Disease	Gene/Locus1	Inh.	Gene/Locus2	Inh.	Gene Interaction	Loci Linked	Pedigree evidence	Replication	Ref.
Long QT syndrome (LQTS)	*KCNH2*/7q	AD	*KCNQ1*/11p	AD	Protein-protein	No	Minimal	Yes	22
LQTS	various LQT genes	AD	various LQT genes	AD	Protein-protein	No	Yes	Yes	23-26
Deafness	*GJB2*/13q	AD	*GJB6*/13q	AD	Protein-protein	Yes	Yes	DNA level	9 50-52
Deafness	*GJB2*/13q	AD	*GJB3*/1p	AD	Protein-protein	No	Minimal	Of prior studies	53
Deafness	*TECTA*/11q	AD	1p	AD	NA	No	Yes	No	30 31
Pendred syndrome/deafness	*SLC26A4*/7q	AD	*FOXI1*/5q	AD	Protein-DNA	No	No	No	87
Deafness suppression	1q	AR	4q	AR	NA	No	Yes	No	72
Deafness	*CDH23*/10q	AR	*ATP2B2*/3p	AD	?	No	Yes	Partial	49
Usher syndrome	*MYO7A*/11q	AR	3q	AD	?	No	Minimal	No	88
Usher syndrome	*CDH23*/10q	AD	*PCDH15*/10q	AD	?	Yes	Yes	Yes	27
Usher syndrome	*CDH23*/10q	AD	*PCDH15*/10q	AD	?	Yes	No	Of prior study	S1
Usher syndrome	*PDZD7*/10q	variable	*GPR98*/5q	variable	Protein-protein	No	Yes	Internal	89
Bartter's syndrome (antenatal w/deafness)	*CLCNKA*/1p	AR	*CLCNKB*/1p	AR	Pathway	Yes	Minimal	Yes	90 S2
Bardet-Biedl syndrome	*BBS2*/16q	Triallelic	various BBS loci	triallelic	Protein-protein	No	Minimal	Yes	8
Bardet-Biedl syndrome	*BBS4*/15q	variable	various BBS genes	variable	Protein-protein	No	Minimal	Yes	61
Bardet-Biedl syndrome	*BBS1*/11q	variable	various BBS genes	variable	Protein-protein	No	Yes	Yes	62
Bardet-Biedl syndrome	various BBS genes	variable	various BBS genes	variable	Protein-protein	No	No	Of prior studies	S3
Bardet-Biedl syndrome	various BBS genes	AR	*CCDC28B*/1p	variable	Protein-protein	No	Minimal	Internal	64
Bardet-Biedl syndrome	*BBS7*/4q	AR	various BBS genes	AD	Protein-protein	No	Minimal	Of prior studies	S4
Bardet-Biedl syndrome (+ciliopathies)	various BBS genes	variable	various BBS genes	variable	Protein-protein	No	Minimal	Of prior studies	19
Bardet-Biedl syndrome	various BBS genes	triallelic	various BBS genes	triallelic	Protein-protein	No	Minimal	Of prior studies	20
Bardet-Biedl syndrome	various BBS genes	triallelic	various BBS genes	triallelic	Protein-protein	No	Not shown	Of prior studies	S5
Joubert syndrome (+ciliopathies)	*CEP41*/7q	AD	various genes	various	Pathway	No	No	No	65
Leber's congenital	*CEP290*/12q	AR	*MKKS/BBS6*/20p	AD	Protein-protein	No	No	Internal	66

