Patient ID	Origin	Semen analysis	*Gene*	Chromosome coordinates (GRCh37)	Refseq ID	HGVS	Pathogenicity prediction*	Expressed in testis
Proband_005	Netherlands	Azoospermia	*CDK5RAP2*	chr9:123215805	NM_018249:c.2722C>T	p.Arg908Trp	SP	Yes, not enhanced
Proband_006	Netherlands	Azoospermia	*ATP1A1*	chr1:116930014	NM_000701:c.291del	p.Phe97LeufsTer44	N/A	Yes, not enhanced
			TLN2	chr15:63029134	NM_015059:c.3416G>A	p.Gly1139Glu	MP	Yes, not enhanced
			HUWE1	chrX:53589090	NM_031407:c.7314_7319del	p.Glu2439_Glu2440del	N/A	Yes, not enhanced
Proband_008	Netherlands	Azoospermia	*ABCC10*	chr6:43417749	NM_001198934:c.4399C>T	p.Arg1467Cys	-	Yes, not enhanced
			CP	chr3:148927135	NM_000096c.644G>A	p.Arg215Gln	-	Not expressed
Proband_010	Netherlands	Azoospermia	*FUS*	chr16:31196402	NM_004960:c.678_686del	p.Gly229_Gly231del	N/A	Yes, not enhanced
			LTBP1	chr2:33246090	NM_206943:c.680C>G	p.Ser227Trp	P	Yes, not enhanced
Proband_012	Netherlands	Extreme oligozoospermia	*RP1L1*	chr8:10480174	NM_178857:c.538G>A	p.Ala180Thr	SP	Yes, not enhanced
Proband_013	Netherlands	Azoospermia	*ERG*	chr21:39755563	NM_182918:c.1202C>T	p.Pro401Leu	MP	Yes, not enhanced
Proband_017	Netherlands	Azoospermia	*CDC5L*	chr6:44413480	NM_001253:c.2180G>A	p.Arg727His	SMP	Yes, not enhanced
Proband_019	Netherlands	Azoospermia	*ABLIM1*	chr10:116205100	NM_002313:c.1798C>T	p.Arg600Trp	SMP	Yes, not enhanced
Proband_020	Netherlands	Azoospermia	*CCDC126*	chr7:23682709	NM_001253:c.2180G>A	p.Thr133Met	-	Yes, enhanced expression in testis
			RASEF	chr9:85607885	NM_152573:c.1976G>A	p.Arg659His	SMP	Yes, not enhanced
Proband_022	Netherlands	Azoospermia	*APC2*	chr19:1453118	NM_005883:c.118G>A	p.Glu40Lys	MP	Yes, not enhanced
Proband_025	Netherlands	Azoospermia	*NEO1*	chr15:73575428	NM_002499:c.3386G>A	p.Arg1129His	SMP	Yes, not enhanced
Proband_028	Netherlands	Extreme oligozoospermia	*OR5P3*	chr11:7846930	NM_153445:c.590T>A	p.Ile197Lys	SP	No expression
Proband_030	Netherlands	Extreme oligozoospermia	*SIKE1*	chr1:115323119	NM_025073:c.110A>C	p.His37Pro	MP	Yes, not enhanced
			TRAF7	chr16:2218149	NM_032271:c.211C>T	p.Arg71Trp	SMP	Yes, not enhanced
Proband_033	Netherlands	Azoospermia	*KRT33B*	chr17:39521752	NM_002279:c.642C>G	p.Asp214Glu	SP	No expression
			SENP7	chr3:101212750	NM_020654:c.153C>G	p.Phe51Leu	-	Yes, not enhanced
			ATP8A1	chr4:42626573	NM_006095:c.343A>G	p.Lys115Glu	SMP	Yes, not enhanced

Proband_038	Netherlands	Azoospermia	*NOC3L*	chr10:96100055	NM_022451:c.1758A>C	p.Lys586Asn	M	Yes, not enhanced
Proband_039	Netherlands	Azoospermia	*NXT2*	chrX:108779109:108785919	N/A	N/A	N/A	Yes, not enhanced
Proband_041	Netherlands	Azoospermia	*ASIC5*	chr4:156763436	NM_017419:c.932G>A	p.Ser311Asn	SM	Not expressed
Proband_042	Netherlands	Azoospermia	*PLCL1*	chr2:198966024	NM_006226:c.2935C>T	p.Arg979Trp	SMP	Yes, not enhanced
			DNAJC2	chr7:102957321	NM_014377:c.1383A>T	p.Leu461Phe	SMP	Yes, enhanced expression in testis
			AK3	chr9:4722547	NM_016282:c.230A>G	p.His77Arg	-	Yes, not enhanced
Proband_043	Netherlands	Azoospermia	*IL33*	chr9:6251221	NM_033439:c.299G>A	p.Gly100Glu	-	Yes, not enhanced
Proband_044	Netherlands	Azoospermia	*PRDM16*	chr1:3328833	NM_022114:c.2072A>T	p.Asp691Val	SMP	Yes, not enhanced
			PPP1R7	chr2:242099831	NM_002712:c.523_527del	p.Lys175GlnfsTer2	N/A	Yes, not enhanced
Proband_045	Netherlands	Azoospermia	*EVC*	chr4:5743515	NM_153717:c.775C>T	p.Gln259Ter	N/A	Yes, not enhanced
			BHMT	chr5:78426892	NM_001713:c.1174C>G	p.Gln392Glu	M	Yes, not enhanced
Proband_048	Netherlands	Extreme oligozoospermia	*MCM6*	chr2:136624195	NM_005915:c.719A>G	p.Asp240Gly	SMP	Yes, not enhanced
Proband_049	Netherlands	Azoospermia	*ATP8B4*	chr15:50168651	NM_024837:c.2851A>G	p.Asn951Asp	SMP	Yes, not enhanced
			ZNF577	chr19:52376320	NM_032679:c.923A>G	p.Tyr308Cys	P	Yes, not enhanced
			NUP210	chr3:13359251	NM_024923:c.5594A>G	p.Asn1865Ser	-	Yes, not enhanced
Proband_050	Netherlands	Extreme oligozoospermia	*HIST1H1D*	chr6:26234816	NM_005320:c.346G>C	p.Glu116Gln	M	Yes, not enhanced
Proband_051	Netherlands	Extreme oligozoospermia	*FNDC8*	chr17:33448840	NM_017559:c.128G>A	p.Arg43Gln	S	Yes, enhanced expression in testis
Proband_052	Netherlands	Severe oligozoospermia	*SOGA1*	chr20:35438426	NM_080627:c.2542C>T	p.Arg848Ter	N/A	Yes, not enhanced
Proband_053	Netherlands	Extreme oligozoospermia	*CD81*	chr11:2417877	NM_004356:c.581T>C	p.Ile194Thr	SMP	Yes, not enhanced
Proband_055	Netherlands	Azoospermia	*OSBPL3*	chr7:24874131	NM_015550:c.1720C>T	p.Gln574Ter	N/A	Yes, not enhanced
Proband_057	Netherlands	Extreme oligozoospermia	*ABCB9*	chr12:123430670	NM_019625:c.1153G>A	p.Glu385Lys	M	Yes, enhanced expression in testis
Proband_060	Netherlands	Azoospermia	*IL12RB2*	chr1:67861761	NM_001559:c.2578C>G	p.Leu860Val	P	Yes, not enhanced
			TOPAZ1	chr3:44286601	NM_001145030:c.2603A>G	p.Gln868Arg	SP	Yes, enhanced expression in testis
Proband_061	Netherlands	Azoospermia	*SEC14L1*	chr17:75208114	NM_001143999:c.1694A>G	p.Tyr565Cys	S	Yes, not enhanced
Proband_062	Netherlands	Extreme oligozoospermia	*FOXF2*	chr6:1391182	NM_001452:c.1000A>G	p.Thr334Ala	SM	Yes, not enhanced
Proband_063	Netherlands	Extreme oligozoospermia	*CNOT4*	chr7:135048789	NM_001190849:c.1657A>G	p.Met553Val	M	Yes, not enhanced
Proband_064	Netherlands	Severe oligozoospermia	*C9orf50*	chr9:132374702	NM_199350:c.1220C>T	p.Ser407Leu	SP	Yes, enhanced expression in testis

