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Review article

Expanded carrier screening: A current perspective

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ABSTRACT

Prenatal carrier screening has expanded to include a large number of genes offered to all couples considering pregnancy or with an ongoing pregnancy. Expanded carrier screening refers to identification of carriers of single-gene disorders outside of traditional screening guidelines. Expanded carrier screening panels include numerous autosomal recessive and X-linked genetic conditions, including those with a very low carrier frequency, as well as those with mild or incompletely penetrant phenotype. Therefore, the clinical utility of these panels is still subject of debate. Priority should be given to carrier screening panels that include a comprehensive set of severe childhood-onset disorders. Psychosocial support and genetic couseling should be available prior to screening and for the return of positive results. Systems are needed to reduce the \risk of misinterpreting results. Finally, attention should be paid on the impact of expanded carrier screening on health care organizations and burden of cost.

Contents

Background on carrier screening

Carrier screening is defined as a genetic study aimed at discovering the presence of carriers for autosomal recessive or X-linked recessive disorders in a not at *a priori* risk population, based on the personal and family genetic disease history [1].

Nowadays we count more than 2000 recessive disorders among autosomal and X-linked [2–5]. Recessive disorders affect at least 25 in 10,000 children and 1 in 100 couples are carriers, with a risk of 25% of having a child affected with an autosomal recessive genetic condition [1,5,6]. Currently, carrier screening is becoming a standard practice for individuals with a positive family history of a recessive disease [7].

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We can identify two different time intervals where carrier screening can be offered to individuals or couples: preconception screening before pregnancy, and prenatal during pregnancy. Although the prenatal screening is at present the one most performed, the preconceptional screening seems to be a better alternative to allow the parents conscious reproductive choices [7]. Newborn screening must be distinguished from carrier screening. The aim of newborn screening is to detect deseases for early treatment by testing directly the newborn. Carrier screening may allow the neonates to obtain medical care earlier than newborn screening. Carrier screening alone, however, without newborn screening would miss many affected neonates [8].

One of the major discussions about carrier scrrening is to whom it should be offered. It can be offered to individuals, usually the woman, or couples, especially when a maternal or paternal mutation is identified. Moreover, populations with different risks for heterozygous carrier frequency can be examined: low risk populations in which the test can be part of a general screening program or high risk populations because of positive family history or being a member of a particular ethnic group [2,7,9,10].

In 2013, the American College of Medical Genetics and Genomics (ACMG) published a position statement on carrier screening.[11] For a disorder to be included in carrier screening, ACMG set the following criteria: the at-risk patients and their partners identified would consider having a prenatal diagnosis; when adult-onset disorders are included in the screening panels, patients must provide consent to screening for these conditions; the causative gene(s), mutations and mutation frequencies should be known in the population being tested so that residual risk in those who test negative can be assessed; there must be a strong clinical association between mutation(s) and the severity of the disorder and compliance with ACMG quality control and proficiency testing. Genetic counseling before testing should be available and post-test genetic counseling for those with positive results is recommended. ACMG discourages including as many disorders as possible, not only because it could be not appropriated belonging to a criteria, but also because it could be unpractical for a provider to discuss each clinical condition included in a multidisease carrier screening panel [11]. Other societies such as, ACOG, the National Society of Genetics Counselors and the Society of Maternal-Fetal Medicine (SMFM) agree with ACMG criteria and reccomendations [12].

In 2017, the ACOG's Committee Opinion, Carrier Screening in the Age of Genomic Medicine, defined similar criteria and recommendations for clinicians to evaluate predefined commercial expanded carrier panels and to determine their appropriateness [13].

- Expanded carrier screening is an acceptable strategy for prepregnancy and prenatal screening
- Counseling should be offered;
- Patients should be counseled regarding residual risk with negative result;
- The reproductive partner of a woman found to be a carrier for a specific condition should be offered screening. If carriers for the same mutation are identified before pregnancy, genetic counseling is encouraged to discuss and maximize reproductive options (donor gametes, preimplantation genetic diagnosis, prenatal diagnosis);
- Given the high variability of genetic panels currently on the market, the disorders selected for inclusion should meet several of the following consensus-determined criteria: have a carrier frequency of 1 in 100 or greater, have a well-defined phenotype, have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life. Additionally, screened conditions should be able to be diagnosed prenatally and may afford opportunities for antenatal intervention to improve perinatal outcomes, changes to delivery management to optimize newborn and infant outcomes, and education of the parents about special care needs after birth. Carrier screening panels should not include conditions primarily associated with a disease of adult onset.

Nowadays, carrier screening has expanded to include a larger number of genes offered to all couples considering pregnancy or with an ongoing pregnancy. Benefits of including too many conditions in expanded panels must be weighed against harms in order to limit the psychological consequences of anxiety, stigmatization and confusion, financial expense, and clinician time and optimize the utility of the screening [14–16].

Stevens et al. established more specific criteria for inclusion of genetic conditions on expanded panels and analyzed several commercially available screening panels to evaluate if they are in line with the committee opinion [14]. On average, 73% of conditions on expanded carrier screening panels they analyzed did not match the criteria recommended by ACMG and ACOG. Terhaar et al. found that with a panel of 218 diseases, the likelihood of identifying a carrier can be as high as 36% [15].

New generation expanded carrier screening

In the age of genomic medicine, the interest in the carrier screening is growing as the genetic tests are becoming widely available and their costs are much more affordable. In the past, carrier screening has evaluated a relatively small group of mutations selected based on two main characteristics: high frequency in specific populations and severe morbidity and mortality. Currently, commercial laboratories offer test panels that screen for four to over 1700 diseases, which are not selected based on racial or ethnic background. The majority of conditions are autosomal-recessive, but some may be X-linked or autosomal-dominant single gene disorders. The rationale for expanded carrier screening is that the majority of carrier individuals have no family history of the genetic condition(s) they carry, or are not aware of their full ancestry or true ethnicity. Table 1 shows one of the preconceptional expanded carrier screening panels available on the market, including more than 700 conditions. These expanded panels include also some conditions that result in only mild to moderate health complications (e.g. factor V Leiden), have significant variations in or poorly defined pehotype (e.g. fragile X) or have onset in adulthood (e.g. BRCA1/2). The frequency of some conditions is unknown in the general population, rendering calculation of residual risk after a positive test inconclusive. Including these type of conditions in a screening panel is in direct conflict with the accepted clinical criteria for screening programs [4,6,12]. Moreover, identifying variants of uncertain clinical significance, may create patient anxiety despite counselling, which will complex and time-consuming with the inclusion of large set of disorders on the expanded screening panel. Therefore, the clinical utility of these exapanded panels is still subject to debate.

Diseases screened

In 1968, Wilson and Jungner outlined the principles for using a screening test for early disease detection [4]. These principles are still used by the World Health Organization and are still valid to justify a screening program. For reproductive screening, the aim is not of early diagnosis but to facilitate reproductive decision making.

One of the biggest challenges in the development of expanded carrier screening is to identify the appropriate criteria to uniform the test and to reduce the huge variability in current commercially available panels. The European Society of Human Genetics

Table 1
Example of one of the preconceptional expanded carrier screening panel available on the market.

