

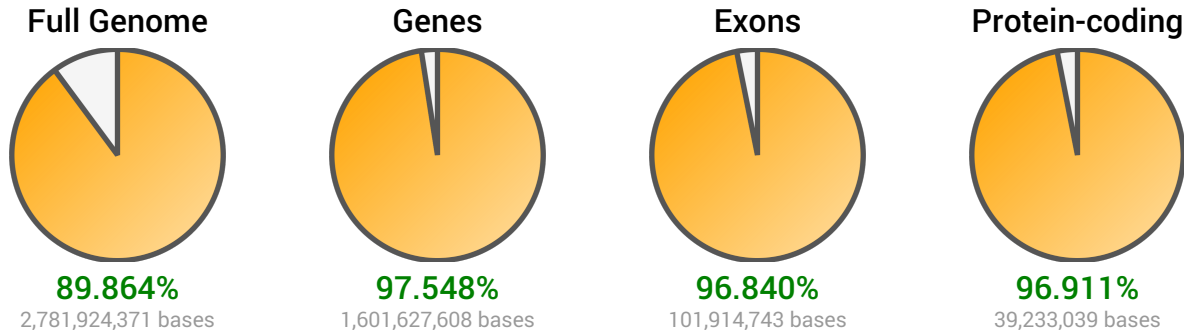


Genome Summary

Name: EUR NA12877 Father
Genome ID: NA12877-200-37-ASM

Sequencing Provider: Complete Genomics
Sequencing Type: Whole Genome

Sequencing Coverage:



Variation Counts:

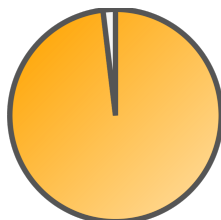
Total number of variations:	5,448,699	Nonsense:	123
Heterozygous:	2,592,737	Frameshift:	457
Homozygous (x2):	1,427,981	Misstart:	41
		Nonstop:	42
Rare variations (MAF <1%):	498,829	Inframe Ins/Del:	264
		Missense:	14,837
SNV:	4,713,414	Splice site:	6,469
MNV:	105,453	Coding synonymous:	15,595
Insertion:	307,525	mRNA untranslated:	116,319
Deletion:	322,307	Intron:	2,619,185

Known Phenotype Summary:

42,032 variations known to affect a disease or trait were assessed

152 disease or trait variations are found in this genome

Phenotype variation coverage



98.1%

Successfully sequenced **41,247** phenotype variations
Missing data for **785** phenotype variations

Clinical classification:

Pathogenic	32
Likely pathogenic	3
Risk factor	72
Drug response	6
Association	33
Protective	6

Selected Phenotype Variation Details:

• Chr7: 117,227,792 G>A

Pathogenic



Phenotype: Cystic fibrosis

Zygosity: Heterozygous (x1)

dbSNP ID: rs76713772

Population Allele Frequency: <0.01%

Gene Impact: **CFTR** SPLICE DISRUPT

Supporting Publications: <http://www.ncbi.nlm.nih.gov/pubmed/11280952>
<http://www.ncbi.nlm.nih.gov/pubmed/2236053>
<http://www.ncbi.nlm.nih.gov/pubmed/2210769>

Phenotype Description:

CFTR-related disorders include cystic fibrosis (CF) and congenital absence of the vas deferens (CAVD). Cystic fibrosis affects epithelia of the respiratory tract, exocrine pancreas, intestine, male genital tract, hepatobiliary system, and exocrine sweat glands, resulting in complex multisystem disease. Pulmonary disease is the major cause of morbidity and mortality in CF. Affected individuals have lower airway inflammation and chronic endobronchial infection, progressing to end-stage lung disease characterized by extensive airway damage (bronchiectasis, cysts, and abscesses) and fibrosis of lung parenchyma. Meconium ileus occurs at birth in 15%-20% of newborns with CF. Pancreatic insufficiency with malabsorption occurs in the great majority of individuals with CF. More than 95% of males with CF are infertile as a result of azoospermia caused by absent, atrophic, or fibrotic Wolffian duct structures. CAVD occurs in men without pulmonary or gastrointestinal manifestations of CF. Affected men have azoospermia and are thus infertile.