Proband_066	Sint Maarten (Caribbean)	Extreme oligozoospermia	*HIPK3*	chr11:32975325:33631588	N/A	N/A	N/A	Yes, not enhanced
			QSER1		N/A	N/A		Yes, not enhanced
			DEPDC7		N/A	N/A		Yes, enhanced expression in testis
			TCP11L1		N/A	N/A		Yes, not enhanced
			CSTF3		N/A	N/A		Yes, not enhanced
			KIAA1549L		N/A	N/A		Yes, not enhanced
			TDRD10	chr1:154493890	NM_182499:c.304G>A	p.Val102Met	P	Yes, enhanced expression in testis
			CWC27	chr5:64077814	NM_005869:c.206C>G	p.Thr69Ser	MP	Yes, not enhanced
Proband_073	Netherlands	Extreme oligozoospermia	*INO80*	chr15:41372056	NM_017553:c.974C>T	p.Ala325Val	SM	Yes, not enhanced
Proband_074	Netherlands	Severe oligoasthenozoospermia	*ZNF709*	chr19:12575362	NM_152601:c.1375dup	p.Ser458ArgfsTer10	N/A	Yes, enhanced expression in testis
			EMILIN1	chr2:27305208	NM_007046:c.769G>A	p.Glu257Lys	MP	Yes, not enhanced
			WDR17	chr4:177067235	NM_170710:c.1619G>A	p.Gly540Glu	MP	Yes, not enhanced
			ZNF311	chr6:28963503	NM_001010877:c.1276C>T	p.Arg426Trp	S	Yes, not enhanced
Proband_076	Netherlands	Azoospermia	*STARD10*	chr11:72466763	NM_006645:c.610_612del	p.Ser204del	N/A	Yes, not enhanced
			GREB1L	chr18:19019514	NM_001142966:c.868_872del	p.Gly290CysfsTer19	N/A	Yes, enhanced expression in testis
Proband_077	Netherlands	Extreme oligozoospermia	*MSH5*	chr6:31721100	NM_172165:c.887_888del	p.His296ArgfsTer90	N/A	Yes, not enhanced
Proband_079	Netherlands	Azoospermia	*ILVBL*	chr19:15226717	NM_006844:c.1558G>A	p.Gly520Arg	SMP	Yes, not enhanced
Proband_080	Netherlands	Extreme oligozoospermia	*HOXA1*	chr7:27134363	NM_005522:c.704A>C	p.Asn235Thr	SMP	Yes, not enhanced
Proband_081	Netherlands	Azoospermia	*ZFHX4*	chr8:77763486	NM_024721:c.4331del	p.Leu1444TrpfsTer8	N/A	Yes, enhanced expression in testis
Proband_083	Netherlands	Azoospermia	*F13B*	chr1:197026291	NM_001994:c.1023C>A	p.Phe341Leu	-	Not expressed
			HNRNPL	chr19:39329152	NM_001533:c.1442G>A	p.Arg481Gln	SMP	Yes, not enhanced
Proband_085	Netherlands	Severe oligoasthenozoospermia	*NLRP10*	chr11:7981967	NM_176821:c.1192G>A	p.Asp398Asn	-	Not expressed
Proband_087	Netherlands	Severe oligoasthenozoospermia	*LEO1*	chr15:52252183	NM_138792:c.1073T>G	p.Ile358Arg	SMP	Yes, not enhanced
Proband_088	Netherlands	Extreme oligozoospermia	*GDAP1L1*	chr20:42893167	NM_024034:c.728C>T	p.Ala243Val	P	Yes, not enhanced
Proband_095	Netherlands	Azoospermia	*MPRIP*	chr17:17062191	NM_015134:c.1921C>T	p.His641Tyr	MP	Yes, not enhanced
			SORCS2	chr4:7728558	NM_020777:c.2797G>A	p.Asp933Asn	SM	Yes, not enhanced
Proband_097	Netherlands	Azoospermia	*TENM2*	chr5:167642269	NM_001122679.2:c.4046delC	p.Pro1349ArgfsTer6	N/A	Yes, not enhanced
Proband_101	Netherlands	Extreme oligozoospermia	*CHST12*	chr7:2472611	NM_001243794:c.337C>T	p.Arg113Cys	-	Not expressed

Proband_102	Netherlands	Extreme oligozoospermia	*HR*	chr8:21973239	NM_005144:c.3544G>A	p.Val1182Met	SMP	Yes, not enhanced
			SMC2	chr9:106885442	NM_006444:c.2186T>C	p.Leu729Ser	MP	Yes, not enhanced
Proband_106	Netherlands	Azoospermia	*TACC2*	chr10:123976284	NM_206862:c.7487C>T	p.Pro2496Leu	SMP	Yes, not enhanced
Proband_108	Netherlands	Severe oligoasthenozoospermia	*CYP4F12*	chr19:15794526	NM_023944:c.871G>A	p.Ala291Thr	-	Not expressed
			RBM5	chr3:50140556	NM_005778:c.524A>G	p.Tyr175Cys	SMP	Yes, not enhanced
			TAF9	chr5:68660785	NM_003187:c.777_779del	p.Asp260del	-	Yes, not enhanced
Proband_115	Netherlands	Severe oligoasthenozoospermia	*CDC42BPG*	chr11:64603286	NM_017525:c.1706C>T	p.Thr569Met	-	Yes, not enhanced
			RPA1	chr17:1756424	NM_002945:c.302T>C	p.Val101Ala	SMP	Yes, not enhanced
Proband_116	Netherlands	Severe oligoasthenozoospermia	*FBXO5*	chr6:153293449	NM_012177:c.1046_1049dup	p.Asp350GlufsTer9	N/A	Yes, not enhanced
Proband_117	Netherlands	Azoospermia	*FLNC*	chr7:128477754	NM_001458:c.914C>T	p.Ala305Val	SMP	Yes, not enhanced
Proband_118	Netherlands	Azoospermia	*CDCA8*	chr1:38166170	NM_001256875:c.400C>T	p.Arg134Cys	S	Yes, enhanced expression in testis
Proband_119	Netherlands	Severe oligoasthenozoospermia	*ZCCHC2*	chr18:60242391	NM_017742:c.3077A>G	p.Asn1026Ser	-	Yes, not enhanced
Proband_121	Netherlands	Azoospermia	*AMPD2*	chr1:110168336	NM_139156:c.194A>T	p.Glu65Val	SMP	Yes, not enhanced
			HIVEP1	chr6:12163643	NM_002114:c.7106C>T	p.Pro2369Leu	-	Yes, not enhanced
			SPEF2	chr5:35792492	NM_024867:c.4498C>G	p.Leu1500Val	-	Yes, not enhanced
Proband_122	Netherlands	Azoospermia	*SIGLEC10*	chr19:51919175	NM_033130:c.1001G>A	p.Arg334Gln	P	Not expressed
Proband_124	Netherlands	Severe oligoasthenozoospermia	*PPP1R3A*	chr7:113518521	NM_002711:c.2626T>G	p.Phe876Val	P	Not expressed

Proband_125	Netherlands	Azoospermia	*CHST4*	chr16:71571634	NM_001166395:c.1054G>A	p.Asp352Asn	-	Not expressed
			STXBP2	chr19:7711198	NM_006949:c.1420C>T	p.Arg474Cys	SMP	Yes, not enhanced
Proband_126	Netherlands	Severe oligoasthenozoospermia	*ABCF3*	chr3:183907504	NM_018358:c.1273C>T	p.Arg425Cys	SMP	Yes, not enhanced
Proband_127	Netherlands	Extreme oligozoospermia	*TMEM62*	chr15:43441280	NM_024956:c.797C>G	p.Pro266Arg	SMP	Yes, not enhanced
			U2AF2	chr19:56170622	NM_007279:c.100_105dup	p.Ser34_Arg35dup	N/A	Yes, not enhanced
Proband_128	Netherlands	Azoospermia	*HELZ2*	chr20:62195532	NM_001037335:c.4643C>T	p.Thr1548Met	SP	Yes, not enhanced
Proband_129	Netherlands	Azoospermia	*FIZ1*	chr19:56104069	NM_032836:c.1235_1237del	p.Lys412del	N/A	Yes, not enhanced
Proband_130	Netherlands	Azoospermia	*MAVS*	chr20:3846631	NM_020746:c.1460C>T	p.Ala487Val	-	Yes, not enhanced
			TMPPE	chr3:33134784	NM_001039770:c.904A>G	p.Asn302Asp	SMP	Yes, not enhanced
Proband_132	Netherlands	Azoospermia	*USH2A*	chr1:216595434	NM_206933:c.245G>T	p.Arg82Leu	P	Yes, not enhanced
Proband_133	Netherlands	Azoospermia	*EMP1*	chr12:13366446	NM_001423:c.112G>C	p.Val38Leu	-	Yes, not enhanced
Proband_134	Netherlands	Extreme oligozoospermia	*ERI3*	chr1:44687249	NM_024066:c.995A>G	p.Gln332Arg	M	Yes, not enhanced
Proband_135	Netherlands	Severe oligozoospermia	*POPDC3*	chr6:105609709	NM_022361:c.76G>A	p.Glu26Lys	SMP	Yes, enhanced expression in testis
Proband_136	Netherlands	Severe oligoasthenozoospermia	*PLEKHA1*	chr10:124189195	NM_001001974:c.956C>G	p.Ala319Gly	M	Not expressed
			BTAF1	chr10:93753563	NM_003972:c.3158T>C	p.Met1053Thr	M	Yes, not enhanced
Proband_137	Netherlands	Azoospermia	*C12orf49*	chr12:117155674	NM_024738:c.559C>T	p.Arg187Trp	SMP	Yes, not enhanced
Proband_138	Netherlands	Severe oligozoospermia	*GRIP1*	chr12:66849967	NM_001379345:c.1198C>T	p.Pro400Ser	M	Yes, not enhanced
Proband_139	Netherlands	Extreme oligozoospermia	*RNF223*	chr1:1007489	NM_001205252:c.458G>A	p.Arg153His	-	Not expressed
			ZNF469	chr16:88494628	NM_001127464:c.756dup	p.Ala253ArgfsTer118	N/A	Not expressed
			MAP3K3	chr17:61759150	NM_203351:c.620C>T	p.Ser207Leu	SMP	Yes, not enhanced
			C17orf74	chr17:7330308	NM_175734:c.998G>A	p.Arg333Gln	-	Yes, not enhanced
			TMPRSS11B	chr4:69107421	NM_182502:c.110A>G	p.His37Arg	SP	Not expressed
Proband_142	Netherlands	Azoospermia	*GPR75-ASB3*	chr2:53921057	NM_016115:c.1333C>T	p.Arg445Cys	SP	Yes, not enhanced
Proband_144	Unknown	Azoospermia	*ODF1*	chr8:103563960	NM_024410:c.5C>G	p.Ala2Gly	SMP	Yes, enhanced expression in testis
Proband_145	Netherlands	Extreme oligozoospermia	*EXOSC10*	chr1:11136965	NM_001001998:c.1919dup	p.Asp640GlufsTer2	N/A	Yes, not enhanced