	Disease Name	PhenOMIM	Gene
1	17-alpha-hydroxylase/17,20-lyase deficiency	202110	*CYP17A1*
2	17-beta-hydroxysteroid dehydrogenase X deficiency	300438	*HSD17B10*
3	3-beta-hydroxysteroid dehydrogenase, type II, deficiency	201810	*HSD3B2*
4	3-hydroxy-3-methylglutaric aciduria	246450	*HMGCL*
5	3-methylglutaconic aciduria type 1	250950	*AUH*
6	3-methylglutaconic aciduria type 3	258501	*OPA3*
7	46XY sex reversal 3	612965	*NR5A1*
8	4-hydroxybutyric aciduria	271980	*ALDH5A1*
9	Aarskog-Scott syndrome	305400	*FGD1*
10	ABCD syndrome	600501	*EDNRB*
11	Achalasia-addisonianism-alacrimia syndrome	231550	*AAAS*
12	Achondrogenesis type 1B	600972	*SLC26A2*
13	Acyl-CoA dehydrogenase 9 deficiency	611126	*ACAD9*
14	Adrenal hyperplasia, congenital, due to 11-beta-hydroxylase deficiency	202010	*CYP11B1*
15	Adrenal insufficiency, congenital, with 46XY sex reversal, partial or complete	613743	*CYP11A1*
16	Adrenocortical insufficiency	612965	*NR5A1*
17	Adrenoleukodystrophy	300100	*ABCD1*
18	Adult neuronal ceroid lipofuscinosis	256730	*PPT1*
19	Adult neuronal ceroid lipofuscinosis 10	610127	*CTSD*
20	Adult neuronal ceroid lipofuscinosis 4A	204300	*CLN6*
21	Aicardi-Goutières syndrome	225750	*TREX1*
22	Aicardi-Goutieres syndrome 2	610181	*RNASEH2B*
23	Aicardi-Goutieres syndrome 3	610329	*RNASEH2C*
24	Aicardi-Goutieres syndrome 4	610333	*RNASEH2A*
25	Aicardi-Goutieres syndrome 5	612952	*SAMHD1*
26	Aldosteronism, glucocorticoid-remediable	103900	*CYP11B1*
27	Allan-Herndon-Dudley syndrome	300523	*SLC16A2*
28	Alpers syndrome	203700	*POLG*
29	Alpha-methylacyl-Coa Racemase deficiency	614307	*AMACR*
30	Alph A-T halassemia	604131	*HBA1*
31	Alph A-T halassemia myelodysplasia syndrome, somatic	300448	*ATRX*
32	Alph A-T halassemia/mental retardation syndrome	301040	*ATRX*
33	Alport syndrome	301050	*COL4A5*
34	Alport syndrome autosomal recessive (gene COL4A3)	203780	*COL4A3*
35	Alport syndrome autosomal recessive (gene COL4A4)	203780	*COL4A4*
36	Alström syndrome	203800	*ALMS1*
37	Amish infantile epilepsy syndrome	609056	*ST3GAL5*
38	Amyotrophic lateral sclerosis 2, juvenile	205100	*ALS2*
39	Anauxetic dysplasia	607095	*RMRP*
40	Angelman syndrome	105830	*UBE3A*
41	Antenatal Bartter syndrome	241200	*KCNJ1*
42	Antenatal Bartter syndrome type 1	601678	*SLC12A1*
43	Antley-Bixler syndrome with genital anomalies and disordered steroidogenesis	201750	*POR*
44	Aplasia/hypoplasia of limbs and pelvis	276820	*WNT7A*
45	Aplastic anemia	609135	*NBN*
46	Apparent mineralocorticoid excess	218030	*HSD11B2*
47	Argininosuccinic aciduria	207900	*ASL*
48	Aromatic L-amino acid decarboxylase deficiency	608643	*DDC*
49	Arthrogryposis - renal dysfunction - cholestasis	208085	*VPS33B*
50	Arthrogryposis, renal dysfunction, and cholestasis 2	613404	*VIPAR*
51	Ataxia - oculomotor apraxia type 1	208920	*APTX*
52	Ataxia with vitamin E deficiency	277460	*TTPA*
53	Ataxi A-T elangiectasia	208900	*ATM*
54	Atelosteogenesis type II	256050	*SLC26A2*
55	Autism, susceptibility to, X-linked 5	300847	*RPL10*
56	Autoimmune lymphoproliferative syndrome, type IA	601859	*FAS*
57	Autoimmune lymphoproliferative syndrome, type IB	601859	*FASLG*
58	Autoimmune lymphoproliferative syndrome, type II	603909	*CASP10*
59	Autoimmune polyendocrinopathy syndrome, type I, with or without reversible metaphyseal dysplasia	240300	*AIRE*
60	Autosomal dominant Charcot-Marie-Tooth disease type 2K	607831	*GDAP1*
61	Autosomal recessive ataxia due to ubiquinone deficiency	612016	*ADCK3*
62	Autosomal recessive Charcot-Marie-Tooth disease with hoarseness	607706	*GDAP1*
63	Autosomal recessive distal spinal muscular atrophy type 4	611067	*PLEKHG5*
64	Autosomal recessive dopa-responsive dystonia	605407	*TH*
65	Autosomal recessive hypophosphatemic rickets 1	241520	*DMP1*
66	Autosomal recessive hypophosphatemic rickets 2	613312	*ENPP1*
67	Autosomal recessive intermediate Charcot-Marie-Tooth disease type A	608340	*GDAP1*
68	Autosomal recessive limb-girdle muscular dystrophy type 2I	607155	*FKRP*
69	Autosomal recessive limb-girdle muscular dystrophy type 2M	611588	*FKTN*
70	Autosomal recessive limb-girdle muscular dystrophy type C	613157	*POMGNT1*
71	Autosomal recessive limb-girdle muscular dystrophy type C	609308	*POMT1*
72	Autosomal recessive limb-girdle muscular dystrophy type C	613158	*POMT2*
73	Autosomal recessive malignant osteopetrosis 1	259700	*TCIRG1*
74	Autosomal recessive malignant osteopetrosis 4	611490	*CLCN7*

Table 1 (*Continued*)

	Disease Name	PhenOMIM	Gene
75	Autosomal recessive nonsyndromic sensorineural deafness type DFNB12	601386	*CDH23*
76	Autosomal recessive nonsyndromic sensorineural deafness type DFNB18	602092	*USH1C*
77	Autosomal recessive nonsyndromic sensorineural deafness type DFNB1A (gene GJB2)	220290	*GJB2*
78	Autosomal recessive nonsyndromic sensorineural deafness type DFNB2	600060	*MYO7A*
79	Autosomal recessive polycystic kidney disease	263200	*PKHD1*
80	Autosomal recessive progressive external ophthalmoplegia	258450	*POLG*
81	Autosomal recessive spastic ataxia of Charlevoix-Saguenay	270550	*SACS*
82	Autosomal recessive spondylocostal dysostosis 1	277300	*DLL3*
83	Bannayan-Riley-Ruvalcaba syndrome	153480	*PTEN*
84	Barth syndrome	302060	*TAZ*
85	Becker muscular dystrophy	300376	*DMD*
86	Beckwith-Wiedemann syndrome	130650	*NSD1*
87	Bet A-T halassemia	613985	*HBB*
88	Bethlem myopathy	158810	*COL6A1*
89	Bethlem myopathy	158810	*COL6A2*
90	Bethlem myopathy	158810	*COL6A3*
91	Bifunctional enzyme deficiency	261515	*HSD17B4*
92	Biotinidase deficiency	253260	*BTD*
93	Björnstad syndrome	262000	*BCS1L*
94	Bloom syndrome	210900	*BLM*
95	Brachytelephalangic chondrodysplasia punctata	302950	*ARSE*
96	Brittle cornea syndrome	229200	*ZNF469*
97	Caffey disease	114000	*COL1A1*
98	Canavan disease	271900	*ASPA*
99	Carbamoylphosphate synthetase deficiency	237300	*CPS1*
100	Cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency 1	604377	*SCO2*
101	Cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency 2	615119	*COX15*
102	Carnitine deficiency, systemic primary	212140	*SLC22A5*
103	Carnitine palmitoyl transferase 1A deficiency	255120	*CPT1A*
104	Carnitine palmitoyl transferase II deficiency, infantile form	600649	*CPT2*
105	Carnitine palmitoyl transferase II deficiency, neonatal form	608836	*CPT2*
106	Carnitine-acylcarnitine translocase deficiency	212138	*SLC25A20*
107	Carpenter syndrome	201000	*RAB23*
108	Cartilage-hair hypoplasia	250250	*RMRP*
109	Cataract - intellectual deficit - hypogonadism	212720	*RAB3GAP2*
110	Cataract 40, X-linked	302200	*NHS*
111	Cerebellar ataxia - intellectual deficit - dysequilibrium syndrome	224050	*VLDLR*
112	Cerebral dysgenesis-neuropathy-ichthyosis-palmoplantar keratoderma syndrome	609528	*SNAP29*
113	Cerebrotendinous xanthomatosis	213700	*CYP27A1*
114	Charcot-Marie-Tooth disease axonal type 2B1	605588	*LMNA*
115	Charcot-Marie-Tooth disease type 4A	214400	*GDAP1*
116	Charcot-Marie-Tooth disease type 4E	605253	*EGR2*
117	Charcot-Marie-Tooth disease type 4F	614895	*PRX*
118	Charcot-Marie-Tooth disease type 4H	609311	*FGD4*
119	Charcot-Marie-Tooth disease, type 1A	118220	*PMP22*
120	Charcot-Marie-Tooth disease, type 1B	118200	*MPZ*
121	Charcot-Marie-Tooth disease, type 1E	118300	*PMP22*
122	Charcot-Marie-Tooth disease, type 2I	607677	*MPZ*
123	Charcot-Marie-Tooth disease, type 2J	607736	*MPZ*
124	Chediak-Higashi syndrome	214500	*LYST*
125	Chilblain lupus 2	614415	*SAMHD1*
126	Childhood-onset hypophosphatasia	241510	*ALPL*
127	Cholestasis, benign recurrent intrahepatic	243300	*ATP8B1*
128	Cholestasis, benign recurrent intrahepatic, 2	605479	*ABCB11*
129	Cholestasis, intrahepatic, of pregnancy, 1	147480	*ATP8B1*
130	Cholestasis, intrahepatic, of pregnancy, 3	614972	*ABCB4*
131	Cholestasis, progressive familial intrahepatic 1	211600	*ATP8B1*
132	Cholestasis, progressive familial intrahepatic 2	601847	*ABCB11*
133	Cholestasis, progressive familial intrahepatic 3	602347	*ABCB4*
134	Chondrodysplasia, Blomstrand type	215045	*PTH1R*
135	Citrullinemia type I	215700	*ASS1*
136	Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency	201910	*CYP21A2*
137	Classic galactosemia	230400	*GALT*
138	Classic maple syrup urine disease	248600	*DBT*
139	Classical homocystinuria	236200	*CBS*
140	COACH syndrome	216360	*TMEM67*
141	Cockayne syndrome type A	216400	*ERCC8*
142	Cockayne syndrome type B	133540	*ERCC6*
143	Coenzyme Q10 deficiency, primary, 5	614654	*COQ9*
144	Coffin-Lowry syndrome	303600	*RPS6KA3*
145	COFS syndrome 1	214150	*ERCC6*
146	Cohen Syndrome type 1	216550	*VPS13B*
147	Cold-induced sweating syndrome	272430	*CRLF1*
148	Combined immunodeficiency with skin granulomas	233650	*RAG1*
149	Combined immunodeficiency with skin granulomas	233650	*RAG2*
150	Combined oxidative phosphorylation defect type 2	610498	*MRPS16*
151	Combined oxidative phosphorylation defect type 5	611719	*MRPS22*