Modes of inheritance*: Autosomal Recessive

• Chr7: 143,048,771 C>T

Pathogenic



Phenotype: Myotonia congenita

Congenital myotonia, autosomal recessive form

Congenital myotonia, autosomal dominant form

Zygosity: Heterozygous (x1)

dbSNP ID: rs55960271

Population Allele Frequency: 0.28%

Gene Impact: **CLCN1** NONSENSE R-894-*

Supporting Publications: <http://www.ncbi.nlm.nih.gov/pubmed/18337100>
<http://www.ncbi.nlm.nih.gov/pubmed/11840191>
<http://www.ncbi.nlm.nih.gov/pubmed/8845168> ... and 1 more

Phenotype Description:

Myotonia congenita is characterized by muscle stiffness present from childhood; all striated muscle groups including the extrinsic eye muscles, the facial muscles, and the tongue may be involved. Men are more severely affected than women. Stiffness is relieved by repeated contractions of the muscle (the "warm-up" phenomenon). Muscles are usually hypertrophic. The autosomal recessive form of myotonia congenita is often associated with more severe stiffness of muscles than the autosomal dominant form. Individuals with the autosomal recessive form may have progressive, minor distal weakness and attacks of transient weakness brought on by movement after rest. The age of onset is variable: in autosomal dominant myotonia congenita, onset of symptoms is usually in infancy or early childhood; in the autosomal recessive form, the average age of onset is slightly older. In both, onset may be as late as the third or fourth decade of life.

Modes of inheritance*: Not available

• Chr15: 89,870,432 C>T

Pathogenic



Phenotype: Cerebellar ataxia infantile with progressive external ophthalmoplegia
Sensory ataxic neuropathy, dysarthria, and ophthalmoparesis
Myoclonic epilepsy myopathy sensory ataxia
Progressive sclerosing poliodystrophy

Zygosity: Heterozygous (x1) dbSNP ID: rs113994095

Population Allele Frequency: 0.05%

Gene Impact: **POLG** MISSENSE A-467-T

Supporting Publications: <http://www.ncbi.nlm.nih.gov/pubmed/19251978>
<http://www.ncbi.nlm.nih.gov/pubmed/17426723>
<http://www.ncbi.nlm.nih.gov/pubmed/16177225> ... and 8 more

Phenotype Description:

POLG-related disorders comprise a continuum of overlapping phenotypes that were clinically defined long before their molecular basis was known. These phenotypes exemplify the diversity that can result from mutation of a given gene. Most affected individuals have some, but not all, of the features of a given phenotype; nonetheless, the following nomenclature can assist the clinician in diagnosis and management. Onset of the POLG-related disorders ranges from infancy to late adulthood. Alpers-Huttenlocher syndrome (AHS), one of the most severe phenotypes, is characterized by childhood-onset progressive and ultimately severe encephalopathy with intractable epilepsy and hepatic failure. Childhood myocerebrohepatopathy spectrum (MCHS) presents between the first few months of life up to about age three years with developmental delay or dementia, lactic acidosis, and a myopathy with failure to thrive. Other findings can include liver failure, renal tubular acidosis, pancreatitis, cyclic vomiting, and hearing loss. Myoclonic epilepsy myopathy sensory ataxia (MEMSA) now describes the spectrum of disorders with epilepsy, myopathy, and ataxia without ophthalmoplegia. MEMSA now includes the disorders previously described as spinocerebellar ataxia with epilepsy (SCAE). The ataxia neuropathy spectrum (ANS) includes the phenotypes previously referred to as mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO). About 90% of persons in the ANS have ataxia and neuropathy as core features. Approximately two thirds develop seizures and almost one half develop ophthalmoplegia; clinical myopathy is rare. Autosomal recessive progressive external ophthalmoplegia (arPEO) is characterized by progressive weakness of the extraocular eye muscles resulting in ptosis and ophthalmoparesis (or paresis of the extraocular muscles) without associated systemic involvement; however, caution is advised because many individuals with apparently isolated arPEO at the onset develop other manifestations of POLG-related disorders over years or decades. Of note, in the ANS spectrum the neuropathy commonly precedes the onset of PEO by years to decades. Autosomal dominant progressive external ophthalmoplegia (adPEO) typically includes a generalized myopathy and often variable degrees of sensorineural hearing loss, axonal neuropathy, ataxia, depression, Parkinsonism, hypogonadism, and cataracts (in what has been called "chronic progressive external ophthalmoplegia plus," or "CPEO+").

