Genome Summary

Name: NA12144 NW European
Genome ID: NA12144_S1
Sequencing Provider: Illumina
Sequencing Type: Exome

Sequencing Coverage:

- **Full Genome**: 4.862%, 150,501,865 bases
- **Genes**: 9.774%, 160,471,602 bases
- **Exons**: 67.413%, 70,945,131 bases
- **Protein-coding**: 87.818%, 35,551,954 bases

Variation Counts:

- Total number of variations: 90,298
- Heterozygous: 47,224
- Homozygous (x2): 21,537
- Rare variations (MAF <1%): 15,270

- SNV: 80,835
- MNV: 0
- Insertion: 4,247
- Deletion: 5,216

- **Nonsense**: 126
- **Frameshift**: 266
- **Misstart**: 35
- **Nonstop**: 32
- **Inframe Ins/Del**: 286
- **Missense**: 15,699
- **Splice site**: 370
- Coding synonymous: 16,721
- mRNA untranslated: 55,242
- Intron: 21,701

Known Phenotype Summary:

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

- **121** disease or trait variations are found in this genome

- **Clinical classification:**
  - Pathogenic: 38
  - Likely pathogenic: 2
  - Risk factor: 55
  - Drug response: 5
  - Association: 14
  - Protective: 7

Phenotype variation coverage

96.1%

Successfully sequenced 40,405 phenotype variations
Missing data for 1,627 phenotype variations
Selected Phenotype Variation Details:

**• Chr3: 49,209,095 C>T**

Phenotype: **Hodgkin lymphoma**

Zygosity: **Heterozygous** (x1)  

**dbSNP ID: rs387906223**

**Population Allele Frequency: 0.30%**

Gene Impact: **KLHDC8B**  **UTR5**


Phenotype Description:

Classic Hodgkin lymphoma is a lymph node cancer of germinal center B-cell origin. Hodgkin lymphoma tumors consist of a minority of malignant cells, known as Reed-Sternberg (RS) cells, mixed with reactive lymphocytes and other benign inflammatory cells. A defining feature of RS cells is the presence of 2 nuclei (summary by Salipante et al., 2009).

**Modes of inheritance**: **Autosomal Recessive**

**• Chr8: 106,813,942 G>A**

Phenotype: **Tetralogy of Fallot**  

**46,XY sex reversal 9**

Zygosity: **Heterozygous** (x1)  

**dbSNP ID: rs187043152**

**Population Allele Frequency: 0.34%**

Gene Impact: **ZFPM2**  

MISSENSE M-544-I  

MISSENSE M-412-I  

MISSENSE M-275-I

Gene Impact: **RP11-152P17.2**  **INTRON**


Phenotype Description:

Critical congenital heart disease (CCHD) is a term that refers to a group of serious heart defects that are present from birth. These abnormalities result from problems with the formation of one or more parts of the heart during the early stages of embryonic development. CCHD prevents the heart from pumping blood effectively or reduces the amount of oxygen in the blood. As a result, organs and tissues throughout the body do not receive enough oxygen, which can lead to organ damage and life-threatening complications. Individuals with CCHD usually require surgery soon after birth. Although babies with CCHD may appear healthy for the first few hours or days of life, signs and symptoms soon become apparent. These can include an abnormal heart sound during a heartbeat (heart murmur), rapid breathing (tachypnea), low blood pressure (hypotension), low levels of oxygen in the blood (hypoxemia), and a blue or purple tint to the skin caused by a shortage of oxygen (cyanosis). If untreated, CCHD can lead to shock, coma, and death. However, most people with CCHD now survive past infancy due to improvements in early detection, diagnosis, and treatment. Some people with treated CCHD have few related health problems later in life. However, long-term effects of CCHD can include delayed development and reduced stamina during exercise. Adults with these heart defects have an increased risk of abnormal heart rhythms, heart failure, sudden cardiac arrest, stroke, and premature death. Each of the heart defects associated with CCHD affects the flow of blood into, out of, or through the heart. Some of the heart defects involve structures within the heart itself, such as the two lower chambers of the heart (the ventricles) or the valves that control blood flow through the heart. Others affect the structure of the large blood vessels leading into and out of the heart (including the aorta and pulmonary artery). Still others involve a combination of these structural abnormalities. People with CCHD have one or more specific heart defects. The heart defects classified as CCHD include coarctation of the aorta, double-outlet right ventricle, D-transposition of the great arteries, Ebstein anomaly, hypoplastic left heart syndrome, interrupted aortic arch, pulmonary atresia with intact septum, single ventricle, total anomalous pulmonary venous connection, tetralogy of Fallot, tricuspid atresia, and truncus arteriosus.