Table 1 (*Continued*)

	Disease Name	PhenOMIM	Gene
152	Combined oxidative phosphorylation deficiency 4	610678	*TUFM*
153	Combined pituitary hormone deficiencies, genetic forms	182230	*HESX1*
154	Combined pituitary hormone deficiencies, genetic forms	613038	*POU1F1*
155	Combined pituitary hormone deficiencies, genetic forms	262600	*PROP1*
156	Combined pituitary hormone deficiency with spine abnormalities	221750	*LHX3*
157	Complete androgen insensitivity syndrome	300068	*AR*
158	Complex I, mitochondrial respiratory chain, deficiency of	252010	*NDUFS6*
159	Congenital bile acid synthesis defect type 4	214950	*AMACR*
160	Congenital disorder of glycosylation type 1a	212065	*PMM2*
161	Congenital disorder of glycosylation type 1b	602579	*MPI*
162	Congenital disorder of glycosylation type 1e	608799	*DPM1*
163	Congenital disorder of glycosylation type 1j	608093	*DPAGT1*
164	Congenital disorder of glycosylation type 2a	212066	*MGAT2*
165	Congenital disorder of glycosylation type 2c	266265	*SLC35C1*
166	Congenital disorder of glycosylation type 2d	607091	*B4GALT1*
167	Congenital disorder of glycosylation type 2f	603585	*SLC35A1*
168	Congenital disorder of glycosylation type Ic	603147	*ALG6*
169	Congenital disorder of glycosylation type Ik	608540	*ALG1*
170	Congenital disorder of glycosylation, type Id	601110	*ALG3*
171	Congenital disorder of glycosylation, type If	609180	*MPDU1*
172	Congenital disorder of glycosylation, type Ig	607143	*ALG12*
173	Congenital disorder of glycosylation, type Ih	608104	*ALG8*
174	Congenital disorder of glycosylation, type Ii	607906	*ALG2*
175	Congenital disorder of glycosylation, type IIb	606056	*MOGS*
176	Congenital disorder of glycosylation, type IIe	608779	*COG7*
177	Congenital disorder of glycosylation, type IIg	611209	*COG1*
178	Congenital disorder of glycosylation, type IIh	611182	*COG8*
179	Congenital disorder of glycosylation, type Il	608776	*ALG9*
180	Congenital disorder of glycosylation, type Im	610768	*DOLK*
181	Congenital disorder of glycosylation, type In	612015	*RFT1*
182	Congenital disorder of glycosylation, type Iq	612379	*SRD5A3*
183	Congenital fibrinogen deficiency (gene FGA)	202400	*FGA*
184	Congenital heart defects, nonsyndromic, 1, X-linked	306955	*ZIC3*
185	Congenital hereditary endothelial dystrophy type II	217700	*SLC4A11*
186	Congenital lipoid adrenal hyperplasia	201710	*STAR*
187	Congenital malabsorptive diarrhea due to paucity of enteroendocrine cells	610370	*NEUROG3*
188	Congenital muscular dystrophy type 1A	607855	*LAMA2*
189	Congenital muscular dystrophy type 1D	608840	*LARGE*
190	Congenital muscular dystrophy type 4B	613152	*FKTN*
191	Congenital muscular dystrophy type 5B	606612	*FKRP*
192	Congenital muscular dystrophy with cerebellar involvement	613151	*POMGNT1*
193	Congenital muscular dystrophy with cerebellar involvement	613155	*POMT1*
194	Congenital muscular dystrophy with cerebellar involvement	613156	*POMT2*
195	Corneal dystrophy - perceptive deafness	217400	*SLC4A11*
196	Corpus callosum agenesis - neuronopathy	218000	*SLC12A6*
197	Corpus callosum hypoplasia-retardation-adducted thumbs-spasticity- hydrocephalus syndrome	307000	*L1CAM*
198	Cowden syndrome 1	158350	*PTEN*
199	Craniofrontonasal dysplasia	304110	*EFNB1*
200	Cutis laxa, autosomal dominant 2	614434	*FBLN5*
201	Cutis laxa, autosomal recessive, type IA	219100	*FBLN5*
202	Cutis laxa, autosomal recessive, type IB	614437	*EFEMP2*
203	Cutis laxa, autosomal recessive, type IIA	219200	*ATP6V0A2*
204	Cystic fibrosis; mucoviscidosis	219700	*CFTR*
205	Cystinosis	219800	*CTNS*
206	Deafness - encephaloneuropathy - obesity - valvulopathy	614651	*PDSS1*
207	Dejerine-Sottas disease	145900	*MPZ*
208	Dejerine-Sottas disease	145900	*PMP22*
209	Dent disease	300009	*CLCN5*
210	Dent disease 2	300555	*OCRL*
211	Desmosterolosis	602398	*DHCR24*
212	Diabetes mellitus, noninsulin-dependent	125853	*ABCC8*
213	Diabetes mellitus, permanent neonatal	606176	*ABCC8*
214	Diabetes mellitus, transient neonatal 2	610374	*ABCC8*
215	Diastrophic dwarfism	222600	*SLC26A2*
216	Dihydropyrimidine dehydrogenase deficiency	274270	*DPYD*
217	Dilated cardiomyopathy with ataxia	610198	*DNAJC19*
218	Donnai-Barrow syndrome	222448	*LRP2*
219	Duchenne muscular dystrophy	310200	*DMD*
220	Dyskeratosis congenita X-linked	305000	*DKC1*
221	Dystrophic epidermolysis bullosa pruriginosa	604129	*COL7A1*
222	Early infantile epileptic encephalopathy	308350	*ARX*
223	Early infantile epileptic encephalopathy	609304	*SLC25A22*
224	Ectodermal dysplasia 1, hypohidrotic, X-linked	305100	*EDA*
225	Ectodermal dysplasia, hypohidrotic, with immune deficiency	300291	*IKBKG*
226	Ectodermal, dysplasia, anhidrotic, lymphedema and immunodeficiency	300301	*IKBKG*
227	Ehlers-Danlos syndrome type 6	225400	*PLOD1*
228	Ehlers-Danlos syndrome, cardiac valvular type	225320	*COL1A2*

Table 1 (*Continued*)