amaurosis(+ciliopathies)									
Short-rib polydactyly (ciliopathy)	*NEK1*/4q	AD	*DYNC2H1*/11q	AD	Pathway	No	No	No	67
Nephrotic syndrome	*NPHS1*/19q	triallelic	*NPHS2*/1q	triallelic	Protein-protein	No	Minimal	Yes	68
Nephrotic syndrome	*NPHS1*/19q	triallelic	*NPHS2*/1q	triallelic	Protein--protein	No	Minimal	Of prior study	S6
Nephrotic syndrome	various genes	various	various genes	various	Protein-protein	No	Minimal	Of prior studies	S7
Hypogonadotropic hypogonadism	*PROKR2*/20p	AD	*KAL1*/Xp	XLR	No	No	Minimal	Yes	69
Hypogonadotropic hypogonadism	*FGFR1*/8p	AD	*NSMD*/9q	AD	No	No	Minimal	Yes	70
Hypogonadotropic hypogonadism	*PROKR2*/20p	AD	*KAL1*/Xp	XLR	No	No	Minimal	Of prior studies	S8
Hypogonadotropic hypogonadism	various HH genes	AD or triallelic	various HH genes	AD or triallelic	No	No	No	Yes	S9
Hypogonadotropic hypogonadism	*NSMD*/9q	AD	*KAL1*/Xp	XLR	No	No	No	Of prior studies	S10
Hypogonadotropic hypogonadism	*NSMD*/9q	AD	*TACR3*/4q	AD	No	No	No	Of prior studies	S10
Hypogonadotropic hypogonadism	*PROKR2*/20p	AD	*FGFR1*/8p	AD	No	No	No	Of prior studies	S11
Hypogonadotropic hypogondism	*FGF8*-related	AD	*FGF8*-related	AD	Pathways	No	No	Internal	71
Hypogonadotropic hypo. (syndromic)	*RNF216*/7p	AR	*OTUD4*/4q	AD	Pathway	No	Yes	No	17
Hirschsprung disease	*RET*/10q	AD	*EDNRB*/13q	AD	Pathways?	No	Minimal	Yes	91
Hirschsprung disease	*RET*/10q	AD	*EDNRB*/13q	AD	Pathways?	No	Yes	Yes	S12
Hirschsprung disease	*RET*/10q	AD	*EDNRB*/EDN3	AD	Pathways?	No	Minimal	Of prior studies	S13
Parkinson's disease	*PARK7*/1p	AD	*PINK1*/1p	AD	Protein-protein	Yes	Minimal	No	92
Parkinson's disease	*PARKIN*/6q	AR	*PINK1*/1p	AD	Same pathway?	No	Minimal	No	S14
Retinitis pigmentosa	*PRPH2*/6p	AD	*ROM1*/11q	AD	Protein-protein	No	Yes	Internal	7
Glaucoma (earlier onset)	*MYOC*/1q	AD	*CYP1B1*/2p	AD	No	No	Yes	Yes	93 S15
Waardenburg syndrome/albinism	*MITF*/3p	AD	*TYR*/11q	AD	Protein-DNA	No	Minimal	Partial	94
Oculocutaneous albinism (OCA)	*TYR*/11q	triallelic	*OCA2*/15q	triallelic	Pathway	No	No	Partial	95
Oculocutaneous albinism (OCA)	three OCA genes	AD	three OCA genes	AD	Pathway	No	No	Internal	S16

Junctional epdermolysis bullosa	*COL17A1*/10q	AR	*LAMB3*/1q	AD	Protein-protein	No	No	No	96
Disfibrinogenemia (slow clotting)	*FGA*/4q	AD	*FGG*/4q	AD	Protein-protein	Yes	No	No	97
Polycystic kidney disease	*PKD1*/16p	AD	*PKD2*/4q	AD	Protein-protein	No	Yes	No	98
Holoprosencephaly	*SHH*/7q	AD	*TGIF1*/18p	AD	Pathway	No	Minimal	Internal	11
Holoprosencephaly	*SHH*/7q	AD	*ZIC2*/13q	AD	Pathway	No	Minimal	No	11
Familial hypercholest. suppression	*LDLR*/19p	AD	13q	AR	NA	No	Yes	No	73
High LDL	*LDLRAP1*/1p	AR	13q	AR	NA	No	Yes	Internal	64
Cystinuria	*SLC3A1*/2p	triallelic	*SLC7A9*/19q	triallelic	Protein-protein	No	Minimal	Yes	99
Cystinuria	*SLC3A1*/2p	triallelic	*SLC7A9*/19q	triallelic	Protein-protein	No	No	Of prior study	S17
Hyperinsulinemia	*PPARG*/3p	AD	*PPP1R3A*/7q	AD	No	No	Minimal	No	100
Hypercholanemia	*TJP2*/9q	AR	*BAAT*/9q	AD	No	Weakly	Yes	No	79
Pheochromocytoma	*TMEM127*/2q	AR*	16p	AR	NA	No	Yes	No	32 33
Familial exudative vitreoretinopathy(FEVR)	*FZD4*/11q	AD	*F5*/1q	AD	No	No	Minimal	No	101
Familial exudative vitreoretinopathy(FEVR)	*FZD4*/11q	AD	*LRP5*/11q	AD	Pathway	Yes	Minimal	No	77
Factor VIII thromboembolism	5q	optimized	11q	optimized	NA	No	Yes	No	102
PMP22-related neuropathies	*PMP22*/17p	AD	various genes	AD or XLR	No	No	Minimal	Partial	103 104
PMP22-related neuropathy	*PMP22*/17p	AD	*MPZ*/1q	AD	No	No	Minimal	Of prior study	S18
Charcot-Marie-Tooth disease (non-PMP22)	*MFN2*/1p	AD	*GDAP1*/8q	AD	No	No	Minimal	No	105
Emery-Dreifuss muscular dystrophy	*LMNA*/1q	AD	*EMD*/Xq	XLR	Protein-protein	No	Minimal	Yes	106
Emery-Dreifuss muscular dystrophy	*LMNA*/1q	AR	*EMD*/Xq	XLR	Protein-protein	No	Yes	Of prior study	S19
Porphyria (acute)	various genes	various	*HFE*/6p	AD	Pathway	No	No	At pathway level	107
Porphyria (acute)	*UROD*/1p	AD	*HMBS*/11q	AD	Pathway	No	No	At pathway level	108
Porphyria (acute)	*CPOX*/3q	AD	*ALAD*/9q	AD	Pathway	No	Minimal	At pathway level	109
Porphyria (acute)	*PPOX*/1q	AD	*CPOX*/3q	AD	Pathway	No	Minimal	Of prior studies	S20
Epilepsy w/febrile seizures	1q	AD	18q	AD	NA	No	Yes	No	110