**Modes of inheritance**: **Autosomal Dominant**  

**Multifactorial**
Swyer syndrome is a condition that affects sexual development. Sexual development is usually determined by an individual's chromosomes; however, in Swyer syndrome, sexual development does not match the affected individual's chromosomal makeup. People usually have 46 chromosomes in each cell. Two of the 46 chromosomes, known as X and Y, are called sex chromosomes because they help determine whether a person will develop male or female sex characteristics. Girls and women typically have two X chromosomes (46,XX karyotype), while boys and men usually have one X chromosome and one Y chromosome (46,XY karyotype). In Swyer syndrome, individuals with one X chromosome and one Y chromosome in each cell, the pattern typically found in boys and men, have female reproductive structures. People with Swyer syndrome have typical female external genitalia. The uterus and fallopian tubes are normally-formed, but the gonads (ovaries or testes) are not functional; affected individuals have undeveloped clumps of tissue called streak gonads. Because of the lack of development of the gonads, Swyer syndrome is also called 46,XY complete gonadal dysgenesis. The residual gonadal tissue often becomes cancerous, so it is usually removed surgically early in life. People with Swyer syndrome are typically raised as girls and have a female gender identity. Because they do not have functional ovaries, affected individuals usually begin hormone replacement therapy during adolescence to induce menstruation and development of female secondary sex characteristics such as breast enlargement and uterine growth. Hormone replacement therapy also helps reduce the risk of reduced bone density (osteopenia and osteoporosis). Women with this disorder do not produce eggs (ova), but they may be able to become pregnant with a donated egg or embryo. Swyer syndrome usually affects only sexual development; such cases are called isolated Swyer syndrome. However, depending on the genetic cause, Swyer syndrome may also occur along with health conditions such as nerve problems (neuropathy) or as part of a syndrome such as campomelic dysplasia, which causes severe skeletal abnormalities.

Modes of inheritance*: Not available

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### Chr8: 145,107,390 C>T

**Phenotype:** 5-Oxoprolinase deficiency

**Zygosity:** Heterozygous (x1)  
**dbSNP ID:** rs185836803

**Population Allele Frequency:** 0.64%

**Gene Impact:** OPLAH  
**MISSENSE V-1089-I**


**Phenotype Description:**

5-Oxoprolinuria can be caused by genetic defects in either of 2 enzymes involved in the gamma-glutamyl cycle of glutathione metabolism: glutathione synthetase (GSS; 601002) or 5-oxoprolinase (OPLAH; 614243). GSS deficiency (266130) is best characterized as an inborn error of glutathione metabolism, but there is debate as to whether OPLAH deficiency represents a disorder or simply a biochemical condition with no adverse clinical effects because patients lack a consistent clinical picture apart from 5-oxoprolinuria (summary by Calpena et al., 2013).

**Modes of inheritance**: Autosomal Recessive

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### Chr1: 161,518,333 A>T

**Phenotype:** Immunodeficiency 20

**Zygosity:** Heterozygous (x1)  
**dbSNP ID:** rs10127939

**Population Allele Frequency:** 5.45%

**Gene Impact:** RP11-25K21.6  
**INTRON**

**Gene Impact:** FCGR3A  
**MISSENSE L-102-H**  
**MISSENSE L-101-H**  
**MISSENSE L-66-H**


**Phenotype Description:**

Immunodeficiency-20 is a rare autosomal recessive primary immunodeficiency characterized by functional deficiency of NK cells. Patient NK cells are defective in spontaneous cell cytotoxicity, but retain antibody-dependent cellular cytotoxicity. Patients typically present early in childhood with severe herpes viral infections, particularly Epstein Barr virus (EBV), and human papillomavirus (HPV) (summary by Grier et al., 2012).

**Modes of inheritance**: Autosomal Recessive
The remaining known phenotype variations affect the following traits and diseases:

- Generalized epilepsy with febrile seizures plus type 5
- MTHFR deficiency, thermolabile type
- Obesity, association with
- Drug addiction, susceptibility to
- Encephalopathy, acute, infection-induced, 4
- Myocardial infarction 1
- Homocysteine, total plasma, elevated
- Lumbar disc herniation, susceptibility to
- Serum level of interleukin-6 soluble receptor
- Calcium oxalate urolithiasis
- Familial medullary thyroid carcinoma
- Lupus nephritis, susceptibility to
- Neutrophil-specific antigens na1/na2
- Trimethylaminuria, mild
- Venous thrombosis, susceptibility to
- Chitotriosidase deficiency
- Legionellosis
- Fasting plasma glucose level quantitative trait locus 5
- Ovarian response to FSH stimulation
- Muscle hypertrophy
- Inflammatory bowel disease 10, susceptibility to
- Obesity, Phenotype modifier, association with
- Human immunodeficiency virus type 1, rapid progression to AIDS
- Schizophrenia, susceptibility to
- Leaniness, susceptibility to
- Leprosy, protection against
- Leprosy 5
- Uric acid concentration, serum, quantitative trait locus 1
- Systemic lupus erythmatosus, association with
- Bietti crystalline corneoretinal dystrophy
- Prekallikrein deficiency
- Neural tube defects, folate-sensitive, susceptibility to
- Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-positive
- Familial hypercholesterolemia
- Asthma, susceptibility to
- Atopy, susceptibility to
- Hypertension, diastolic, resistance to
- Cancer progression and tumor cell motility
- Hemochromatosis type 1
- C3HEX, ability to smell
- Myocardial infarction
- Microvascular complications of diabetes 1
- Asthma and atopy, susceptibility to
- Diabetes mellitus, insulin-dependent, 5
- Superoxide dismutase 2 polymorphism
- Asthma-related traits, susceptibility to, 2
- Coronary artery disease, susceptibility to
- Plasminogen activator inhibitor type 1 deficiency
- Phenylthiocarbamide tasting...

Get full details on the remaining 117 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:

<table>
<thead>
<tr>
<th>Variation</th>
<th>Gene</th>
<th>Impact</th>
<th>Allele Freq.</th>
<th>Gene Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chr1: 38,077,350 T&gt;A</td>
<td>RSPO1</td>
<td>SPLICE DISRUPT</td>
<td>0.00%</td>
<td>Palmoplantar hyperkeratosis</td>
</tr>
<tr>
<td>Chr1: 38,077,350 T&gt;G</td>
<td>RSPO1</td>
<td>SPLICE DISRUPT</td>
<td>0.00%</td>
<td>Palmoplantar hyperkeratosis</td>
</tr>
<tr>
<td>Chr1: 112,524,445 INS G</td>
<td>KCND3</td>
<td>FRAMESHIFT</td>
<td>0.01%</td>
<td>Brugada syndrome · Spinocerebellar ataxia</td>
</tr>
<tr>
<td>Chr5: 140,907,265 C&gt;A</td>
<td>DIAPH1</td>
<td>SPLICE DISRUPT</td>
<td>0.01%</td>
<td>Deafness</td>
</tr>
<tr>
<td>Chr6: 32,549,399 DEL C</td>
<td>HLA-DRB1</td>
<td>FRAMESHIFT</td>
<td>0.70%</td>
<td>Multiple sclerosis · Pemphigoid · Rheumatoid arthritis · Sarcoidosis</td>
</tr>
</tbody>
</table>

+ 12 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:

<table>
<thead>
<tr>
<th>Variation</th>
<th>Gene</th>
<th>Impact</th>
<th>Allele Freq.</th>
<th>Gene Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chr1: 983,635 C&gt;T</td>
<td>AGRN</td>
<td>MISSENSE</td>
<td>0.02%</td>
<td>Myasthenic syndrome</td>
</tr>
<tr>
<td>Chr1: 33,478,888 C&gt;T</td>
<td>AK2</td>
<td>MISSENSE</td>
<td>0.56%</td>
<td>Reticular dysgenesis</td>
</tr>
<tr>
<td>Chr1: 35,227,163 G&gt;A</td>
<td>RP1-34M23.5</td>
<td>MISSENSE</td>
<td>0.01%</td>
<td>Neural tube defects</td>
</tr>
<tr>
<td>Chr1: 160,393,859 A&gt;G</td>
<td>VANGL2</td>
<td>MISSENSE</td>
<td>0.10%</td>
<td>Neural tube defects</td>
</tr>
<tr>
<td>Chr1: 214,557,463 T&gt;G</td>
<td>PTPN14</td>
<td>MISSENSE</td>
<td>0.00%</td>
<td>Choanal atresia and lymphedema</td>
</tr>
</tbody>
</table>

+ 58 additional variations
**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).

**Multifactorial**
A phenotypic outcome (physical characteristic or disease predisposition) that is determined by more than one gene.

† **Confidence Star Levels:**

- ![Star](image)
  Review Status: Classified by single submitter with no evidence provided, or multiple conflicting interpretations

- ![Star](image)
  Review Status: Classified by single submitter with evidence

- ![Star](image)
  Review Status: Classified by multiple submitters

- ![Star](image)
  Review Status: Reviewed by expert panel

- ![Star](image)
  Review Status: Reviewed by professional society

Human genome reference version: HomoSapiens_GRCh37
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