sequencing data and using a principal component analysis to exclude samples that did not cluster with the bulk of the UCL-exomes samples, which are predominantly of European origin, [ii] removing all samples with a history of retinal disease and [iii] excluding related control samples, we were left with 1,465 unrelated controls.

Genes are ranked based on the binomial P-value test which tests for equal proportion of non-synonymous and splice altering rare variants between cases and controls, against the alternative of an excess of the same class of variants in cases. To define “rare” variants we utilized two cohorts: a subset of 25% of UCL-exomes controls (366 unrelated control samples, randomly sampled and not included directly in the case-control analysis; minor allele frequency of <0.3%) as well as the NHLBI Exome Sequencing Project dataset (minor allele frequency of <0.1% was used).

Table S3. Prioritization of variants identified by exome sequencing in three probands with *TTLL5*-retinopathy

	subject CD1	subject CD2	subject CD3
All exonic variants	21,111	21,742	22,783
Total non-synonymous and splice altering rare[a] variants	450	485	716
Homozygous non-synonymous and splice altering rare[a] variants	11	9	47
Homozygous presumed loss-of-function rare[a] variants	3[b]	0	3[c]
Genes with two heterozygous presumed loss-of-function rare[a] variants	0	1[d]	0

[a]Rare variants: variants with: [i] minor allele frequency of <0.3% in 366 randomly sampled internal UCL-exomes controls and [ii] minor allele frequency of <0.1% in the ~6500 samples in the NHLBI Exome Sequencing Project dataset.
[b]c.[202G>T];[(202G>T)], p.[(Glu68*];[(Glu68*)] in ENST00000449873-*TBX15* [MIM *604127]; c.[1628_1631del];[(1628_1631del)], p.[(543_544del)];[(543_544del)] in ENST00000464606-*ZC3HAV1* [MIM *607312]; c.[1586_1589delAGAG];[(1586_1589delAGAG)], p.[(Glu529fs)];[(Glu529fs)] in ENST00000298832-*TTLL5* [MIM *612268].
[c]c.[321_322insAC];[(321_322insAC)], p.[(Thr107fs)];[(Thr107fs)] in ENST00000408995-*FHL2* [MIM 602633]; c.[91G>T];[(91G>T)], p.[(Glu31*)];[(Glu31*)] in ENST00000377294-*ZKSCAN4* [MIM *611643] and c.[1627G>T];[(1627G>T)], p.[(Glu543*)];[(Glu543*)] in ENST00000298832-*TTLL5* [MIM *612268].
[d]c.[401delT(;)3354G>A], p.[(Leu134fs)(;)(Trp1118*)] in ENST00000298832-*TTLL5* [MIM *612268].

Exome sequencing was performed using a solution-phase exome capture (SureSelectXT Human All Exon V5, Agilent, CA, USA) and the Illumina HiSeq2000 sequencer (Illumina, CA, USA). Reads were aligned to the hg19 human reference sequence using Novoalign version 2.07.19 (Novocraft, Selangor, Malaysia). Genome Analysis Tool Kit (GATK) version 2.7.4 and ANNOVAR (2013Nov17 version; Open Bioinformatics, MA, USA) were used for variant calling and annotation of single nucleotide polymorphisms and small insertions/deletions. Filtering of variants and case-control analysis were carried out using R scripts.

Each of these three individuals was born to consanguineous parents. Prior exome sequencing of DNA from subject CD3, homozygosity mapping in samples from subject CD3 and his affected brother (subject CD4) was performed (Human Mapping 50K Array Xba 240, Affymetrix, CA, USA). This had yielded four regions of shared homozygosity that were over 10 cM; *TTLL5* was in the largest shared chromosomal segment.