	Disease Name	PhenOMIM	Gene
229	Ehlers-Danlos syndrome, type I	130000	*COL1A1*
230	Ehlers-Danlos syndrome, type VIIA	130060	*COL1A1*
231	Eiken syndrome	600002	*PTH1R*
232	Ellis-van Creveld syndrome	225500	*EVC2*
233	Ellis-van Creveld syndrome	225500	*EVC*
234	Encephalopathy due to prosaposin deficiency	611721	*PSAP*
235	Epidermolysis bullosa simplex with muscular dystrophy	226670	*PLEC*
236	Epidermolysis bullosa simplex with pyloric atresia	612138	*PLEC*
237	Epilepsy, progressive myoclonic 2A (Lafora)	254780	*EPM2A*
238	Epilepsy, progressive myoclonic 2B (Lafora)	254780	*NHLRC1*
239	Epilepsy, pyridoxine-dependent	266100	*ALDH7A1*
240	Epileptic encephalopathy, early infantile, 15	615006	*ST3GAL3*
241	Epileptic encephalopathy, early infantile, 2	300672	*CDKL5*
242	Epileptic encephalopathy, early infantile, 8	300607	*ARHGEF9*
243	Epileptic encephalopathy, early infantile, 9	300088	*PCDH19*
244	Escobar syndrome	265000	*CHRNG*
245	Ethylmalonic encephalopathy	602473	*ETHE1*
246	Exudative vitreoretinopathy 2, X-linked	305390	*NDP*
247	Fabry disease	301500	*GLA*
248	Failure of tooth eruption, primary	125350	*PTH1R*
249	Familial dysautonomia	223900	*IKBKAP*
250	Familial hypomagnesemia - hypercalciuria - nephrocalcinosis - severe ocular involvement	248190	*CLDN19*
251	Familial Mediterranean fever	249100	*MEFV*
252	Fanconi anemia complementation group C	227645	*FANCC*
253	Fatal infantile lactic acidosis with methylmalonic aciduria	245400	*SUCLG1*
254	Fatal mitochondrial disease due to combined oxidative phosphorylation deficiency 3	610505	*TSFM*
255	Favism	134700	*G6PD*
256	Fertile eunuch syndrome	228300	*GNRHR*
257	Fetal akinesia deformation sequence	208150	*RAPSN*
258	Fetal akinesia deformation sequence	208150	*DOK7*
259	Fetal Gaucher disease	608013	*GBA*
260	FG syndrome 4	300422	*CASK*
261	Fibular hypoplasia or aplasia - femoral bowing - oligodactyly	228930	*WNT7A*
262	Fraser syndrome (gene FRAS1)	219000	*FRAS1*
263	Fraser syndrome (gene FRAS2)	219000	*FREM2*
264	Free sialic acid storage disease, infantile form	269920	*SLC17A5*
265	French-Canadian type Leigh syndrome	220111	*LRPPRC*
266	Fucosidosis	230000	*FUCA1*
267	Fukuyama congenital muscular dystrophy	253800	*FKTN*
268	Fumaric aciduria	606812	*FH*
269	Galactokinase deficiency with cataracts	230200	*GALK1*
270	Gallbladder disease 1	600803	*ABCB4*
271	Gaucher disease type 2	230900	*GBA*
272	Gaucher disease type 3	231000	*GBA*
273	Gaucher disease type 3C	231005	*GBA*
274	Geleophysic dysplasia 1	231050	*ADAMTSL2*
275	Generalized junctional epidermolysis bullosa, non-Herlitz type	226650	*COL17A1*
276	Glutaric acidemia type 2 (gene ETFA)	231680	*ETFA*
277	Glutaric acidemia type 2 (gene ETFB)	231680	*ETFB*
278	Glutaric acidemia type 2 (gene ETFDH)	231680	*ETFDH*
279	Glutaryl-CoA dehydrogenase deficiency	231670	*GCDH*
280	Glutathione synthetase deficiency with 5-oxoprolinuria	266130	*GSS*
281	Glycine encephalopathy	605899	*AMT*
282	Glycine encephalopathy	605899	*GCSH*
283	Glycine encephalopathy	605899	*GLDC*
284	Glycogen storage disease due to acid maltase deficiency	232300	*GAA*
285	Glycogen storage disease due to glucose-6-phosphatase deficiency type 1a	232200	*G6PC*
286	Glycogen storage disease due to glucose-6-phosphatase deficiency type b	232220	*SLC37A4*
287	Glycogen storage disease due to glucose-6-phosphatase deficiency type c	232240	*SLC37A4*
288	Glycogen storage disease due to glycogen branching enzyme deficiency, childhood combined hepatic and myopathic form	232500	*GBE1*
289	Glycogen storage disease due to glycogen debranching enzyme deficiency	232400	*AGL*
290	Glycogen storage disease due to muscle glycogen phosphorylase deficiency	232600	*PYGM*
291	GM1 gangliosidosis type 1	230500	*GLB1*
292	GM1 gangliosidosis type 2	230600	*GLB1*
293	GM1 gangliosidosis type 3	230650	*GLB1*
294	GRACILE syndrome	603358	*BCS1L*
295	Greenberg dysplasia	215140	*LBR*
296	Griscelli disease type 1	214450	*MYO5A*
297	Griscelli disease type 2	607624	*RAB27A*
298	Guanidinoacetate methyltransferase deficiency	612736	*GAMT*
299	Hemochromatosis, type 2A	602390	*HFE2*
300	Hemolytic anemia due to G6PD deficiency	300908	*G6PD*
301	Hemolytic anemia due to red cell pyruvate kinase deficiency	266200	*PKLR*
302	Hemophagocytic lymphohistiocytosis, familial, 2	603553	*PRF1*
303	Hemophagocytic lymphohistiocytosis, familial, 3	608898	*UNC13D*
304	Hemophagocytic lymphohistiocytosis, familial, 4	603552	*STX11*

Table 1 (*Continued*)

	Disease Name	PhenOMIM	Gene
305	Hemophagocytic lymphohistiocytosis, familial, 5	613101	*STXBP2*
306	Hemophilia A	306700	*F8*
307	Hemophilia B	306900	*F9*
308	Hepatic venoocclusive disease with immunodeficiency	235550	*SP110*
309	Hepatoencephalopathy due to combined oxidative phosphorylation deficiency type 1	609060	*GFM1*
310	Hereditary fructose intolerance	229600	*ALDOB*
311	Hereditary sensory and autonomic neuropathy type 4	256800	*NTRK1*
312	Hermansky-Pudlak syndrome 2	608233	*AP3B1*
313	Hermansky-pudlak syndrome 9	614171	*PLDN*
314	Heterotaxy, visceral, 1, X-linked	306955	*ZIC3*
315	Histidinemia	235800	*HAMP*
316	Holocarboxylase synthetase deficiency	253270	*HLCS*
317	Hoyeraal-Hreidarsson syndrome	300240	*DKC1*
318	Hyaline fibromatosis syndrome	228600	*ANTXR2*
319	Hyperammonemia due to N-acetylglutamate synthetase deficiency	237310	*NAGS*
320	Hyper-IgE recurrent infection syndrome, autosomal recessive	243700	*DOCK8*
321	Hyperinsulinemic hypoglycemia, familial, 1	256450	*ABCC8*
322	Hyperornithinemia-hyperammonemia-homocitrullinuria	238970	*SLC25A15*
323	Hypoglycemia of infancy, leucine-sensitive	240800	*ABCC8*
324	Hypogonadotropic hypogonadism 7 without anosmia	146110	*GNRHR*
325	Hypomyelination - congenital cataract	610532	*FAM126A*
326	Hypoparathyroidism - intellectual deficit - dysmorphism syndrome	241410	*TBCE*
327	Hypophosphatemic rickets	300554	*CLCN5*
328	Ichthyosis follicularis - alopecia - photophobia	308205	*MBTPS2*
329	Ichthyosis, autosomal recessive 4B (harlequin)	242500	*ABCA12*
330	Ichthyosis, congenital, autosomal recessive 1	242300	*TGM1*
331	Ichthyosis, congenital, autosomal recessive 4A	601277	*ABCA12*
332	Ichthyosis, leukocyte vacuoles, alopecia, and sclerosing cholangitis 607626		*CLDN1*
333	Immunodeficiency 10	612783	*STIM1*
334	Immunodeficiency 17, CD3 gamma deficient	615607	*CD3G*
335	Immunodeficiency 18, SCID variant	615615	*CD3E*
336	Immunodeficiency 19	615617	*CD3D*
337	Immunodeficiency 27A, mycobacteriosis, AR	209950	*IFNGR1*
338	Immunodeficiency 28, mycobacteriosis	614889	*IFNGR2*
339	Immunodeficiency 29, mycobacteriosis	614890	*IL12B*
340	Immunodeficiency 30	614891	*IL12RB1*
341	Immunodeficiency 31A, mycobacteriosis, autosomal dominant	614892	*STAT1*
342	Immunodeficiency 31B, mycobacterial and viral infections, autosomal recessive	613796	*STAT1*
343	Immunodeficiency 31C, autosomal dominant	614162	*STAT1*
344	Immunodeficiency 33	300636	*IKBKG*
345	Immunodeficiency 35	611521	*TYK2*
346	Immunodeficiency 9	612782	*ORAI1*
347	Immunodeficiency, common variable, 1	607594	*ICOS*
348	Immunodeficiency, common variable, 3	613493	*CD19*
349	Immunodeficiency-centromeric instability-facial anomalies syndrome 1	242860	*DNMT3B*
350	Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked	304790	*FOXP3*
351	Incontinentia pigmenti, type II	308300	*IKBKG*
352	Infantile bilateral striatal necrosis	271930	*NUP62*
353	Infantile hypophosphatasia	241500	*ALPL*
354	Infantile neuroaxonal dystrophy 2A	256600	*PLA2G6*
355	Infantile neuroaxonal dystrophy 2B	610217	*PLA2G6*
356	Infantile onset spinocerebellar ataxia	271245	*C10orf2*
357	Interleukin 1 receptor antagonist deficiency	612852	*IL1RN*
358	Isolated CoQ-cytochrome C reductase deficiency	124000	*BCS1L*
359	Isolated growth hormone deficiency type III	307200	*BTK*
360	Isolated thyroid-stimulating hormone deficiency	275100	*TSHB*
361	Isovaleric acidemia	243500	*IVD*
362	Jeune syndrome	611263	*IFT80*
363	Johanson-Blizzard syndrome	243800	*UBR1*
364	Joubert syndrome 4	609583	*NPHP1*
365	Joubert syndrome 6	610688	*TMEM67*
366	Joubert syndrome with hepatic defect	216360	*RPGRIP1L*
367	Joubert syndrome with ocular defect	608629	*AHI1*
368	Joubert syndrome with oculorenal defect 5	610188	*CEP290*
369	Junctional epidermolysis bullosa - pyloric atresia	226730	*ITGA6*
370	Junctional epidermolysis bullosa with piloric atresia	226730	*ITGB4*
371	Junctional epidermolysis bullosa, Herlitz type (gene LAMA3)	226700	*LAMA3*
372	Junctional epidermolysis bullosa, Herlitz type (gene LAMB3)	226700	*LAMA3*
373	Junctional epidermolysis bullosa, Herlitz type (gene LAMC2)	226700	*LAMC2*
374	Junctional epidermolysis bullosa, non-Herlitz type	226650	*ITGB4*
375	Junctional epidermolysis bullosa, non-Herlitz type (gene LAMA3)	226650	*LAMA3*
376	Junctional epidermolysis bullosa, non-Herlitz type (gene LAMB3)	226650	*LAMB3*
377	Junctional epidermolysis bullosa, non-Herlitz type (gene LAMC2)	226650	*LAMC2*
378	Juvenile neuronal ceroid lipofuscinosis 3	204200	*CLN3*
379	Kahrizi syndrome	612713	*SRD5A3*
380	Kelley-Seegmiller syndrome	300323	*HPRT1*
381	Kennedy disease	313200	*AR*