Proband_146	Unknown	Severe oligoasthenozoospermia	*OTOA*	chr16:21728238	NM_144672:c.1499C>T	p.Ala500Val	-	Yes, enhanced expression in testis
Proband_148	Netherlands	Azoospermia	*CRHR1*	chr17:43907477	NM_001145148:c.452G>A	p.Arg151Gln	SMP	Not expressed
			HTT	chr4:3213834	NM_002111:c.6595dup	p.Ala2199GlyfsTer9	N/A	Yes, not enhanced
Proband_149	Netherlands	Azoospermia	*SNED1*	chr2:242012773	NM_001080437:c.3910A>G	p.Ile1304Val	-	Yes, not enhanced
			PCDHB1	chr5:140431405	NM_013340:c.354_358dup	p.Glu120GlyfsTer17	N/A	Yes, not enhanced
Proband_150	Netherlands	Azoospermia	*SPECC1L*	chr22:24761453	NM_001145468:c.2837G>A	p.Arg946Gln	MP	Yes, not enhanced
Proband_153	Netherlands	Azoospermia	*IQSEC1*	chr3:13008948	NM_014869:c.4T>A	p.Trp2Arg	MP	Yes, not enhanced
Proband_154	Netherlands	Azoospermia	*ARHGAP33*	chr19:36276183	NM_052948:c.1814G>A	p.Arg605Gln	SP	Yes, not enhanced
			C10orf107	chr10:63445916	NM_173554:c.188A>G	p.Asn63Ser	-	Yes, not enhanced
Proband_156	Netherlands	Azoospermia	*LRRN2*	chr1:204587973	NM_201630:c.1148C>T	p.Thr383Met	SMP	Yes, not enhanced
			SRCIN1	chr17:36714613	NM_025248:c.2051C>T	p.Ala684Val	M	Not expressed
Proband_157	Netherlands	Azoospermia	*REN*	chr1:204124193	NM_000537:c.1163C>T	p.Thr388Ile	SM	Not expressed
			SIPA1L3	chr19:38643580	NM_015073:c.3634G>A	p.Glu1212Lys	SM	Yes, not enhanced
Proband_158	Netherlands	Azoospermia	*TP53TG5*	chr20:44003729	NM_014477:c.718A>T	p.Thr240Ser	SMP	Yes, enhanced expression in testis
			DHX36	chr3:153994607	NM_020865:c.2770G>A	p.Asp924Asn	M	Yes, not enhanced
			YEATS2	chr3:183524758	NM_018023:c.3889C>A	p.Leu1297Ile	M	Yes, not enhanced
Proband_160	Netherlands	Azoospermia	*SDF4*	chr1:1158720	NM_016176:c.481G>A	p.Glu161Lys	SMP	Yes, not enhanced
			ITSN2	chr2:24522905	NM_006277:c.1217G>A	p.Arg406Gln	SMP	Not expressed
Proband_165	Netherlands	Extreme oligozoospermia	*MYOF*	chr10:95168662	NM_013451:c.611G>A	p.Arg204Gln	MP	Yes, not enhanced
			RASAL2	chr1:178435121	NM_170692:c.3421G>T	p.Glu1141Ter	N/A	Yes, not enhanced
Proband_166	Netherlands	Azoospermia	*C6orf25*	chr6:31691437	NM_138272:c.83G>A	p.Gly28Glu	SMP	Not expressed
Proband_168	Netherlands	Extreme oligozoospermia	*KLC1*	chr14:104129206	NM_001130107:c.740del	p.Ser247Ter	N/A	Yes, not enhanced
Proband_170	Netherlands	Azoospermia	*PRPF4B*	chr6:4049340	NM_003913:c.2026C>T	p.Arg676Cys	SMP	Yes, not enhanced
Proband_173	United Kingdom	Azoospermia	*ZNF629*	chr16:30793127	NM_001080417:c.2522C>G	p.Pro841Arg	SMP	No expression
			CXXC11	chr2:242812032	NM_173821:c.124G>A	p.Gly42Ser	-	No expression
			IRAK2	chr3:10255045	NM_001570:c.683A>T	p.His228Leu	SMP	No expression
Proband_178	United Kingdom	Severe Oligozoospermia	*MICU1*	chr10:74322772	NM_006077:c.211G>A	p.Gly71Ser	M	Yes, not enhanced

Proband_178	United Kingdom	Severe Oligozoospermia	*GHRHR*	chr7:31016058	NM_000823:c.989C>T	p.Ser330Leu	SMP	Not expressed
Proband_179	United Kingdom	Azoospermia	*CELSR2*	chr1:109807146	NM_001408:c.5360T>C	p.Val1787Ala	SM	Yes, not enhanced
			BASP1	chr5:17275915	NM_006317:c.590C>T	p.Pro197Leu	M	Not expressed

* Representation of which tool marks the variant as pathogenic; S=SIFT, M=MUTATIONTASTER, P=POLYPHEN