Modes of inheritance*: Autosomal Recessive

Myoclonic epilepsy myopathy sensory ataxia, commonly called MEMSA, is part of a group of conditions called the POLG-related disorders. The conditions in this group feature a range of similar signs and symptoms involving muscle-, nerve-, and brain-related functions. The signs and symptoms of MEMSA typically appear during young adulthood. This condition had previously been known as spinocerebellar ataxia with epilepsy (SCAE). The first symptom of MEMSA is usually cerebellar ataxia, which refers to problems with coordination and balance due to defects in the part of the brain that is involved in coordinating movement (cerebellum). Recurrent seizures (epilepsy) usually develop later, often in combination with uncontrollable muscle jerks (myoclonus). The seizures usually begin in the right arm and spread to become generalized throughout the body. Additionally, affected individuals may have severe brain dysfunction (encephalopathy) or muscle weakness (myopathy). The myopathy can affect muscles close to the center of the body (proximal), such as the muscles of the hips, thighs, upper arms, or neck, or muscles farther away from the center of the body (distal), such as the muscles of the hands or feet. The myopathy may be especially noticeable during exercise (exercise intolerance).

Modes of inheritance*: Not available

• Chr17: 78,013,765 DEL C

Pathogenic



Phenotype: Ciliary dyskinesia, primary, 15

Zygosity: Heterozygous (x1) dbSNP ID: rs397515393

Population Allele Frequency: 0.05%

Gene Impact: **CCDC40** FRAMESHIFT A-83-V

Supporting Publications: <http://www.ncbi.nlm.nih.gov/pubmed/23255504>
<http://www.ncbi.nlm.nih.gov/pubmed/21131974>

Phenotype Description:

Primary ciliary dyskinesia (PCD) is associated with situs abnormalities, abnormal sperm motility, and abnormal ciliary structure and function that

result in retention of mucus and bacteria in the respiratory tract leading to chronic oto-sino-pulmonary disease. More than 75% of full-term neonates with PCD have 'neonatal respiratory distress' requiring supplemental oxygen for days to weeks. Chronic airway infection, apparent in early childhood, results in bronchiectasis that is almost uniformly present in adulthood. Nasal congestion and sinus infections, apparent in early childhood, persist through adulthood. Chronic/recurrent ear infection, apparent in most young children, can be associated with transient or later irreversible hearing loss. Situs inversus totalis (mirror-image reversal of all visceral organs with no apparent physiologic consequences) is present in 50% of individuals with PCD; heterotaxy (discordance of right and left patterns of ordinarily asymmetric structures that can be associated with significant malformations) is present in approximately 6%. Approximately 50% of males with PCD are infertile as a result of abnormal sperm motility.

Modes of inheritance*: Autosomal Recessive

The remaining known phenotype variations affect the following traits and diseases:

Obesity, association with • Encephalopathy, acute, infection-induced, 4, susceptibility to • Myocardial infarction 1 • Lumbar disc herniation, susceptibility to • Low density lipoprotein cholesterol level quantitative trait locus 6 • Muscle AMP deaminase deficiency • Radial aplasia-thrombocytopenia syndrome • Serum level of interleukin-6 soluble receptor • Retinitis pigmentosa 35 • Calcium oxalate urolithiasis • Hyperlipidemia, familial combined, susceptibility to • Lupus nephritis, susceptibility to • Neutrophil-specific antigens na1/na2 • Trimethylaminuria, mild • Trimethylaminuria • Prostate cancer, susceptibility to • Venous thrombosis, susceptibility to • Thyrotoxic periodic paralysis • Lymphoproliferative disorders, susceptibility to • Fasting plasma glucose level quantitative trait locus 5 • Ovarian response to FSH stimulation • Fetal hemoglobin quantitative trait locus 5 • Gastric cancer susceptibility after h. pylori infection • Lactase persistence • Febrile seizures, familial, 3a • Osteoarthritis susceptibility 1 • Cataract 39, multiple types • Alkaline phosphatase, placental, allele-3 polymorphism • Gilbert syndrome, susceptibility to • Bilirubin, serum level of, quantitative trait locus 1 • Obesity, age at onset of • Biotinidase deficiency • Phenotype modifier, association with • Hyperglycinuria • Tuberculosis, susceptibility to • Schizophrenia, susceptibility to • Hypertension, essential, susceptibility to • Diabetes mellitus type 2 • Leanness, susceptibility to • Recombination rate quantitative trait locus 1 • Hypertension, salt-sensitive essential, susceptibility to • Alcoholism, susceptibility to • Alcohol dependence • Congenital human immunodeficiency virus • Bietti crystalline corneoretinal dystrophy • Prekallikrein deficiency • Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-positive • Asthma, susceptibility to • Skin/hair/eye pigmentation, variation in, 8 • Hemochromatosis type 1 ... and more...

Get full details on the remaining **148** known phenotype variations within the Enlis Genome Research software.

Interesting Variations of Uncertain Significance:

Filter steps:

- **Protein-disrupting variations** (Nonsense, Frameshift, Misstart, Splice Disrupt)
- **Phenotype Genes** - Within a gene already implicated in a disease or trait
- Global allele frequency < 1%
- Uncertain clinical significance

Results:

Variation	Gene	Impact	Allele Freq.	Gene Phenotype
Chr1: 24,664,149 DEL C	GRHL3	FRAMESHIFT	0.01%	Van der Woude syndrome
Chr1: 67,519,652 DEL T	SLC35D1	FRAMESHIFT	0.00%	Schneckenbecken dysplasia
Chr1: 154,600,474 T>C	ADAR	MISSTART	0.05%	Aicardi-Goutieres syndrome • Dyschromatosis symmetrica hereditaria
Chr1: 156,737,772 INS G	PRCC	FRAMESHIFT	0.00%	Renal cell carcinoma
Chr2: 38,301,971 DEL G	CYP1B1	FRAMESHIFT	0.00%	Glaucoma • Peters anomaly

+ 39 additional variations

Filter steps:

- **Predicted deleterious variations**
- **Phenotype Genes** - Within a gene already implicated in a disease or trait
- Global allele frequency < 1%
- Uncertain clinical significance

Results:

Variation	Gene	Impact	Allele Freq.	Gene Phenotype
Chr1: 24,194,671 G>A	FUCA1	MISSENSE	0.01%	Fucosidosis
Chr1: 33,359,375 C>T	HPCA	MISSENSE	0.00%	Dystonia
Chr1: 33,502,381 G>C	AK2	MISSENSE	0.11%	Reticular dysgenesis
Chr1: 45,288,277 A>C	PTCH2	MISSENSE	0.00%	Basal cell carcinoma • Basal cell nevus syndrome • Medulloblastoma
Chr1: 55,330,998 C>T	DHCR24	MISSENSE	0.01%	Desmosterolosis

+ 48 additional variations

Notes

* Mode of inheritance definitions:

Autosomal Dominant

Autosomal dominant inheritance refers to genetic conditions that occur when a mutation is present in one copy of a given gene (i.e., the person is heterozygous).

Autosomal Recessive

Autosomal recessive inheritance refers to genetic conditions that occur only when mutations are present in both copies of a given gene (i.e., the person is homozygous for a mutation, or carries two different mutations of the same gene, a state referred to as compound heterozygosity).