Table 1 (*Continued*)

	Disease Name	PhenOMIM	Gene
382	Ketoacidosis due to beta-ketothiolase deficiency	203750	*ACAT1*
383	Krabbe disease	245200	*GALC*
384	Krabbe disease	611722	*PSAP*
385	Lacticacidemia due to PDX1 deficiency	245349	*PDHX*
386	Late infantile neuronal ceroid lipofuscinosis	610951	*MFSD8*
387	Late infantile neuronal ceroid lipofuscinosis 5	256731	*CLN5*
388	Late infantile neuronal ceroid lipofuscinosis 6	601780	*CLN6*
389	Late infantile neuronal ceroid lipofuscinosis 8	600143	*CLN8*
390	Lathosterolosis	607330	*SC5DL*
391	Leigh syndrome	256000	*BCS1L*
392	Leigh syndrome	256000	*DLD*
393	Leigh syndrome	256000	*NDUFAF2*
394	Leigh syndrome	256000	*NDUFS4*
395	Leigh syndrome	256000	*NDUFS7*
396	Leigh syndrome due to cytochrome c oxidase deficiency	256000	*COX15*
397	Leigh syndrome due to mitochondrial complex I deficiency	256000	*NDUFS3*
398	Leigh syndrome due to mitochondrial complex I deficiency	256000	*NDUFS8*
399	Leigh syndrome due to mitochondrial COX4 deficiency	256000	*COX10*
400	Leigh syndrome with nephrotic syndrome	607426	*COQ2*
401	Leigh syndrome with nephrotic syndrome	614652	*PDSS2*
402	Leigh syndrome, due to COX deficiency	256000	*SURF1*
403	Leigh syndrome, X-linked	308930	*PDHA1*
404	Leprechaunism	246200	*INSR*
405	Lesch-Nyhan syndrome	300322	*HPRT1*
406	Lethal acantholytic epidermolysis bullosa	609638	*DSP*
407	Lethal ataxia with deafness and optic atrophy	301835	*PRPS1*
408	Lethal congenital contractural syndrome 2	607598	*ERBB3*
409	Lethal congenital contracture syndrome type 1	253310	*GLE1*
410	Lethal osteosclerotic bone dysplasia	259775	*FAM20C*
411	Lethal restrictive dermopathy	275210	*LMNA*
412	Lethal restrictive dermopathy	275210	*ZMPSTE24*
413	Leukocyte adhesion deficiency, type III	612840	*FERMT3*
414	Leydig cell adenoma, somatic, with precocious puberty	176410	*LHCGR*
415	Leydig cell hypoplasia with hypergonadotropic hypogonadism	238320	*LHCGR*
416	Leydig cell hypoplasia with pseudohermaphroditism	238320	*LHCGR*
417	Lhermitte-Duclos syndrome	158350	*PTEN*
418	Limb girdle dystrophy with epidermolysis bullosa simplex	613723	*PLEC*
419	Lissencephaly 3	611603	*TUBA1A*
420	Lissencephaly syndrome, Norman-Roberts type	257320	*RELN*
421	Lissencephaly, X-linked	300067	*DCX*
422	Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency	609016	*HADH*
423	Luteinizing hormone resistance, female	238320	*LHCGR*
424	Lymphoproliferative syndrome, X-linked, 2	300635	*XIAP*
425	Macrocephaly/autism syndrome	605309	*PTEN*
426	Macroglobulinemia, Waldenstrom	153600	*MYD88*
427	Macular degeneration, age-related, 3	608895	*FBLN5*
428	Mandibuloacral dysplasia with type A lipodystrophy	248370	*LMNA*
429	Mandibuloacral dysplasia with type B lipodystrophy	608612	*ZMPSTE24*
430	Mannosidosis, alpha-, types I and II	248500	*MAN2B1*
431	Maple syrup urine disease	248600	*DLD*
432	Maple syrup urine disease (gene BCKDHA)	248600	*BCKDHA*
433	Maple syrup urine disease (gene BCKDHB)	248600	*BCKDHB*
434	Marinesco-Sjögren syndrome	248800	*SIL1*
435	Masa syndrome	303350	*L1CAM*
436	Meckel syndrome type 1	249000	*MKS1*
437	Meckel syndrome, type 5	611561	*RPGRIP1L*
438	Medium chain acyl-CoA dehydrogenase deficiency	201450	*ACADM*
439	Megalencephalic leukoencephalopathy with subcortical cysts	604004	*MLC1*
440	Menkes disease	309400	*ATP7A*
441	Mental retardation and microcephaly with pontine and cerebellar hypoplasia	300749	*CASK*
442	Mental retardation, autosomal recessive 1	249500	*PRSS12*
443	Mental retardation, autosomal recessive 12	611090	*ST3GAL3*
444	Mental retardation, autosomal recessive 13	613192	*TRAPPC9*
445	Mental retardation, autosomal recessive 5	611091	*NSUN2*
446	Mental retardation, autosomal recessive, 6	611092	*GRIK2*
447	Mental retardation, with or without nystagmus	300422	*CASK*
448	Mental retardation, X-linked	300495	*NLGN4X*
449	Mental retardation, X-linked 19	300844	*RPS6KA3*
450	Mental retardation, X-linked 21/34	300143	*IL1RAPL1*
451	Mental retardation, X-linked 30/47	300558	*PAK3*
452	Mental retardation, X-linked 41	300849	*GDI1*
453	Mental retardation, X-linked 46	300436	*ARHGEF6*
454	Mental retardation, X-linked 63	300387	*ACSL4*
455	Mental retardation, X-linked 72	300271	*RAB39B*
456	Mental retardation, X-linked 9	309549	*FTSJ1*
457	Mental retardation, X-linked 90	300850	*DLG3*
458	Mental retardation, X-linked 93	300659	*BRWD3*

Table 1 (*Continued*)