1. Eicher, E. M., & Beamer, W. G. Inherited ateliotic dwarfism in mice. Characteristics of the mutation, little, on chromosome 6. *The Journal of heredity* , **67**, 87–91 (1976)
2. Zaqout, S., Bessa, P., Kramer, N., Stoltenburg-Didinger, G. & Kaindl, A.M. CDK5RAP2 Is Required to Maintain the Germ Cell Pool during Embryonic Development. *Stem Cell Reports* **8**, 198-204 (2017).
3. Guo, F. et al. The Transcriptome and DNA Methylome Landscapes of Human Primordial Germ Cells. *Cell* **161**, 1437-52 (2015).
4. Newton, L.D. *et al.* Na+/K+ATPase regulates sperm capacitation through a mechanism involving kinases and redistribution of its testis-specific isoform. *Molecular Reproduction Dev* **77**, 136-48 (2010).
5. Fok, K.L. *et al.* Huwe1 Regulates the Establishment and Maintenance of Spermatogonia by Suppressing DNA Damage Response. *Endocrinology* **158**, 4000-4016 (2017).
6. Bose, R. *et al.* Ubiquitin Ligase Huwe1 Modulates Spermatogenesis by Regulating Spermatogonial Differentiation and Entry into Meiosis. *Sci Rep* **7**, 17759 (2017).
7. Karlberg, S. *et al.* Testicular failure and male infertility in the monogenic Mulibrey nanism disorder. *J Clin Endocrinol Metab* **96**, 3399-407 (2011)
8. Kuroda, M. *et al.* Male sterility and enhanced radiation sensitivity in TLS(-/-) mice. *Embo j* **19**, 453-62 (2000)
9. An, J. *et al.* The histone methyltransferase ESET is required for the survival of spermatogonial stem/progenitor cells in mice. *Cell Death Dis* **5**, e1196 (2014).
10. Guo, J. *et al.* The adult human testis transcriptional cell atlas. *Cell Res* (2018).
11. Shintani, T., Takeuchi, Y., Fujikawa, A. & Noda, M. Directional neuronal migration is impaired in mice lacking adenomatous polyposis coli 2. *J Neurosci* **32**, 6468-84 (2012).
12. Mohamed, N.E., Hay, T., Reed, K.R., Smalley, M.J. & Clarke, A.R. APC2 is critical for ovarian WNT signalling control, fertility and tumour suppression. *BMC Cancer* **19**, 677 (2019).
13. Molinar-Inglis, O., Oliver, S.L., Rudich, P., Kunttas, E. & McCartney, B.M. APC2 associates with the actin cortex through a multipart mechanism to regulate cortical actin organization and dynamics in the Drosophila ovary. *Cytoskeleton (Hoboken)* **75**, 323-335 (2018).
14. Yamashita, Y.M., Jones, D.L. & Fuller, M.T. Orientation of asymmetric stem cell division by the APC tumor suppressor and centrosome. *Science* **301**, 1547-50 (2003).
15. Laurentino, S.S. *et al.* Regucalcin is broadly expressed in male reproductive tissues and is a new androgen-target gene in mammalian testis. *Reproduction* **142**, 447-56 (2011).
16. Helary, L. *et al.* DNAJC2 is required for mouse early embryonic development. *Biochem Biophys Res Commun* **516**, 258-263 (2019).
17. Jean Wu, Colin Carlock, Cindy Zhou, Susumu Nakae, John Hicks, Henry P. Adams, Yahuan Lou, *The Journal of Immunology* , **194**, 2140-2147 (2015)
18. Kim HG, Kurth I, Lan F, et al. Mutations in CHD7, encoding a chromatin-remodeling protein, cause idiopathic hypogonadotropic hypogonadism and Kallmann syndrome. *American Journal of Human Genetics* , **83**, 511-519. (2008)
19. Goswami S, Korrodi-Gregório L, Sinha N, Bhutada S, Bhattacharjee R, Kline D, Vijayaraghavan S. Regulators of the protein phosphatase PP1γ2, PPP1R2, PPP1R7, and PPP1R11 are involved in epididymal sperm maturation. *J Cell Physiol* . **234**, 3105-3118. (2019)
20. Wen Z, Zhu H, Zhang A, et al. Cdc14a has a role in spermatogenesis, sperm maturation and male fertility. *Exp Cell Res* . **395**, 112178. (2020)
21. Ruiz-Perez, V.L. et al. Evc is a positive mediator of Ihh-regulated bone growth that localises at the base of chondrocyte cilia. *Development* **134**, 2903-12 (2007).
22. Kruse, R. *et al.* Characterization of the CLASP2 Protein Interaction Network Identifies SOGA1 as a Microtubule-Associated Protein. *Mol Cell Proteomics* **16**, 1718-1735 (2017).
23. Rubinstein, E. *et al.* Reduced fertility of female mice lacking CD81. *Dev Biol* **290**, 351-8 (2006).
24. Rubinstein, E., Ziyyat, A., Wolf, J.P., Le Naour, F. & Boucheix, C. The molecular players of sperm-egg fusion in mammals. *Semin Cell Dev Biol* **17**, 254-63 (2006)
25. Luangpraseuth-Prosper, A. et al. TOPAZ1, a germ cell specific factor, is essential for male meiotic progression. Dev Biol 406, 158-71 (2015).
26. Baillet, A. et al. TOPAZ1, a novel germ cell-specific expressed gene conserved during evolution across vertebrates. PLoS One 6, e26950 (2011).
27. Seabra, C.M. *et al.* A novel Alu-mediated microdeletion at 11p13 removes WT1 in a patient with cryptorchidism and azoospermia. *Reprod Biomed Online* **29**, 388-91 (2014).
28. Serber, D. W., Runge, J. S., Menon, D. U., & Magnuson, T. The Mouse INO80 Chromatin-Remodeling Complex Is an Essential Meiotic Factor for Spermatogenesis. *Biology of reproduction* , **94**, 8. (2016)
29. Yin H, Ma H, Hussain S, et al. A homozygous FANCM frameshift pathogenic variant causes male infertility, *Genet Med* . **21**, 62-70. (2019)
30. de Vries SS, Baart EB, Dekker M, Siezen A, de Rooij DG, de Boer P, te Riele H. Mouse MutS-like protein Msh5 is required for proper chromosome synapsis in male and female meiosis. *Genes Dev* . **13**, 523-31. (1999)
31. Becherel, O.J. *et al.* Senataxin plays an essential role with DNA damage response proteins in meiotic recombination and gene silencing. *PLoS Genet* **9**, e1003435 (2013).
32. Panteleyev, A.A. *et al.* Molecular basis for the rhino Yurlovo (hr(rhY)) phenotype: severe skin abnormalities and female reproductive defects associated with an insertion in the hairless gene. *Exp Dermatol* **7**, 281-8 (1998).
33. O'Bryan MK, Clark BJ, McLaughlin EA, et al. RBM5 is a male germ cell splicing factor and is required for spermatid differentiation and male fertility. *PLoS Genet* . **9**, e1003628. (2013)
34. Plug, A.W. *et al.* ATM and RPA in meiotic chromosome synapsis and recombination. *Nat Genet* **17**, 457-61 (1997).
35. Shi, B. *et al.* Dual functions for the ssDNA-binding protein RPA in meiotic recombination. *PLoS Genet* **15**, e1007952 (2019).
36. Tung, J.J. & Jackson, P.K. Emi1 class of proteins regulate entry into meiosis and the meiosis I to meiosis II transition in Xenopus oocytes. *Cell Cycle* **4**, 478-82 (2005).
37. Elborn JS. Cystic fibrosis. *Lancet* . **388**, 2519-2531. (2016)
38. Sironen A, Kotaja N, Mulhern H, et al. Loss of SPEF2 function in mice results in spermatogenesis defects and primary ciliary dyskinesia. *Biol Reprod* . **85**, 690-701. (2011)
39. Schmahl J, Rizzolo K, Soriano P. The PDGF signaling pathway controls multiple steroid-producing lineages. *Genes Dev* . **22**, 3255-67. (2008)
40. Yang, K. *et al.* The small heat shock protein ODF1/HSPB10 is essential for tight linkage of sperm head to tail and male fertility in mice. *Mol Cell Biol* **32**, 216-25 (2012).
41. Yang, K., Grzmil, P., Meinhardt, A. & Hoyer-Fender, S. Haplo-deficiency of ODF1/HSPB10 in mouse sperm causes relaxation of head-to-tail linkage. *Reproduction* **148**, 499-506 (2014).
42. Hetherington, L. *et al.* Deficiency in Outer Dense Fiber 1 Is a Marker and Potential Driver of Idiopathic Male Infertility. *Mol Cell Proteomics* **15**, 3685-3693 (2016).
43. Jamin SP, Petit FG, Kervarrec C, et al. EXOSC10/Rrp6 is post-translationally regulated in male germ cells and controls the onset of spermatogenesis. *Sci Rep* . **7**, 15065. (2017)
44. Phillip M, Arbelle JE, Segev Y, Parvari R. Male hypogonadism due to a mutation in the gene for the beta-subunit of follicle-stimulating hormone. *N Engl J Med.* **338**, 1729-1732. (1998)
45. Yan J, Zhang H, Liu Y, et al. Germline deletion of huntingtin causes male infertility and arrested spermiogenesis in mice. *J Cell Sci.* **129**, 492-501. (2016)
46. Clarkson PA, Davies HR, Williams DM, Chaudhary R, Hughes IA, Patterson MN. Mutational screening of the Wilms's tumour gene, WT1, in males with genital abnormalities. *J Med Genet* . **30**, 767-772, (1993)
47. Sugino Y, Usui T, Okubo K, et al. Genotyping of congenital adrenal hyperplasia due to 21-hydroxylase deficiency presenting as male infertility: case report and literature review. *J Assist Reprod Genet* . **23,** 377-380 (2006)