† Confidence Star Levels:



Review Status: Classified by single submitter with no evidence provided, or multiple conflicting interpretations



Review Status: Classified by single submitter with evidence



Review Status: Classified by multiple submitters



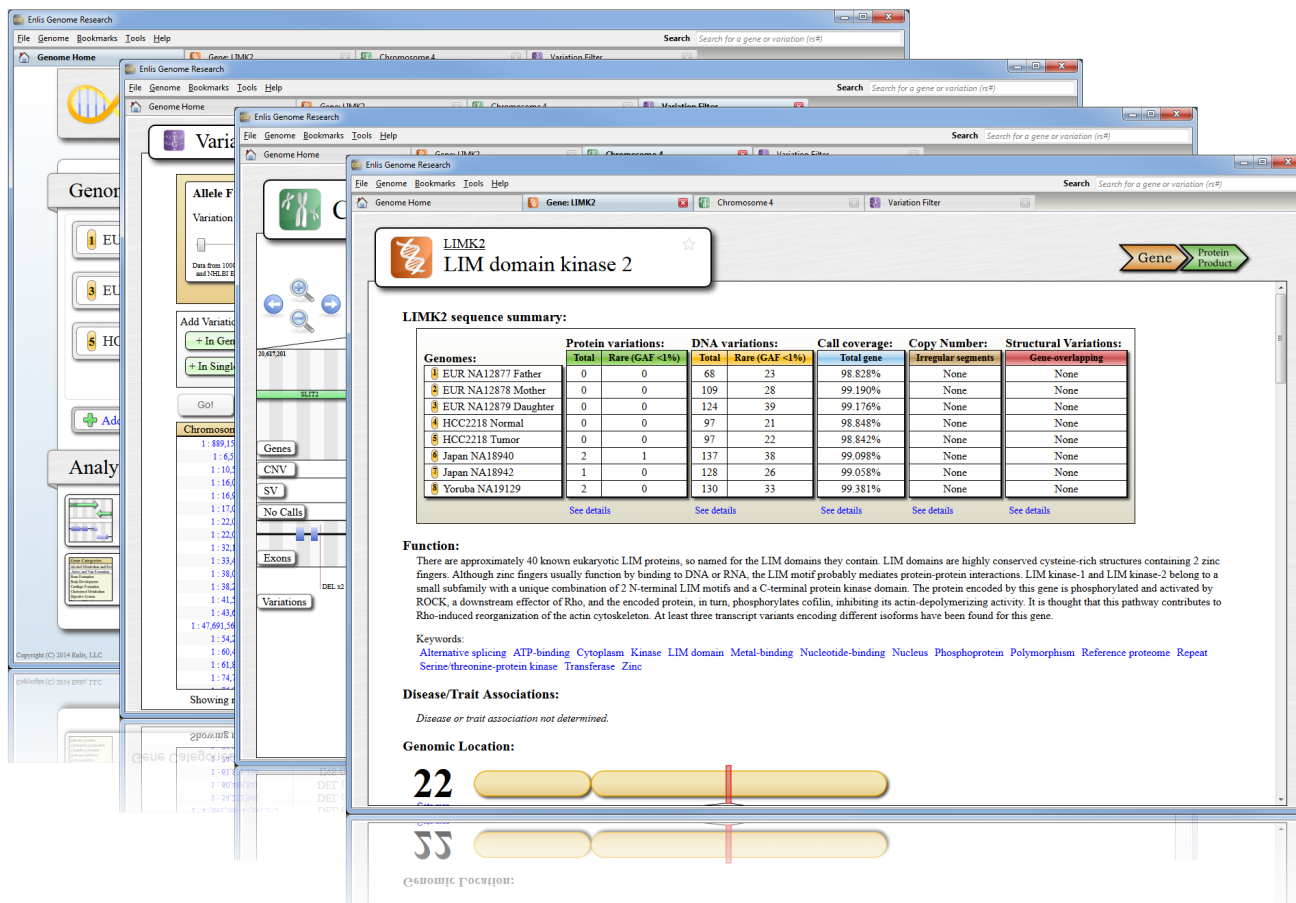
Review Status: Reviewed by expert panel



Review Status: Reviewed by professional society

Human genome reference version: [HomoSapiens_GRCh37](#)

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- Variation Filter - highly optimized with a point-and-click interface
- Gene Categories and Pathway Tool - evaluate over 20,000 built-in gene categories
- Homozygous Region Tool - to find regions associated with recessive disease and much more...

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