	Disease Name	PhenOMIM	Gene
459	Mental retardation, X-linked 96	300802	*SYP*
460	Mental retardation, X-linked 97	300803	*ZNF711*
461	Mental retardation, X-linked syndromic 16	305400	*FGD1*
462	Mental retardation, X-linked syndromic 5	304340	*AP1S2*
463	Mental retardation, X-linked syndromic, Christianson type	300243	*SLC9A6*
464	Mental retardation, X-linked syndromic, Nascimento-type	300860	*UBE2A*
465	Mental retardation, X-linked syndromic, Raymond type	300799	*ZDHHC9*
466	Mental retardation, X-linked syndromic, Turner type	300706	*HUWE1*
467	Mental retardation, X-linked, FRAXE type	309548	*AFF2*
468	Mental retardation, X-linked, Snyder-Robinson type	309583	*SMS*
469	Mental retardation, X-linked, syndromic 14	300676	*UPF3B*
470	Mental retardation, X-linked, syndromic 15 (Cabezas type)	300354	*CUL4B*
471	Mental retardation, X-linked, syndromic, Claes-Jensen type	300534	*KDM5C*
472	Mental retardation, X-linked, with cerebellar hypoplasia and distinctive facial appearance	300486	*OPHN1*
473	Mental retardation, X-linked, with isolated growth hormone deficiency	300123	*SOX3*
474	Mental retardation-hypotonic facies syndrome, X-linked	309580	*ATRX*
475	Metachromatic leukodystrophy	250100	*ARSA*
476	Metachromatic leukodystrophy	249900	*PSAP*
477	Metaphyseal chondrodysplasia, Murk Jansen type	156400	*PTH1R*
478	Metaphyseal dysplasia without hypotrichosis	250460	*RMRP*
479	Methylmalonic acidemia with homocystinuria, type cblC	277400	*MMACHC*
480	Methylmalonic acidemia with homocystinuria, type cblD	277410	*MMACHC*
481	Mevalonic aciduria	610377	*MVK*
482	Micro syndrome	600118	*RAB3GAP1*
483	Microphthalmia, syndromic 2	300166	*BCOR*
484	Mitochondrial complex I deficiency	252010	*NDUFA1*
485	Mitochondrial complex I deficiency	252010	*NDUFAF2*
486	Mitochondrial complex I deficiency	252010	*NDUFAF4*
487	Mitochondrial complex I deficiency	252010	*NDUFS3*
488	Mitochondrial complex I deficiency	252010	*NDUFS4*
489	Mitochondrial complex I deficiency	252010	*NDUFV1*
490	Mitochondrial complex IV deficiency	220110	*COX10*
491	Mitochondrial complex IV deficiency	220110	*COX6B1*
492	Mitochondrial complex IV deficiency	220110	*FASTKD2*
493	Mitochondrial complex IV deficiency		*SCO1*
494	Mitochondrial DNA depletion syndrome 1 (MNGIE type)	603041	*TYMP*
495	Mitochondrial DNA depletion syndrome 5 (encephalomyopathic with or without methylmalonic aciduria)	612073	*SUCLA2*
496	Mitochondrial DNA depletion syndrome 8A (encephalomyopathic type with renal tubulopathy)	612075	*RRM2B*
497	Mitochondrial DNA depletion syndrome 8B (MNGIE type)	612075	*RRM2B*
498	Mitochondrial DNA depletion syndrome, hepatocerebral form due to DGUOK deficiency 3	251880	*DGUOK*
499	Mitochondrial DNA depletion syndrome, myopathic form	609560	*TK2*
500	Mitochondrial neurogastrointestinal encephalomyopathy	613662	*POLG*
501	Mitochondrial respiratory chain complex III deficiency	124000	*UQCRB*
502	Mitochondrial respiratory chain complex III deficiency	124000	*UQCRQ*
503	Mitochondrial trifunctional protein deficiency	609015	*HADHA*
504	Mitochondrial trifunctional protein deficiency	609015	*HADHB*
505	Mohr-Tranebjaerg syndrome	304700	*TIMM8A*
506	Mowat-Wilson syndrome	235730	*ZEB2*
507	Mucolipidosis type 2	252500	*GNPTAB*
508	Mucolipidosis type 3	252600	*GNPTAB*
509	Mucolipidosis type 4	252650	*MCOLN1*
510	Mucopolysaccharidosis Ih	607014	*IDUA*
511	Mucopolysaccharidosis Ih/s	607015	*IDUA*
512	Mucopolysaccharidosis Is	607016	*IDUA*
513	Mucopolysaccharidosis type 2	309900	*IDS*
514	Mucopolysaccharidosis type 3A (Sanfilippo syndrome type A)	252900	*SGSH*
515	Mucopolysaccharidosis type 4B	253010	*GLB1*
516	Mucopolysaccharidosis type 6	253200	*ARSB*
517	Mucopolysaccharidosis type 7	253220	*GUSB*
518	Mucopolysaccharidosis type IIIB (Sanfilippo B)	252920	*NAGLU*
519	MULIBREY nanism	253250	*TRIM37*
520	Multiple epiphyseal dysplasia type 4	226900	*SLC26A2*
521	Multiple pterygium syndrome, lethal type	253290	*CHRNA1*
522	Multiple pterygium syndrome, lethal type	253290	*CHRND*
523	Multiple pterygium syndrome, lethal type	253290	*CHRNG*
524	Muscle-eye-brain disease	613153	*FKRP*
525	Muscle-eye-brain disease	613154	*LARGE*
526	Myasthenia gravis, neonatal transient	100730	*CHRNG*
527	Myasthenia, limb-girdle, familial	254300	*DOK7*
528	Myasthenic syndrome, fast-channel congenital	608930	*CHRNA1*
529	Myasthenic syndrome, fast-channel congenital	608930	*CHRND*
530	Myasthenic syndrome, slow-channel congenital	601462	*CHRNA1*
531	Myasthenic syndrome, slow-channel congenital	601462	*CHRND*

Table 1 (*Continued*)

	Disease Name	PhenOMIM	Gene
532	Myopathy, tubular aggregate, 1	160565	*STIM1*
533	Myopathy, tubular aggregate, 2	615883	*ORAI1*
534	Nance-Horan syndrome	302350	*NHS*
535	Navajo neurohepatopathy	256810	*MPV17*
536	Nemaline myopathy 2	256030	*NEB*
537	Neonatal adrenoleukodystrophy (gene PEX12)	266510	*PEX12*
538	Neonatal adrenoleukodystrophy (gene PEX26)	614873	*PEX26*
539	Neonatal adrenoleukodystrophy (gene PEX5)	202370	*PEX5*
540	Nephrolithiasis, type I	310468	*CLCN5*
541	Nephronophthisis 2, infantile	602088	*INVS*
542	Nephrotic syndrome, tupe 3	610725	*PLCE1*
543	Nephrotic syndrome, type 1	256300	*NPHS1*
544	Nephrotic syndrome, type 2	600995	*NPHS2*
545	Nephrotic syndrome, type 5, with or without ocular abnormalities	614199	*LAMB2*
546	Neurodegeneration due to 3-hydroxyisobutyryl-CoA hydrolase deficiency	250620	*HIBCH*
547	Neurodegeneration due to cerebral folate transport deficiency	613068	*FOLR1*
548	Neuronal ceroid lipofuscinosis 2	204500	*TPP1*
549	Neuropathy, congenital hypomyelinating	605253	*MPZ*
550	Neutropenia, severe congenital 3, autosomal recessive	610738	*HAX1*
551	Niemann-Pick disease type A	257200	*SMPD1*
552	Niemann-Pick disease type B	607616	*SMPD1*
553	Niemann-Pick disease type C1	257220	*NPC1*
554	Niemann-Pick disease type C2	607625	*NPC2*
555	Nijmegen breakage syndrome	251260	*NBN*
556	Norrie disease	310600	*NDP*
557	ntal retardation, autosomal recessive 7	611093	*TUSC3*
558	Occipital horn syndrome	304150	*ATP7A*
559	Oculocerebrorenal syndrome	309000	*OCRL*
560	Omenn syndrome	603554	*DCLRE1C*
561	Omenn syndrome (gene RAG1)	603554	*RAG1*
562	Omenn syndrome (gene RAG2)	603554	*RAG2*
563	Opitz GBBB syndrome, type I	300000	*MID1*
564	Ornithine transcarbamylase deficiency	311250	*OTC*
565	Osteogenesis imperfecta type 8	610915	*LEPRE1*
566	Osteogenesis imperfecta type VII	610682	*CRTAP*
567	Osteogenesis imperfecta, type I	166200	*COL1A1*
568	Osteogenesis imperfecta, type II	166210	*COL1A1*
569	Osteogenesis imperfecta, type III	259420	*COL1A1*
570	Osteogenesis imperfecta, type IV	166220	*COL1A1*
571	Osteopetrosis with renal tubular acidosis	259730	*CA2*
572	Osteopetrosis, autosomal recessive 5	259720	*OSTM1*
573	Paget disease, juvenile	239000	*TNFRSF11B*
574	Panhypopituitarism, X-linked	312000	*SOX3*
575	Pantothenate kinase-associated neurodegeneration	234200	*PANK2*
576	Partial androgen insensitivity syndrome	312300	*AR*
577	Pelizaeus-Merzbacher-like due to GJC2 mutation	608804	*GJC2*
578	Peroxisomal acyl-CoA oxidase deficiency	264470	*ACOX1*
579	Peroxisome biogenesis disorder 11A (Zellweger)	614883	*PEX13*
580	Peroxisome biogenesis disorder 11B	614885	*PEX13*
581	Peroxisome biogenesis disorder 6A (Zellweger)	614870	*PEX10*
582	Peroxisome biogenesis disorder 6B	614871	*PEX10*
583	Perrault syndrome	233400	*HSD17B4*
584	Phenylketonuria	261600	*PAH*
585	Pierson syndrome	609049	*LAMB2*
586	Pitt-Hopkins syndrome	610954	*TCF4*
587	Plasminogen deficiency type 1	217090	*PLG*
588	Pontocerebellar hypoplasia type 2A	277470	*TSEN54*
589	Pontocerebellar hypoplasia type 4	225753	*TSEN54*
590	Porphyria, congenital erythropoietic	263700	*UROS*
591	Precocious puberty, male	176410	*LHCGR*
592	Primary lateral sclerosis, juvenile	606353	*ALS2*
593	Progressive epilepsy - intellectual deficit, Finnish type	610003	*CLN8*
594	Properdin deficiency, X-linked	312060	*CFP*
595	Propionic acidemia (gene PCCA)	606054	*PCCA*
596	Propionic acidemia (gene PCCB)	606054	*PCCB*
597	*CLCN5*		
598	Proximal spinal muscular atrophy type 1	253300	*SMN1*
599	Proximal spinal muscular atrophy type 2	253550	*SMN1*
600	Proximal spinal muscular atrophy type 3	253400	*SMN1*
601	Proximal spinal muscular atrophy type 4	271150	*SMN1*
602	Pseudohermaphroditism, male, with gynecomastia	264300	*HSD17B3*
603	Pseudohypoaldosteronism type 1, autosomal recessive (gene SCNN1A)	264350	*SCNN1A*
604	Pseudohypoaldosteronism type 1, autosomal recessive (gene SCNN1B)	264350	*SCNN1B*
605	Pseudohypoaldosteronism type 1, autosomal recessive (gene SCNN1G)	264350	*SCNN1G*
606	Pseudovaginal perineoscrotal hypospadias	264600	*SRD5A2*
607	Pycnodysostosis	265800	*CTSK*
608	Pyogenic bacterial infections, recurrent, due to MYD88 deficiency	612260	*MYD88*