Mouse model	Comments	Conclusion variant/gene	Conclusion patient
Yes, Sertoli cell only described[2]	Centrosomal protein regulating centriole engagement and microtubule nucleation (UniProt: Q96SN8). Drosophila models shows meiotic and post-meiotic defects in sperm, mouse model a complete loss of male germ cells. This deficiency occurs in fetal life during the PGC-to-gonocyte transition and seems to result from the dysregulation of mitotic quiescence initiation[2]. In human, CDK5RAP2 is detected in both male and female FGCs[3], which is in line a potential role in maintaining the germ cell pool during embryonic development. Recessive variants described in microcephaly (OMIM: 604804).	Possibly causative	Candidate de novo point mutation (CDK5RAP2)
Yes, no infertility described	Catalyzes the hydrolysis of ATP (UniProt: P05023). Involved in sperm capacitation[4]. Gene very intolerant to LoF variation (pLi = 1; LOEUF = 0.12). Missense variants in this gene described in Charcot-Marie-Tooth disease (OMIM: 618036).	Unclear	Multiple candidate genes
Yes, no infertility described	Role in actin cytoskeleton for cell migration and adhesion (UniProt: Q9Y4G6). Expressed in spermatogonial stem cells[3]	Unclear	
Yes, Sertoli cell only	E3 ubiquitin-protein ligase (UniProt: Q7Z6Z7). Mouse model shows Sertoli cell only phenotype and HUWE1 is required for entry into meiosis and earliest steps in spermatogonial differentiation[5,6]. Interacts with known infertility gene TRIM37[7]. Glutamic acid repeat not well conserved. Expressed in spermatogonial stem cells, differentiating spermatognia and early primary spermatocytes[3]. Missense variants described in intellectual disability (OMIM: 309590)	Possibly causative	
Yes, no infertility described	1 fertile fathers in control cohort shares the exact mutation, Variant predicted to be benign by 3/3 prediction methods. ATP-dependent transporter (UniProt: Q5T3U5).	Not causative	No candidates
Yes, no infertility described	Variant predicted to be benign by 3/3 prediction methods. Copper binding function (UniProt: P00450). Interacts with known infertility gene APOA. Known gene for recessive Cerebellar ataxia (OMIM: 604290).	Unlikely causative	
Yes, maturation arrest[8]	4 fertile fathers in control cohort share the exact mutation, Involved in transcription regulation, RNA splicing, RNA transport,DNA repair and damage response (UniProt: P35637). Expressed in spermatogonial stem cells, differentiating spermatognia and early and late primary spermatocytes[3], Known gene for dominant essential tremor (OMIM: 614782)	Not causative	No candidates
Yes, no infertility described	Variant predicted to be benign by 2/3 prediction methods. Controls TGF-beta activation by maintaining it in a latent state during storage in extracellular space (UniProt: Q14766). Interacts with known infertility gene APOA. Expressed in spermatogonial stem cells[3]	Unlikely causative	
Yes, no infertility described	1 fertile father in control cohort shares the exact mutation, Outer segement of photoreceptors (UniProt: Q8IWN7). Known gene for dominant occult macular dystrophy (OMIM: 613587)	Not causative	No candidates
Yes, no infertility described	Transcriptional regulator recruiting SETDBP1 histone methyltransferase (UniProt: P11308). SETDB1 is crucial for maintainace of embryonic stem cell pools including spermatogonial stem/progenitor cells[9]	Unclear	Candidate de novo point mutation (ERG)
Not described	DNA-binding protein involved in cell cycle control (UniProt: Q99459).	Possibly causative	Candidate de novo point mutation (CDC5L)
Not described	Actin binding protein with potential role in retina development and exon guidance (UniProt: O14639). Expressed in late primary spermatocytes[10]	Possibly causative	Candidate de novo point mutation (ABLIM1)
Not described	2 fertile fathers in control cohort share the exact same mutation, Variant predicted to be benign by 3/3 prediction methods. Protein function unknown (UniProt: Q96EE4). Expressed in round and elongating spermatids and sperm[10]	Not causative	Candidate de novo point mutation (RASEF)
Not described	Binds predominantly GDP, and also GTP (UniProt: Q8IZ41)	Unclear	
Yes, female infertility described[11]	Stabilizes microtubules and may regulate actin fiber dynamics through the activation of Rho family GTPases (UniProt: O95996). APC2 is required for oogenesis in mouse and Drosophila[12,13] and is important for asymetric stem cell division of spermatogonial stem cells in Drosophila[14]. Gene known for recessive Sotos syndrome (OMIM: 617169)	Unclear	Candidate de novo point mutation (APC2)
Yes, no infertility described	2 fertile fathers in control cohort share the exact same mutation, Multi-functional cell surface receptor regulating cell adhesion in many diverse developmental processes (UniProt: Q92859)	Not causative	No candidates
Yes, no infertility described	Odorant receptor (Potential). May be involved in taste perception (UniProtKB:Q8WZ94)	Unclear	Candidate de novo point mutation (OR5P3)
Yes, no infertility described	Physiological suppressor of IKK-epsilon and TBK1 that plays an inhibitory role in virus- and TLR3-triggered IRF3. Inhibits TLR3-mediated activation of interferon-stimulated response elements (ISRE) and the IFN-beta promoter. May act by disrupting the interactions of IKBKE or TBK1 with TICAM1/TRIF, IRF3 and DDX58/RIG-I. Does not inhibit NF-kappa-B activation pathways (UniProtKB:Q9BRV8)	Unclear	Multiple candidate genes
Yes, no infertility described	E3 ubiquitin ligase capable of auto-ubiquitination, following phosphorylation by MAP3K3. Potentiates MAP3K3-mediated activation of the NF-kappa-B, JUN/AP1 and DDIT3 transcriptional regulators. Induces apoptosis when overexpressed. Plays a role in the phosphorylation of MAPK1 and/or MAPK3 (UniProtKB: Q6Q0C0) Interacts with known infertility gene TRIM37[7]	Possibly Causative	
Not described	Keratin, type I (UniProt: Q14525)	Unlikely causative	Candidate de novo point mutation (ATP8A1)
Yes, reduced female infertility	Variant predicted to be benign by 3/3 prediction methods.	Unlikely causative	
Yes, no infertility described	Catalytic component of a P4-ATPase flippase complex (UniProt: Q9Y2Q0)	Unclear	

Yes, no infertility described	Variant predicted to be benign by 2/3 prediction methods. May be required for adipogenesis (UniProt: Q8WTT2)	Unlikely causative	No candidates
Yes, no infertility described	Regulator of protein export for NES-containing proteins and mRNA nuclear export (UniProt Q9NPJ8). Gene is dispensable for fertility in mice[15]. No LoF variation found in this gene in gnomAD	Unlikely causative	No candidates
Yes, no infertility described	Cation channel that gives rise to very low constitutive currents in the absence of activation. The activated channel exhibits selectivity for sodium, and is inhibited by amiloride. (UniProtKB: Q9NY37)	Unclear	Candidate de novo point mutation (ASIC5)
Yes, no infertility described	Involved in an inositol phospholipid-based intracellular signaling cascade (UniProt: Q15111)	Unclear	Multiple candidate genes
Yes, no infertility described	Acts both as a chaperone in the cytosol and as a chromatin regulator in the nucleus (UniProt: Q99543). Is expressed in PGCs[3]. Gene is required for early embryonic development in mice[16]	Possibly causative	
Not described	Variant predicted to be benign by 3/3 prediction methods. Involved in maintaining the homeostasis of cellular nucleotides by catalyzing the interconversion of nucleoside phosphates (UniProt: Q9UIJ7).	Unlikely causative	
Yes, reduced female infertility[17]	Cytokine that binds to and signals through the IL1RL1/ST2 receptor which in turn activates NF-kappa-B and MAPK signaling pathways in target cells (PubMed:16286016). Involved in the maturation of Th2 cells inducing the secretion of T-helper type 2-associated cytokines. (UniProtKB: O95760)	Unlikely causative	No candidates
Yes, no infertility described	Binds DNA and functions as a transcriptional regulator (UniProtKB: Q9HAZ2). Interacts with known infertility gene CHD7[18].	Unclear	Multiple candidate genes
Yes, maturation arrest[19]	Gene is extremely LoF intolerant (pLi=0.99, LOEUF=0.24) Interacts with known infertility gene CDC14A[20]	Possibly Causative	
Yes, infertility of unknown type[21]	Component of the EvC complex that positively regulates ciliary Hedgehog (Hh) signaling (UniProt: P57679). Known gene for recessive Ellis van Creveld syndrome (OMIM: 225500). Gene not intolerant to LoF variation (Pli = 0, LOEUF = 1.06)	Unclear	Candidate de novo LoF mutation (EVC)
Yes, no infertility described	Variant predicted to be benign by 2/3 prediction methods. Involved in the regulation of homocysteine metabolism (UniProt: Q93088)	Unlikely causative	
Yes, no infertility described	Component of helicase essential for 'once per cell cycle' DNA replication initiation and elongation in eukaryotic cells (UniProt: Q14566). Expressed in PGCs, spermatogonial stem cells and differentiating spermatogonia[3,10]. Gene known for dominant lactase persistence/non-persistence (OMIM: 223100). Knock-down of MCM6 in germ cells in Drosophila resulted in sterility	Possibly causative	Candidate de novo point mutation (MCM6)
Not described	Component of a P4-ATPase flippase complex which catalyzes the hydrolysis of ATP (UniProt: Q8TF62)	Unlikely causative	No candidates
Not described	Variant predicted to be benign by 2/3 prediction methods. May be involved in transcriptional regulation (UniProt: Q9BSK1).	Unlikely causative	
Yes, no infertility described	Variant predicted to be benign by 3/3 prediction methods. Nucleoporin essential for nuclear pore assembly and fusion, nuclear pore spacing, as well as structural integrity (UniProt: Q8TEM1).	Unlikely causative	
Not described	Variant predicted to be benign by 2/3 prediction methods. Histone H1 protein binds to linker DNA between nucleosomes forming the macromolecular structure known as the chromatin fiber (UniProt: P16402)	Unlikely causative	No candidates
Not described	Fibronectin type III domain-containing protein (UniProt: Q8TC99). Expressed in elongated spermatids and sperm[10]	Unlikely causative	No candidates
Not described	Regulates autophagy by playing a role in the reduction of glucose production in an adiponectin- and insulin-dependent manner (UniProt: O94964). Microtubule-associated protein[22]. Very LoF intolerant gene (pLi = 1; LOEUF = 0.19)	Unclear	No candidates
Yes, reduced female infertility[23]	Structural component of specialized membrane microdomains known as tetraspanin-enriched microdomains (UniProt: P60033). Gene is important for fertilization[24]. CD82 is expressed in PGCs[3]. Known gene for recessive immunodeficiency (OMIM: 613496)	Possibly causative	Candidate de novo point mutation (CD81)
Yes, no infertility described	Phosphoinositide-binding protein which associates with both cell and endoplasmic reticulum (ER) membranes (UniProt: Q9H4L5). Gene not extremely intolerant to LoF variation (pLi = 0; LOEUF = 0.54)	Unclear	Candidate de novo point mutation (OSBPL3)
Yes, no infertility described	Variant predicted to be benign by 2/3 prediction methods. ATP-dependent low-affinity peptide transporter which translocates a broad spectrum of peptides from the cytosol to the lysosomal lumen (UniProt: Q9NP78)	Unlikely causative	No candidates
Yes, no infertility described	Variant predicted to be benign by 2/3 prediction methods. Receptor for interleukin-12. This subunit is the signaling component coupling to the JAK2/STAT4 pathway (UniProt: Q99665)	Unlikely causative	Candidate de novo point mutation (TOPAZ1)
Yes, maturation arrest at the level of spermatocytes[25]	Important for normal spermatogenesis and male fertility. Specifically required for progression to the post-meiotic stages of spermatocyte development (UniProt: Q8N9V7). Gene is abundantly expressed during meiosis[26]	Possibly causative	
Not described	1 fertile father in control cohort shares the exact mutation, Variant predicted to be benign in 2/3 prediction methods, May play a role in innate immunity by inhibiting the antiviral RIG-I signaling pathway (UniProt: Q92503)	Not causative	No candidates
Yes, no infertility described	Probable transcription activator for a number of lung-specific genes (UniProt: Q12947). Knock-down of FOXF2 in cysts cells in Drosophila resulted in sterility	Unclear	Candidate de novo point mutation (FOXF2)
Yes, no infertility described	Variant predicted to be benign by 2/3 prediction methods. Has E3 ubiquitin ligase activity, promoting ubiquitination and degradation of target proteins (UniProt: O95628)	Unlikely causative	No candidates
Not described	Expressed in elongated spermatids[10]. Uncharacterized protein (UniProt Q5SZB4)	Possibly causative	Candidate de novo point mutation (C9orf50)