Table S4. Primer sequences and conditions used for *TTLL5* mutation screening

Primer name	Primer sequence	Primer name	Primer sequence
TTLL5_ex2F	tgtggcatattgaggcacat	TTLL5_ex18F	tgtcttttcctttgccactt
TTLL5_ex2R	ggcccagaaagagagcctta	TTLL5_ex18R	cccctccacttttttccaatc
TTLL5_ex3F	gggagatgtgatttcccaca	TTLL5_ex19F	ggtgttgggtggcactttat
TTLL5_ex3R	gggctggggatatctgctta	TTLL5_ex19R	aagagcaaaggccaaaatgt
TTLL5_ex4F	ggtgtaatttttccccccatc	TTLL5_ex20F	gagagtgacatgtgggtgct
TTLL5_ex4R	ctggtaaagccactccaaaa	TTLL5_ex20R	aaatgcccaaccaatgagac
TTLL5_ex5F	aaccctcccattccttgaac	TTLL5_ex21F	cataatagaagcatcctcaaaggcc
TTLL5_ex5R	gttgcagtgagccaagatca	TTLL5_ex21R	caaagatttgcttcacattgaag
TTLL5_ex6F	cactacaggggacttgagg	TTLL5_ex22F	ccttttgttctgggtcttg
TTLL5_ex6R	tgccagtgtgcccttacata	TTLL5_ex22R	ccactgggccttcagaagta
TTLL5_ex7F	cctccttccctcgctctatt	TTLL5_ex23F	cattctgcaacttttacttggg
TTLL5_ex7R	ttcctgccagtaaggcaaac	TTLL5_ex23R	catgaaaatagcaacataattggc
TTLL5_ex8F	tgggtaccttggaggaaact	TTLL5_ex24F	agaaaattcactgcgggatg
TTLL5_ex8R	aaggaacctgctgcctttct	TTLL5_ex24R	tactgtcccccattctccac
TTLL5_ex9F	cctccgaagtcaaggtgtgt	TTLL5_ex25F	ggctgtgggtgtcttcatct
TTLL5_ex9R	agcacagcagttgaggaggt	TTLL5_ex25R	ccccttcttttcacccttct
TTLL5_ex10F	gtccatgggttttggagttg	TTLL5_ex26F	gacatgcctgctctgtttca
TTLL5_ex10F	aatggagaagcagcaggaga	TTLL5_ex26R	gctactggatgcaatgcaaa
TTLL5_ex11F	agaaagaatttgccgccttc	TTLL5_ex27F	ggattctaggttatggtaacc
TTLL5_ex11R	cagcttgtcaactgcaggaa	TTLL5_ex27R	cttcacaatgcctgtaacag
TTLL5_ex12F	tcccttggcacctacattct	TTLL5_ex28F	tccttcctgagtgcctttgt
TTLL5_ex12R	ctcaggggacttctgaccaa	TTLL5_ex28R	cttagtcaggtgccagagga
TTLL5_ex13F	gcccataagcacagcagaat	TTLL5_ex29F	ggtttagtgggggagtgaga
TTLL5_ex13R	atggccctagatccaggttt	TTLL5_ex29R	actccccatgagctgtccaa
TTLL5_ex14F	tttttgcccaggatttttcc	TTLL5_ex30F	gctgcactggcaacattaga
TTLL5_ex14R	ggagccaagtgtcgtagaaa	TTLL5_ex30R	aatttgtagcccacgctgag
TTLL5_ex15F	gagggtgtgtgtgggagagt	TTLL5_ex31F	aggcccatgctttcttgata
TTLL5_ex15R	ctgtgccttgtttctgagca	TTLL5_ex31R	atgcccatttgccaatgttt
TTLL5_ex16F	gaatttgagcttataaatctttag	TTLL5_ex32F	gagctttccacttagaggtgaac
TTLL5_ex16R	gatagttatgacccaagaatatg	TTLL5_ex32R	cttttatatcatctctgtgcagcag
TTLL5_ex17F	gacaaactcatgtcttacattg	All primers work at 60°C. Ensembl transcript ID ENST00000298832 was used.	
TTLL5_ex17R	cacaaagtttaggacagtcccc		

Table S5. Presumed loss-of-function variants in *TTLL5* identified in the Broad 26K dataset (26,000 exomes) and the internal UCL-exomes control cohort (1,465 unrelated exomes)