Table 1 (*Continued*)

	Disease Name	PhenOMIM	Gene
609	Pyridoxal phosphate-responsive seizures	610090	*PNPO*
610	Pyruvate carboxylase deficiency	266150	*PC*
611	Pyruvate dehydrogenase phosphatase deficiency	608782	*PDP1*
612	Renal-hepatic-pancreatic dysplasia	208540	*NPHP3*
613	Renpenning syndrome	309500	*PQBP1*
614	Rett syndrome, congenital variant	613454	*FOXG1*
615	Rhizomelic chondrodysplasia punctata type 1	215100	*PEX7*
616	Rhizomelic chondrodysplasia punctata type 3	600121	*AGPS*
617	Rigid spine syndrome	602771	*SEPN1*
618	Roberts syndrome	269000	*ESCO2*
619	Roussy-Levy syndrome	180800	*MPZ*
620	Roussy-Levy syndrome	180800	*PMP22*
621	Sandhoff disease	268800	*HEXB*
622	Sanfilippo syndrome type C	252930	*HGSNAT*
623	Schneckenbecken dysplasia	269250	*SLC35D1*
624	Schwartz-Jampel syndrome	255800	*HSPG2*
625	Seckel syndrome	210600	*ATR*
626	Senior-Loken syndrome	610189	*CEP290*
627	Senior-Loken syndrome	606996	*NPHP4*
628	Senior-Loken syndrome 1	266900	*NPHP3*
629	Senior-Loken syndrome 5	609254	*IQCB1*
630	Sensory ataxic neuropathy - dysarthria - ophthalmoparesis	607459	*POLG*
631	Severe combined immunodeficiency due to adenosine deaminase deficiency	102700	*ADA*
632	Severe combined immunodeficiency due to complete RAG1/2 deficiency	601457	*RAG1*
633	Severe combined immunodeficiency due to complete RAG1/2 deficiency	601457	*RAG2*
634	Severe combined immunodeficiency due to DCLRE1C deficiency	602450	*DCLRE1C*
635	Severe combined immunodeficiency with microcephaly, growth retardation, and sensitivity to ionizing radiation	611291	*NHEJ1*
636	Severe combined immunodeficiency with sensitivity to ionizing radiation	602450	*LIG4*
637	Severe generalized recessive dystrophic epidermolysis bullosa	226600	*COL7A1*
638	Severe neonatal-onset encephalopathy with microcephaly	300673	*MECP2*
639	Severe T-cell immunodeficiency - congenital alopecia - nail dystrophy	601705	*FOXN1*
640	Short-rib thoracic dysplasia 3 with or without polydactyly	613091	*DYNC2H1*
641	Shwachman-Diamond syndrome	260400	*SBDS*
642	Sialidosis, type I	256550	*NEU1*
643	Sialidosis, type II	256550	*NEU1*
644	Sickle cell anemia	603903	*HBB*
645	Simpson-Golabi-Behmel syndrome type 2	300209	*OFD1*
646	Simpson-Golabi-Behmel syndrome, type 1	312870	*GPC3*
647	Síndrome de Dursun	612541	*G6PC3*
648	Sjogren-Larsson syndrome	270200	*ALDH3A2*
649	Smith-Lemli-Opitz syndrome	270400	*DHCR7*
650	Sotos syndrome 1	117550	*NSD1*
651	Spastic paralysis, infantile onset ascending	607225	*ALS2*
652	Spastic paraplegia type 2, X-linked	312920	*PLP1*
653	Spinal muscular atrophy with respiratory distress	604320	*IGHMBP2*
654	Stocco dos Santos X-linked mental retardation syndrome	300434	*SHROOM4*
655	Stormorken syndrome	185070	*STIM1*
656	Stüve-Wiedemann syndrome	601559	*LIFR*
657	Subcortical laminal heteropia, X-linked	300067	*DCX*
658	Succinyl CoA:3-oxoacid CoA transferase deficiency	245050	*OXCT1*
659	Sudden infant death with dysgenesis of the testes syndrome	608800	*TSPYL1*
660	Sulfite oxidase deficiency due to molybdenum cofactor deficiency type A (gene MOCS1)	252150	*MOCS1*
661	Sulfite oxidase deficiency due to molybdenum cofactor deficiency type A (gene MOCS2)	252150	*MOCS2*
662	Sulfocysteinuria	272300	*SUOX*
663	Surfactant metabolism dysfunction, pulmonary, 1	265120	*SFTPB*
664	Surfactant metabolism dysfunction, pulmonary, 2	610913	*SFTPC*
665	Surfactant metabolism dysfunction, pulmonary, 3	610921	*ABCA3*
666	Syndromic microphthalmia type 9	601186	*STRA6*
667	Tay-Sachs disease	272800	*HEXA*
668	T-B+ severe combined immunodeficiency due to gamma chain deficiency	300400	*IL2RG*
669	T-B+ severe combined immunodeficiency due to JAK3 deficiency	600802	*JAK3*
670	T-B+ severe combined immunodeficiency, X-linked	312863	*IL2RG*
671	Tetra-amelia, autosomal recessive	273395	*WNT3*
672	Thrombocythemia 2	601977	*MPL*
673	Thrombocytopenia, congenital amegakaryocytic	604498	*MPL*
674	Thrombotic thrombocytopenic purpura, familial	274150	*ADAMTS13*
675	Tooth agenesis, selective, X-linked 1	313500	*EDA*
676	Trichothiodystrophy, complementation group A	601675	*GTF2H5*
677	Tyrosinemia type 1	276700	*FAH*
678	Tyrosinemia type 2	276600	*TAT*
679	Tyrosinemia type 3	276710	*HPD*
680	Ullrich congenital muscular dystrophy	254090	*COL6A1*
681	Ullrich congenital muscular dystrophy	254090	*COL6A2*
682	Ullrich congenital muscular dystrophy	254090	*COL6A3*
683	Unverricht-Lundborg disease	254800	*CSTB*
684	Usher syndrome type 1	276900	*MYO7A*
685	Usher syndrome type 1C	276904	*USH1C*

Table 1 (*Continued*)