Yes, no infertility described	Serine/threonine-protein kinase involved in transcription regulation, apoptosis and steroidogenic gene expression (UniProt: Q9H422). Overlaps with previously described CNV[27]. Gene moderately intolerant to LoF variation (pLi = 0.28)	Unclear	Multiple novel candidate genes
Not described	Glutamine and serine-rich protein (UniProt Q2KHR3). Overlaps with previously described CNV[27]. Gene very intolerant to LoF variation (pLi = 1)		
Not described	DEP domain-containing protein (UniProt: Q96QD5). Overlaps with previously described CNV[27]. Gene tolerant to LoF variation (pLi = 0)		
Not described	T-complex protein 11-like protein (UniProt: Q9NUJ3). Overlaps with previously described CNV[27]. Gene tolerant to LoF variation (pLi = 0)		
Yes, no infertility described	One of the multiple factors required for polyadenylation and 3'-end cleavage of mammalian pre-mRNAs (UniProt: Q12996). Overlaps with previously described CNV[27]. Gene very intolerant to LoF variation (pLi = 0.98)		
Yes, no infertility described	UPF0606 protein (UniProt: Q6ZVL6). Overlaps with previously described CNV[27]. Gene tolerant to LoF variation (pLi = 0)		
Not described	Tudor domain-containing protein (UniProt: Q5VZ19). Variant predicted to be benign by 2/3 prediction methods.	Unlikely causative	
Yes, male infertility of unknown type (MGI:1914535)	As part of the spliceosome, plays a role in pre-mRNA splicing (UniProt: Q6UX04). Known gene for recessive Retinitis pigmentosa (OMIM: 250410)	Possibly causative	
Yes, Meiotic arrest[28]	ATPase component of the chromatin remodeling INO80 complex which is involved in transcriptional regulation, DNA replication and DNA repair (UniProtKB: Q9ULG1) Interacts with knocn infertility gene FANCM[29]	Possibly Causative	Candidate de novo point mutation (INO80)
Not described	May be involved in transcriptional regulation (UniProt: Q8N972). Gene tolerant to LoF variation (pLi = 0; LOEUF = 1.86)	Unclear	Multiple novel candidate genes
Yes, no infertility described	May be responsible for anchoring smooth muscle cells to elastic fibers, and may be involved not only in the formation of the elastic fiber, but also in the processes that regulate vessel assembly (UniProt: Q9Y6C2)	Unclear	
Not described	WD repeat-containing protein (UniProt: Q8IZU2)	Unclear	
Not described	Variant predicted to be benign by 2/3 prediction methods. May be involved in transcriptional regulation (UniProt: Q5JNZ3)	Unlikely causative	
Yes, no infertility described	May play metabolic roles in sperm maturation or fertilization. Phospholipid transfer protein that preferentially selects lipid species containing a palmitoyl or stearoyl chain on the sn-1 and an unsaturated fatty acyl chain (18:1 or 18:2) on the sn-2 position. Able to transfer phosphatidylcholine (PC) and phosphatidyetanolamline (PE) between membranes (UniProtKB: Q9Y365)	Possibly Causative	Multiple novel candidate genes
Yes, male infertility of unknown type (MGI:3576497)	Plays a major role in early metanephros and genital development (UniProtKB: Q9C091), Known gene for Renal hypodysplasia (OMIM=617782) Gene is extremely LoF intolerant (pLI=1, LOEUF=0.07)	Possibly Causative	
Yes, Meiotic defects[30]	Involved in DNA mismatch repair and meiotic recombination processes. Facilitates crossovers between homologs during meiosis (UniProtKB: O43196) Gene is not LoF intolerant (pLI=0, LOEUF=0.7)	Unlikely causative	No candidates
Not described	Acetolactate synthase-like protein (UniProt A1L0T0)	Unclear	Candidate de novo point mutation (ILVBL)
Yes, no infertility described	Sequence-specific transcription factor (By similarity). Regulates multiple developmental processes including brainstem, inner and outer ear, abducens nerve and cardiovascular development and morphogenesis as well as cognition and behavior (UniProt: P49639).	Unclear	Candidate de novo point mutation (HOXA1)
Yes, no infertility described	May be involved in transcriptional regulation (UniProtKB: Q86UP3), Gene is extremely LoF intolerant (Pli=1, LOEUF=0.14)	Unclear	Candidate de novo LoF mutation (ZFHX4)
Not described	Variant predicted to be benign by 3/3 prediction methods. The B chain of factor XIII is not catalytically active, but is thought to stabilize the A subunits and regulate the rate of transglutaminase formation by thrombin (UniProt: P05160)	Unlikely causative	Candidate de novo point mutation (HNRNPL)
Yes, no infertility described	Splicing factor binding to exonic or intronic sites and acting as either an activator or repressor of exon inclusion (UniProt: P14866).	Possibly causative	
Yes, no infertility described	Inhibits autoprocessing of CASP1, CASP1-dependent IL1B secretion, PYCARD aggregation and PYCARD-mediated apoptosis but not apoptosis induced by FAS or BID (UniProt: Q8CW26). Variant predicted to be benign by 2/3	Unlikely causative	No candidates
Yes, no infertility described	Component of the PAF1 complex (PAF1C) which has multiple functions during transcription by RNA polymerase II and is implicated in regulation of development and maintenance of embryonic stem cell pluripotency (UniProt Q8WVC0).	Possibly causative	Candidate de novo point mutation (LEO1)
Not described	3 fertile fathers in cohort present with the exact same mutation. Variant predicted to be benign by 2/3 prediction	Not causative	No candidates
Not described	Targets myosin phosphatase to the actin cytoskeleton. Required for the regulation of the actin cytoskeleton by RhoA and ROCK1 (UniProt: Q6WCQ1)	Unclear	Candidate de novo point mutation (MPRIP)
Yes, no infertility described	The heterodimer formed by NGFR and SORCS2 functions as receptor for the precursor forms of NGF (proNGF) and BDNF (proBDNF) (UniProt: Q96PQ0)	Unlikely causative	
Yes, no infertility described	Gene is extremely LoF intolerant (Pli=1, LOEUF=0.19)	Unclear	Candidate de novo LoF mutation (TENM2)
Yes, no infertility described	Catalyzes the transfer of sulfate to position 4 of the N-acetylgalactosamine (GalNAc) residue of chondroitin and desulfated dermatan sulfate. (UniProtKB: Q9NRB3)	Unlikely causative	No candidates