***TTLL5* presumed loss-of-function variants**			**Broad 26K dataset allele count** (52,000 alleles)	**UCL-exomes control cohort allele count** (2,930 alleles)	**Cases**[a]
Genomic build position (hg19)	**Nucleotide**	**Protein**			
14:76156564	c.401delT	p.Leu134Argfs*45	0	0	heterozygous state in CD2
14:76165584	c.556delA	p.Arg186Glyfs*7	1	0	-
14: 76173403	c.629dupA	p.Tyr210*	1	0	-
14:76184249	c.789_793delGTTCA	p.Gln263Hisfs*19	1	0	-
14: 76200373	c.1166C>G	p.Ser389*	2	0	-
14: 76201609	c.1258C>T	p.Ala420*	1	0	-
14: 76211845	c.1408C>T	p.Arg470*	2	0	-
14: 76211872	c.1435C>T	p.Arg479*	1	0	-
14: 76219296	c.1548delC	p.Asp516fs*3	0	1	-
14: 76230991	c.1586_1589delAGAG	p.Glu529Valfs*2	0	0	homozygous state in CD1
14: 76231034	c.1627G>T	p.Glu543*	0	1	homozygous state in CD3 & CD4
14: 76231034	c.1627G>A	p.Glu543Leu	14	0	homozygous state in CD5
14:76231061	c.1654C>T	p.Arg552*	1	1	-
14:76232616	c.1920G>A	p.Trp640*	3	0	-
14:76238090	c.2029C>T	p.Arg677*	4	0	-
14:76238192	c.2132_2133insGATA	p.Met712Ilefs*15	1	2	-
14: 76241952	c.2264_2265dupTT	p.Ile756Leufs*29	1	0	-
14:76243171	c.2365C>T	p.Gln789*	1	0	-
14:76245995	c.2466dupT	p.Lys823*	3	0	-
14: 76249626	c.2739C>A	p.Cys913*	1	0	-
14:76249741	c.2854C>T	p.Gln952*	1	0	-
14: 76249777	c.2890C>T	p.Arg964*	1	0	-
14:76330011	c.3329delG	p.Ser1110Thrfs*13	1	0	-
14:76330037	c.3354G>A	p.Trp1118*	0	0	heterozygous state in CD2
14:76330140	c.3457C>T	p.Gln1153*	1	0	-
14:76330187	c.3504_3517delGAGTCGAGCCCGGC	p.Ser1169Profs*11	2	0	-
14:76368485	c.3744dupG	p.Ser1249Valfs*15	1	0	-
14:76368504	c.3760C>T	p.Gln1254*	1	0	-
14:76420778	c.3835delA	p.Thr1279Leufs*20	1	0	-
Combined frequency of presumed loss-of-function variants			0.0903% (47 total)	0.17% (5 total)	-

[a]Case group: 28 probands with [i] a retinal dystrophy with early cone photoreceptor involvement, [ii] an unknown molecular diagnosis after previous genetic screening or no previous genetic testing, [iii] no features of *ABCA4*-retinopathy on fundus autofluorescence imaging.

The cDNA is numbered according to Ensembl transcript ID ENST00000298832. See text for more details on the Broad 26K and UCL-exomes control cohorts.

All exome sequences (UCL-exomes and Broad 26K) were generated using the Illumina technology (HiSeq or GAIIx instruments). UCL-exomes FASTQ files were aligned against the human reference genome hg19 using Novoalign (version 2.07.19). Variant were called using the GATK version 2.7.4. All UCL-exomes samples (cases and controls) and all Broad 26K samples (~28,000 samples overall) were called jointly using the GATK UnifiedGenotyper module, following BAM file reduction as implemented by GATK using default options (same 2.7.4 release). We used the Illumina TruSeq target region for variant calling, with +- 100 base-pairs on the side of each target region. We followed the GATK best practices and implemented variant recalibration, with separate models for SNPs and insertions-deletions. We excluded read depth from our recalibration model owing to the large read depth variability generated by the heterogeneous capture kits used in the multiple studies that form UCL-exomes. Variants with PASS filter and the highest level recalibration tranche (VQSRTrancheSNP99.00to99.90) were retained. We used a variant Phred quality threshold of 30 and a genotype (i.e. sample based) Phred quality threshold of 20, with the exception of heterozygous call for which we found the error model overly permissive and for which we used a more stringent genotype Phred quality threshold of 40.