Hemachromatosis	*HFE*/6p	various	*HAMP*/19q	AD	Pathway	No	Minimal	No	111
Progressive external ophthalmoplegia (PEO)	*C10orf2*/10q	AD	*POLG*/15q	AD	No	No	No	No	112
Epilepsy w/febrile seizures	*SCN1A*/2q	AD	*SCN2A*/2q	AD	No	Yes	Minimal	No	113
Photosensitivity in epilepsy	7q	optimized	16p	optimized	NA	No	Yes	No	114
Split-hand/foot malformation	1q	AD	6q	AD	NA	No	Yes	No	115
Iminoglycinuria	*SLC36A2*/5q	AR	*SLC6A20*/3p	AD	Pathway	No	Yes	Internal	116
Keratoconus	1p	AD	8q	AD	NA	No	Yes	No	117
Limb-girdle muscular dystrophy	*SGCB*/4q	AD	*SGCD*/5q	AD	Protein-protein	No	No	No	118
Ullrich congenital muscular dystrophy	*COL6A1*/21q	AD	*COL6A2*/21q	AD	Protein-protein	Yes	No	No	119
Pseudoxanthoma elasticum	*ABCC6*/16p	AD	*GGCX*/2p	AD	No	No	Minimal	No	120
Hereditary motor neuropathy	*DSCL2*/11q	AD	16p	AD	NA	No	Yes	No	121
Cleft lip	1q	AD	2p	AD	NA	No	Yes	No	122
Fuchs corneal dystrophy	*ZEB1*/10p	AD	9p	AD	NA	No	Yes	No	29
Axenfeld-Rieger syndrome	*PITX2*/4q	AD	*FOXC1*/6p	AD	Protein-protein	No	Minimal	No	123
Colorectal cancer	*MUTYH*/1p	AD	*OGG1*/3p	AD	Pathway	No	Minimal	No	124
Rotor syndrome (hyperbilirubinemia)	*SLCO1B1*/12p	AR	*SLCO1B3*/12p	AR	Pathway	Yes	Yes	Internal	28
Dent's disease	*CLCN5*/Xp	XLR	*OCRL*/Xq	XLR	Pathway?	Weakly	Minimal	No	78
Facioscapulohumeral muscular dystrophy type 2	*DUX4*/4q	AD	*SMCHD1*/18p	AD	Protein/DNA	No	Yes	Internal	16
Epidermolysis bullosa simplex	*KRT5*/12q	AD	*KRT14*/17q	AD	Protein-protein	No	Minimal	No	125
Melanoma susceptibility	*CDKN2A*/9p	AD	*MC1R*/16q	various	No	No	Yes	Yes	21 S21-S23
Hypotrichosis (nonsyndromic)	*CDH3*/16q	AR	12q	AR	NA	No	Yes	Internal	75
Cone rod dystrophy & deafness	*MERTK*/2q	AR	*DFNB59*/2q	AR	No, two diseases	Weakly	Yes	No	80
Oculocutaneous albinism & cytopenia	*SLC45A2*/5p	AR	*G6PC3/17q*	AR	No, two diseases	No	Minimal	No	43

Online Supplementary Table S1. This is an extended version of Table 1 with a catalog of publications of cases of human digenic inheritance. The extended version includes extra rows for multiple gene pairs in the same paper and for replication studies. The extended version includes extra columns to describe the mode of inheritance at each locus and whether the genes/proteins are known to interact. The possible modes of inheritance are: AD (autosomal dominant), AR (autosomal recessive), XLR (X-linked recessive), triallelic (two variant alleles in one gene and one variant allele in the other gene), or optimized (the penetrance function or other parameters used for genetic linkage analysis were determined by some numerical optimization procedure using at least some of the pedigree data as input). References with only numbers are in the References of the main document. References cited only in Table S1 are listed below it with indices S1 through S23.

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