Yes, female infertility described[32]	Histone demethylase that specifically demethylates both mono- and dimethylated 'Lys-9' of histone H3. May act as a transcription regulator controlling hair biology (via targeting of collagens), neural activity, and cell cycle (UniProt O43593). Known gene for recessive Alopecia universalis (OMIM: 203655) and Atrichia (OMIM: 209500) and dominant Hypotrichosis (OMIM: 146550)	Unlikely causative	Candidate de novo point mutation (SMC2)
Yes, no infertility described	Central component of the condensin complex, a complex required for conversion of interphase chromatin into mitotic-like condense chromosomes. The condensin complex probably introduces positive supercoils into relaxed DNA in the presence of type I topoisomerases and converts nicked DNA into positive knotted forms in the presence of type II topoisomerases (UniProt: O95347). Expressed in in spermatogenic stem cells, differentiating spermatogonia and early and late primary spermatocytes[10].	Possibly causative	
Yes, no infertility described	9 males in gnomAD carry the same variant. Plays a role in the microtubule-dependent coupling of the nucleus and the centrosome. Involved in the processes that regulate centrosome-mediated interkinetic nuclear migration (INM) of neural progenitors (By similarity). May play a role in organizing centrosomal microtubules (UniProt: O95359). Expressed in PGCs[3]. Interacts with known infertility gene AURKC	Unlikely causative	No candidates
Yes, no infertility described	A cytochrome P450 monooxygenase involved in the metabolism of endogenous polyunsaturated fatty acids (PUFAs). Mechanistically, uses molecular oxygen inserting one oxygen atom into a substrate, and reducing the second into a water molecule, with two electrons provided by NADPH via cytochrome P450 reductase (UniProtKB: Q9HCS2)	Unlikely causative	Candidate de novo point mutation (RBM5)
Yes, spermatid differentiation arrest[33]	Component of the spliceosome A complex. Regulates alternative splicing of a number of mRNAs. May modulate splice site pairing after recruitment of the U1 and U2 snRNPs to the 5' and 3' splice sites of the intron. (UniProtKB: P52756)	Possibly Causative	
Yes, no infertility described	Essential for cell viability. TAF9 and TAF9B are involved in transcriptional activation as well as repression of distinct but overlapping sets of genes. (UniProtKB: Q16594)	Unlikely causative	
Not described	8 fertile fathers in cohort present with the exact same mutation, Variant predicted to be benign by 3/3 prediction methods. May act as a downstream effector of CDC42 in cytoskeletal reorganization (UniProt: Q6DT37)	Not causative	Candidate de novo point mutation (RPA1)
Yes, no infertility described	As part of the heterotrimeric replication protein A complex (RPA/RP-A), binds and stabilizes single-stranded DNA intermediates, that form during DNA replication or upon DNA stress. It prevents their reannealing and in parallel, recruits and activates different proteins and complexes involved in DNA metabolism (UniProt: P27694). Epxressed in PGCs[3]. Plays an important role in meiotic recombination[34,35]. Interacts with known infertility genes TEX15 and FANCA.	Possibly causative	
Yes, no infertility described	Regulator of APC activity during mitotic and meiotic cell cycle, also known as EMI1 (UniProt: Q9UKT4). Required for entry into meiosis and transition from meiosis I to meiosis II in Xenopus oocytes[36]. Expressed in early primary spermatocytes[10]. Gene is extremely intolerant to LoF variation (pLi = 0.97; LOEUF = 0.32).	Possibly causative	Candidate de novo LoF mutation (FBXO5)
Yes, no infertility described	Muscle-specific filamin, which plays a central role in muscle cells, probably by functioning as a large actin-cross-linking protein. (UniProtKB: Q14315), Interacts with known infertility gene CFTR[37].	Unclear	Candidate de novo point mutation (FLNC)
Yes, no infertility described	2 fertile fathers in control cohort share the exact same mutation, Variant predicted to be benign by 2/3 prediction methods. Component of the chromosomal passenger complex (CPC), a complex that acts as a key regulator of mitosis. The CPC complex has essential functions at the centromere in ensuring correct chromosome alignment and segregation and is required for chromatin-induced microtubule stabilization and spindle assembly. Major effector of the TTK kinase in the control of attachment-error-correction and chromosome alignment (UniProt: Q53HL2). Interacts with known infertility gene AURKC	Not causative	No candidates
Not described	Variant predicted to be benign by 3/3 prediction methods. Zinc finger CCHC domain-containing protein (UniProt: Q9C0B9)	Unlikely causative	No candidates
Yes, no infertility described	AMP deaminase plays a critical role in energy metabolism (UniProtKB: Q01433)	Unclear	Candidate de novo point mutation (AMPD2)
Yes, no infertility described	13 fertile fathers in cohort present with the exact same mutation, This protein specifically binds to the DNA sequence 5'-GGGACTTTCC-3' which is found in the enhancer elements of numerous viral promoters such as those of SV40, CMV, or HIV-1 (UniProtKB: P15822)	Not causative	
Yes, abnormal flagellum morphology[38]	Required for correct axoneme development in spermatozoa. Important for normal development of the manchette and sperm head morphology. Essential for male fertility. Plays a role in localization of the intraflagellar transport protein IFT20 to the manchette, suggesting function as an adapter for dynein-mediated protein transport during spermatogenesis (UniProtKB: Q9C093)	Unlikely causative	
Not described	3 fertile fathers in cohort present with the exact same mutation, Variant predicted to be benign by 2/3 prediction methods. Putative adhesion molecule that mediates sialic-acid dependent binding to cells (UniProt: Q96LC7)	Not causative	No candidates
Yes, no infertility described	Variant predicted to be benign by 2/3 prediction methods. Seems to act as a glycogen-targeting subunit for PP1. PP1 is essential for cell division, and participates in the regulation of glycogen metabolism, muscle contractility and protein synthesis. Plays an important role in glycogen synthesis but is not essential for insulin activation of glycogen synthase (UniProt: Q16821). Known gene for dominant Insulin resistance (OMIM: 125853)	Unlikely causative	No candidates

Yes, no infertility described	1 fertile father in control cohort shares the exact mutation,Variant predicted to be benign by 3/3 prediction methods. Sulfotransferase that utilizes 3'-phospho-5'-adenylyl sulfate (PAPS) as sulfonate donor to catalyze the transfer of sulfate to position 6 of non-reducing N-acetylglucosamine (GlcNAc) residues within mucin-associated glycans that ultimately serve as SELL ligands (UniProt: Q8NCG5)	Not causative	Candidate de novo point mutation (STXBP2)
Yes, no infertility described	Involved in intracellular vesicle trafficking and vesicle fusion with membranes. Contributes to the granule exocytosis machinery through interaction with soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins that regulate membrane fusion (UniProt: Q15833).	Unclear	
Not described	3 fertile fathers in cohort present with the exact same mutation, Displays an antiviral effect against flaviviruses such as west Nile virus (WNV) in the presence of OAS1B (UniProt: Q9NUQ8). Expressed in PGCs[3].	Not causative	No candidates
Not described	Transmembrane protein (UniProt: Q0P6H9). Expressed in 10 week old PGCs[3]	Unclear	Candidate de novo point mutation (*U2AF2*)
Not described	Plays a role in pre-mRNA splicing and 3'-end processing. By recruiting PRPF19 and the PRP19C/Prp19 complex/NTC/Nineteen complex to the RNA polymerase II C-terminal domain (CTD), and thereby pre-mRNA, may couple transcription to splicing (UniProt: P26368). Expressed in spermatogonial stem cells, differentiating spermatogonia and early and late primary spermatocytes[3]. Interacts with known infertility gene WT1. Knock-down of U2AF2 in cysts cells in Drosophila resulted in subfertility	Possibly causative	
Yes, no infertility described	Helicase that acts as a transcriptional coactivator for a number of nuclear receptors including PPARA, PPARG, THRA, THRB and RXRA (UniProt: Q9BYK8). Interacts with known infertility gene APOA1.	Unclear	Candidate de novo point mutation (HELZ2)
Yes, no infertility described	May be a transcriptional repressor of NRL function in photoreceptors (UniProtKB: Q9WTJ4)	Unclear	Candidate de novo point mutation (FIZ1)
Yes, no infertility described	Variant predicted to be benign by 3/3 prediction methods. Required for innate immune defense against viruses (UniProtKB: Q7Z434)	Unlikely causative	Candidate de novo point mutation (TMPPE)
Not described	Involved in hydrolase activity (UniProtKB - Q6ZT21)	Unclear	
Yes, no infertility described	Variant predicted to be benign by 2/3 prediction methods. Involved in hearing and vision as member of the USH2 complex. In the inner ear, required for the maintenance of the hair bundle ankle formation, which connects growing stereocilia in developing cochlear hair cells. In retina photoreceptors, the USH2 complex is required for the maintenance of periciliary membrane complex that seems to play a role in regulating intracellular protein transport (UniProt: O75445). Known gene for recessive Usher syndrome (OMIM: 276901)	Unlikely causative	No candidates
Not described	Variant predicted to be benign by 3/3 prediction methods. Epithelial membrane protein (UniProt: P54849)	Unlikely causative	No candidates
Yes, no infertility described	Variant predicted to be benign in 2/3 prediction methods. Involved in 3'-5'-exoribonuclease activity (UniProtKB: O43414)	Unlikely causative	No candidates
Yes, no infertility described	May play a role in the maintenance of heart function mediated, at least in part, through cAMP-binding (UniProtKB: Q9HBV1)	Unclear	Candidate de novo point mutation (POPDC3)
Yes, [39]	Variant predicted to be benign by 2/3 prediction methods, Binds specifically to phosphatidylinositol 3,4-diphosphate (PtdIns3,4P2), but not to other phosphoinositides. May recruit other proteins to the plasma membrane (UniProtKB: Q9HB21)	Unlikely causative	No candidates
Yes, no infertility described	Variant predicted to be benign by 2/3 prediction methods, Regulates transcription in association with TATA binding protein (UniProtKB: O14981)	Unlikely causative	
Not described	Positively regulates hepatic SREBP signaling pathway by modulating the proper localization of SCAP (SREBP cleavage-activating protein) to the endoplasmic reticulum, thereby controlling the level of functional SCAP (UniProtKB: Q9H741)	Unclear	Candidate de novo point mutation (C12orf49)
Yes, no infertility described	13 males in gnomAD carry the same mutation. Variant predicted to be benign by 2/3 prediction methods, May play a role as a localized scaffold for the assembly of a multiprotein signaling complex and as mediator of the trafficking of its binding partners at specific subcellular location in neurons (UniProtKB: Q9Y3R0)	Unlikely causative	No candidates
Yes, no infertility described	10 males in gnomAD carry the same mutation, Variant predicted to be benign by 3/3 prediction methods, Involved in metal ion binding (UniProtKB: E7ERA6)	Unlikely causative	Multple novel candidate genes
Yes, no infertility described	May be involved in transcriptional regulation (UniProtKB: Q96JG9), (Pli score = 0.72, LOEUF= 0.37)	Unclear	
Yes, no infertility described	Component of a protein kinase signal transduction cascade. Mediates activation of the NF-kappa-B, AP1 and DDIT3 transcriptional regulators, (UniProtKB: Q99759), Interacts with known infertility gene CDC14A[20]	Possibly Causative	
Yes, no infertility described	Variant predicted to be benign by 3/3 prediction methods, Uncharacterized protein (UniProtKB: Q0P670)	Unlikely causative	
Yes, no infertility described	Serine protease (UniProtKB: Q86T26)	Unclear	
Not described	This protein is involved in the pathway protein ubiquitination, which is part of Protein modification (UniProtKB - A0A6D2WFD3)	Unclear	Candidate de novo point mutation (GPR75-ASB3)
Yes, male infertility due to detachment of the sperm head[40,41]	Component of the outer dense fibers (ODF) of spermatozoa. ODF are filamentous structures located on the outside of the axoneme in the midpiece and principal piece of the mammalian sperm tail and may help to maintain the passive elastic structures and elastic recoil of the sperm tail (UniProt: Q14990). ODF1 is reduced in infertile males[42]. ODF1 is expressed in round and elongating spermatids and sperm[10].	Possibly causative	Candidate de novo point mutation (ODF1)
Yes, [43]	Putative catalytic component of the RNA exosome complex which has 3'->5' exoribonuclease activity and participates in a multitude of cellular RNA processing and degradation events. (UniProtKB: Q01780) Gene is not LoF intolerant (Pli=0, LOEUF=0.74)	Unclear	Candidate de novo point mutation (EXOSC10)