	Disease Name	PhenOMIM	Gene
686	Usher syndrome type 1G	606943	*USH1G*
687	Usher syndrome type 2A	276901	*USH2A*
688	Usher syndrome type 2C	605472	*GPR98*
689	Usher syndrome type 3A	276902	*CLRN1*
690	Very long chain acyl-CoA dehydrogenase deficiency	201475	*ACADVL*
691	Vitamin B12-responsive methylmalonic acidemia type cblA	251100	*MMAA*
692	Vitamin B12-responsive methylmalonic acidemia type cblB	251110	*MMAB*
693	Vitamin B12-unresponsive methylmalonic acidemia type mut-	251000	*MUT*
694	Vitamin D-dependent rickets type 2A	277440	*VDR*
695	Vitamin D-dependent rickets, type I	264700	*CYP27B1*
696	Waardenburg-Shah syndrome 4A	277580	*EDNRB*
697	Waardenburg-Shah syndrome 4B	613265	*EDN3*
698	Walker-Warburg syndrome (gene POMGNT1)	253280	*POMGNT1*
699	Walker-Warburg syndrome (gene POMT1)	236670	*POMT1*
700	Walker-Warburg syndrome (gene POMT2)	613150	*POMT2*
701	Weyers acrodental dysostosis	193530	*EVC*
702	Wilson disease	277900	*ATP7B*
703	Wiskott-Aldrich syndrome	301000	*WAS*
704	Wolcott-Rallison syndrome	226980	*EIF2AK3*
705	Wrinkly skin syndrome	278250	*ATP6V0A2*
706	Xeroderma pigmentosum complementation group A	278700	*XPA*
707	Xeroderma pigmentosum complementation group E	278740	*DDB2*
708	Xeroderma pigmentosum, group C	278720	*XPC*
709	Xeroderma pigmentosum/Cockayne syndrome complex complementation group B	610651	*ERCC3*
710	Xeroderma pigmentosum/Cockayne syndrome complex complementation group D	278730	*ERCC2*
711	Xeroderma pigmentosum/Cockayne syndrome complex complementation group F	278760	*ERCC4*
712	Xeroderma pigmentosum/Cockayne syndrome complex complementation group G	278780	*ERCC5*
713	X-linked agammaglobulinemia	300755	*BTK*
714	X-linked centronuclear myopathy	310400	*MTM1*
715	X-linked Charcot-Marie-Tooth disease type 5	311070	*PRPS1*
716	X-linked creatine transporter deficiency	300352	*SLC6A8*
717	X-linked distal spinal muscular atrophy	300489	*ATP7A*
718	X-linked hyper-IgM syndrome	308230	*CD40LG*
719	X-linked intellectual deficit with marfanoid habitus	309520	*MED12*
720	X-linked lymphoproliferative disease	308240	*SH2D1A*
721	Odontoonychodermal dysplasia	257980	*WNT10A*
722	X-linked spinal muscular atrophy type 2	301830	*UBA1*
723	Zellweger syndrome 1A	214100	*PEX1*
724	Zellweger syndrome 7A	614872	*PEX26*

analysed the mutations screened by different laboratories, 74–210 mutations, and only 29 were found in common [17]. This poor method uniformity doesn't allow expanded carrier screening be a recommended test by clinicians.

Lazarin et al. based a classification algorithm on four tiers of severity: profound, severe, moderate and mild. The disease characteristics chosen were: life span, intellectual disability, impaired mobility, physical malformations and dysmorphic features, sensory impairment, immunodeficiency/cancer, mental illness, reduced fertility, available treatment, and expressivity [18]. In this background, variants of uncertain significance and non pathogenic mutations increase the complexity in choosing the appropriate panel and counselling of patients.

In 2017, the ACOG published a committee opinion about common genetic conditions for which carrier screening is recommended: [19]

- Spinal Muscolar Atrophy. This screening should be offered to all women during preconceptional or prenatal period, and to patients with a family history of SMA.
- Cystic Fibrosis. This screening should be offered to all women during preconceptional or prenatal period. Today about two thousand mutations of the CFTR gene are known and the complete analysis of the gene is not recommended for routine screening.
- Hemoglobinopathies. A complete blood count with red blood cells indices should be offered to all women during and before pregnancy, also to diagnose their risk of anemia. If a low mean corpuscular volume results, a hemoglobin electophoresis would also be indicated, especially in some at risk populations: African, Mediterranean, Middle Easten, Southeast Asia or West Indian descendants.
- Fragile X Syndrome. This screening should be offered to all women during preconception and prenatal period, if a family history or suggestive intellectual disorders occur. If a woman has unexplained ovarian insufficiency or high levels of FSH before the age of 40, an FMR1 premutation could be present and the screening should be reccommended. Prenatal diagnosis for fagile X syndrome should be offered to known carriers of premutation or full mutation.
- Tay-Sachs Disease. This screening should be offered to all women during preconception and prenatal period, if either member of a couple belongs to some particular ethnicity, such as Ashkenazi Jewish, French-Canadian or Cajun, or if there is a suggestive family history.
- Expanded carrier screening does not replace the above risk-based screening recommendations

Analytic and clinical validity and utility

Analytic validity of a genetic test defines its ability to accurately and reliably measure the genotype of interest. Current commercial providers use mostly microarray-based genetic tests covering the most frequent sequence variants in selected genes. Alternatively, whole genes, and not only selected sequence variants can be sequenced by next-generation sequencing (NGS) [7].

Clinical validity of a genetic test defines its ability to detect or predict the associated disorder, including carrier status. It is currently difficult to assess the clinical validity of screening panels due to various confounding factors. Many genes are characterized by numerous variants, not all of them are pathogenic, equally associated with severe phenotype and not all of them are necessarily reported in commercially available panels [7].

As to clinical utility, a genetic test is designed to provide clinical practice with a valid support to improve patient outcomes. In this case, the aim of preconception carrier screening is to facilitate reproductive choices and autonomy of couples. Options for future parents include preimplantation genetic diagnosis, prenatal diagnosis, using donor sperms or oocytes, adoption, or accepting the risk of conceiving an affected child [20,21].

Expanded carrier screening may also support prenatal diagnosis with early management of genetic disorders [20–22]. For example screening for ornithine transcarbamylase deficiency, a rare and potentially fatal disoder in a male neonate, could improve the prognosis [22]. This will also help the parents to better approach the pregnancy and be ready for psychosocial consequences of having a child with a genetic condition.

Another aspect of the expanded carrier screening is the clinical implication on the carrier patient. The screening may reveal genetic conditions that may predispose the carrier to increased morbidity and mortality. Carriers of ataxia telangiectasia have a major risk of breast cancer [23] and heterozygosus variants of glucocerebrosidase gene is linked to Parkinson's disease [24].

Attention should be also paid to the impact of expanded carrier screening on the health care organizations and burden of cost. Lynch et al. found that the median time for results disclosure is about 64 min, ranging from 5 to 229 min with preparation work being the most time-consuming activity. [25] Carrier screening requires significant increases in genetic counseling time, and new resources to reduce preparation work or develop other strategies such as the creation of new models to deliver this type of service are needed. [25]

Expanded carrier screening and Noninvasive prenatal diagnosis

Sequencing of cell-free DNA in maternal plasma has enabled definitive noninvasive prenatal diagnosis for monogenic disorders and also for pregnancies with unexpected fetal anomalies. The current standard for testing for Mendelian disorders is gene panels and that is available for many ultrasound abnormalities like holoprosencephaly, congenital heart disease, skeletal dysplasia, and others. Most Mendelian disorders however, are associated with normal prenatal ultrasound findings. Future developments may be toward noninvasive prenatal diagnosis with fetal whole exome or whole genome sequencing. This has been performed on limited disorders so farand to generalize it to diagnose the large number of Mendelian disorders on the expanded carrier screening panels is premature for now [26]. In fact, this highlights even more the importance of clear guidelines for expanded carrier screening panels.

Ethical issues

The introduction of expanded carrier screening raises many concerns about complex decisions, including preimplantation genetic diagnosis, prenatal diagnosis, and pregnancy management and may impact the psychological well-being, perceptions of health, and feelings of discrimination or stigmatization with social consequences. Studies have also demonstrated increased distress levels among carriers [10].Already pregnancy is a very high emotional state where expanded carrier screening is only one aspect of many evaluations that the pregnant patient has to deal with. Therefore, careful appraisal of the advantages and disadvantages for universal screening before conception is necessary. Obtaining consent has been considered much more challenging as the carrier screening panels expand [7]. Women may also have a legitimate interest in not knowing their genetic make up to avoid serious pshychological consequences.

Conclusion

Expanded carrier screening aims to identify couples who have an increased risk of having an affected child in order to facilitate informed reproductive decision making. New genetic testing technologies enable the expansion of screening to multiple conditions including those with very low carrier frequency, and those with mild or incompletely penetrant phenotypes. Priority should be given to carrier screening panels that include a comprehensive set of severe childhood-onset disorders. Panels should have high clinical validity and clinical utility. Psychosocial support and genetic couseling should be available prior to screening and for the return of positive results. Systems are needed to reduce the risk of misinterpreting results. Finally, attention should be paid on the impact of expanded carrier screening on health care organization and burden of cost.

Conflicts of interest

The authors report no conflict of interest

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