Yes, no infertility described	1 fertile father in control cohort shares the exact mutation, Variant predicted to be benign by 3/3 prediction methods. May act as an adhesion molecule (UniProt: Q7RTW8). Known gene for recessive deafness (OMIM:607039)	Not causative	No candidates
Yes, no infertility described	G-protein coupled receptor for CRH (corticotropin-releasing factor) and UCN (urocortin). Has high affinity for CRH and UCN. Ligand binding causes a conformation change that triggers signaling via guanine nucleotide-binding proteins (G proteins) and down-stream effectors, such as adenylate cyclase. Promotes the activation of adenylate cyclase, leading to increased intracellular cAMP levels (UniProtKB: P34998), Interacts with known infertility gene FSHB[44]	Unclear	Multiple novel candidate genes
Yes, early stage arrest[45]	May play a role in microtubule-mediated transport or vesicle function.(UniProtKB: P42858) Gene is extremely LoF intolerant (Pli=1, LOEUF=0.18) Gene is associated with Autosomal dominant Huntington disease (OMIM: 613004)	Possibly Causative	
Yes, no infertility described	Variant predicted to be benign by 3/3 prediction methods, Involved in calcium ion binding (UniProtKB: Q8TER0)	Unlikely causative	Candidate de novo LoF mutation (PCDHB1)
Yes, no infertility described	Potential calcium-dependent cell-adhesion protein. May be involved in the establishment and maintenance of specific neuronal connections in the brain. (UniProtKB: Q9Y5F3), Gene is not LoF intolerant (Pli= 0, LOUEF =1.31)	Unclear	
Yes, no infertility described	Involved in cytokinesis and spindle organization. May play a role in actin cytoskeleton organization and microtubule stabilization and hence required for proper cell adhesion and migration. (UniProtKB: Q69YQ0)	Possibly Causative	Candidate de novo point mutation (SPECC1L)
Yes, no infertility described	Guanine nucleotide exchange factor for ARF1 and ARF6 (UniProt: Q6DN90).	Unclear	Candidate de novo point mutation (IQSEC1)
Yes, no infertility described	May be involved in several stages of intracellular trafficking. (UniProtKB: O14559)	Unclear	Candidate de novo point mutation (ARHGAP33)
Yes, male infertility of unknown type (MGI:1920537)	1 fertile father in control cohort shares the exact mutation, Calcium-binding protein. May be involved in the control of sperm flagellar movement (UniProtKB: Q8IVU9)	Not causative	
Yes, no infertility described	Involved in the development and maintenance of excitatory synapse in the vertebrate nervous system. Regulates surface expression of AMPA receptors and instructs the development of functional glutamate release sites (UniProtKB: O43300)	Unclear	Candidate de novo point mutation (LRRN2)
Yes, no infertility described	Variant predicted to be benign by 2/3 prediction methods. Acts as a negative regulator of SRC by activating CSK which inhibits SRC activity and downstream signaling, leading to impaired cell spreading and migration (UniProtKB: Q9C0H9)	Unlikely causative	
Yes, no infertility described	Renin is a highly specific endopeptidase, whose only known function is to generate angiotensin I from angiotensinogen in the plasma, initiating a cascade of reactions that produce an elevation of blood pressure and increased sodium retention by the kidney (UniProtKB: P00797). Interacts with known infertility genes WT1[46] and CYP21A2[47]	Unclear	Multiple novel candidate genes
Yes, no infertility described	Plays a critical role in epithelial cell morphogenesis, polarity, adhesion and cytoskeletal organization in the lens (UniProtKB - O60292)	Unclear	
Not described	May play a significant role in p53/TP53-mediating signaling pathway. (UniProtKB: Q9Y2B4)	Possibly Causative	Candidate de novo point mutation (TP53TG5)
Yes, no infertility described	Variant predicted to be benign by 2/3 prediction methods, Multifunctional ATP-dependent helicase that unwinds G-quadruplex (G4) structures (UniProtKB: Q9H2U)	Unlikely causative	
Yes, no infertility described	Variant predicted to be benign by 2/3 prediction methods, Chromatin reader component of the ATAC complex, a complex with histone acetyltransferase activity on histones H3 and H4 (UniProtKB: Q9ULM3)	Unlikely causative	
Yes, no infertility described	May regulate calcium-dependent activities in the endoplasmic reticulum lumen or post-ER compartment (UniProtKB: Q9BRK5)	Possibly Causative	Multiple novel candidate genes
Yes, no infertility described	Adapter protein that may provide indirect link between the endocytic membrane traffic and the actin assembly machinery (UniProtKB: Q9NZM3), Interacts with known infertility gene CFTR[37]	Unclear	
Yes, no infertility described	1 fertile father in control cohort shares the exact mutation, Calcium/phospholipid-binding protein that plays a role in the plasmalemma repair mechanism of endothelial cells that permits rapid resealing of membranes disrupted by mechanical stress. Involved in endocytic recycling. (UniProtKB: Q9NZM1)	Not causative	Candidate de novo LoF mutation (RASAL2)
Yes, no infertility described	Inhibitory regulator of the Ras-cyclic AMP pathway (UniProtKB: Q9UJF2), Gene relatively intolerant to LoF mutations (pLi score = 0.8, LOEUF=0.34)	Possibly Causative	
Yes, no infertility described	Inhibitory receptor that acts as a critical regulator of hematopoietic lineage differentiation, megakaryocyte function and platelet production (UniProtKB: O95866)	Unclear	Candidate de novo point mutation (C6orf25)
Yes, no infertility described	Kinesin is a microtubule-associated force-producing protein that may play a role in organelle transport. (UniProtKB: Q07866), Gene is not LoF intolerant (pLi= 0.37, LOUEF =0.41)	Unclear	Candidate de novo LoF mutation (KLC1))
Yes, no infertility described	Has a role in pre-mRNA splicing (UniProtKB: Q13523)	Unclear	Candidate de novo point mutation (PRPF4B)
Yes, no infertility described	May be involved in transcriptional regulation. (UniProtKB :Q9UEG4)	Unclear	Candidate de novo point mutation (ZNF629)
Yes, no infertility described	Variant predicted to be benign by 3/3 prediction methods. Olfactory receptor binding (UniProtKB: Q14D33)	Unlikely causative	
Yes, no infertility described	Binds to the IL-1 type I receptor following IL-1 engagement, triggering intracellular signaling cascades leading to transcriptional up-regulation and mRNA stabilization (UniProtKB: O43187)	Unlikely causative	
Yes, no infertility described	Variant predicted to be benign by 2/3 prediction methods. Key regulator of mitochondrial calcium uniporter (MCU) that senses calcium level via its EF-hand domains (UniProtKB : Q9BPX6)	Unlikely causative	No candidates

Yes, infertility of unknown type[1]	Receptor for GRF, coupled to G proteins which activate adenylyl cyclase. Stimulates somatotroph cell growth, growth hormone gene transcription and growth hormone secretion. (UniProtKB: Q02643)	Unlikely causative	No candidates
Yes, no infertility described	Receptor that may have an important role in cell/cell signaling during nervous system formation (UniProtKB: Q9HCU4)	Unclear	Candidate de novo point mutation (CELSR2)
Yes, no infertility described	Involved in protein domain specific binding (UniProtKB: P80723)	Unlikely causative	