1 Gene
2 alleles A; a
3 genotypes AA; Aa; aa
Simple Mendelian Traits

Conventional statement

They are controlled by a single gene,

Without environmental influence

These traits are found in a population in a non-continous pattern, as each subject shows one of the two possible phenotypes.
Non continuous traits

(AA + Aa)

RED FLOWERS

(aa)

WHITE FLOWERS
2012, new data from genome studies

They are controlled (mainly) by a single gene,

Without (large) environmental influence
Genotype

Phenotype

Action of other genes

Environmental Influences
Phenotypic traits in man...
...and diseases
Genetic Diseases

- Chromosomal
- Monogenic or Mendelian
  (autosomal – x linked – dominant – recessive)
- Multifactorial (combined effect of more than one gene and environmental factors)
- Mitochondrial
Human Genetics

scheduled crosses impossible
long time for the next generation
small number of children

We start with pedigree drawing and analysis
Male, female (unaffected)
Sex unknown
Affected male and female
Three unaffected males
Examined personally
Deceased (and affected)
Individual without offspring
Consanguineous marriage
Offspring with parentage unacknowledged or different from expected
Abortion (spontaneous or induced)
Twins
Monozygotic twins
Heterozygote (autosomal recessive)
Heterozygote (X-linked)
Propositus

Figure 1.1 Symbols used in drawing a pedigree.
Human Pedigrees
Two people who are related have an higher chance of being heterozygous for the same trait if compared to two people who are not related.
OMIM Statistics for November 1, 2009

Number of Entries

<table>
<thead>
<tr>
<th>Description</th>
<th>Autosomal</th>
<th>X-Linked</th>
<th>Y-Linked</th>
<th>Mitochondrial</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Gene with known sequence</td>
<td>12266</td>
<td>604</td>
<td>48</td>
<td>35</td>
<td>12953</td>
</tr>
<tr>
<td>+ Gene with known sequence and phenotype</td>
<td>331</td>
<td>21</td>
<td>0</td>
<td>2</td>
<td>354</td>
</tr>
<tr>
<td># Phenotype description, molecular basis known</td>
<td>2400</td>
<td>214</td>
<td>4</td>
<td>26</td>
<td>2644</td>
</tr>
<tr>
<td>% Mendelian phenotype or locus, molecular basis unknown</td>
<td>1646</td>
<td>141</td>
<td>5</td>
<td>0</td>
<td>1792</td>
</tr>
<tr>
<td>Other, mainly phenotypes with suspected mendelian basis</td>
<td>1874</td>
<td>137</td>
<td>2</td>
<td>0</td>
<td>2013</td>
</tr>
<tr>
<td>Total</td>
<td>18517</td>
<td>1117</td>
<td>59</td>
<td>63</td>
<td>19756</td>
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</table>
### OMIM Entry Statistics:

<table>
<thead>
<tr>
<th>Prefix</th>
<th>Autosomal</th>
<th>X Linked</th>
<th>Y Linked</th>
<th>Mitochondrial</th>
<th>Totals</th>
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<tr>
<td>Gene description</td>
<td>12,940</td>
<td>635</td>
<td>48</td>
<td>35</td>
<td>13,658</td>
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<tr>
<td>Gene and phenotype, combined</td>
<td>193</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>202</td>
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<tr>
<td>Phenotype description, molecular basis known</td>
<td>2,997</td>
<td>257</td>
<td>4</td>
<td>28</td>
<td>3,286</td>
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<tr>
<td>Phenotype description or locus, molecular basis unknown</td>
<td>1,638</td>
<td>134</td>
<td>5</td>
<td>0</td>
<td>1,777</td>
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<tr>
<td>Other, mainly phenotypes with suspected mendelian basis</td>
<td>1,805</td>
<td>128</td>
<td>2</td>
<td>0</td>
<td>1,935</td>
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<tr>
<td>Totals</td>
<td>19,573</td>
<td>1,161</td>
<td>59</td>
<td>65</td>
<td>20,858</td>
</tr>
</tbody>
</table>
Autosomal Recessive Diseases:

Locus alpha, 1 gene

2 Alleles   A (dominant) # a (recessive)

Genotypes       AA #Aa # aa

Phenotype       Healthy # affected
Both parents are carriers

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>a</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>AA</td>
<td>Aa</td>
</tr>
<tr>
<td>a</td>
<td>Aa</td>
<td>aa</td>
</tr>
</tbody>
</table>
Autosomal recessive inheritance

- Usually observed only in one generation
- Both males and females affected
Autosomal recessive pedigrees:

-- a family affected with a well known disease, whose inheritance is defined as AR

-- a family affected with a well known disease, whose inheritance is undefined

-- a family affected with a disease, whose diagnosis is uncertain
A couple in which both parents are carriers has a 25% risk (or 1 in 4) for a child homozygous for the recessive allele, aa.

3/4 children carry at least one dominant -A allele- and will show the dominant phenotype.
Relevant points:

remember that if we are dealing with phenotypes and diseases we must take into account the age at which the phenotype becomes clinically evident.
For some diseases at birth, for others in paediatric ages or even in adulthood.

Roberts Syndrome
OMIM 268300

Scheie Syndrome
OMIM 252800

AR Retinitis Pigmentosa
late onset
OMIM 268025
### One carrier parent

<table>
<thead>
<tr>
<th>Carrier</th>
<th>Carrier</th>
<th>Noncarrier</th>
<th>Noncarrier</th>
</tr>
</thead>
</table>

### Table

<table>
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<tr>
<th></th>
<th>A</th>
<th>a</th>
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<tbody>
<tr>
<td>A</td>
<td>AA</td>
<td>Aa</td>
</tr>
<tr>
<td>A</td>
<td>AA</td>
<td>Aa</td>
</tr>
</tbody>
</table>

### Table

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>A</th>
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</thead>
<tbody>
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<td>AA</td>
<td>AA</td>
</tr>
<tr>
<td>A</td>
<td>AA</td>
<td>AA</td>
</tr>
</tbody>
</table>
Recessive Phenotype And Reproduction

<table>
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<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>Aa</td>
<td>Aa</td>
</tr>
<tr>
<td>a</td>
<td>aa</td>
<td>aa</td>
</tr>
</tbody>
</table>
Recurrence risk for carriers and affected

Relevant point:

If the recessive phenotype is lethal or causes infertility, these crosses (#) are not observed.
Recessive Inheritance
Recessive diseases:

We have assumed that the genotypes AA and Aa show the same phenotype. In general it is true when the phenotype is studied only at clinical level. If we analyze the phenotype more deeply, i.e by biochemical techniques, imaging techniques, and so on, carriers can often be identified.
If we know that the child is affected with an AR disease, than we can deduct the genotypes.

Be aware of exceptions!

1- parents both carriers
2- one parent carrier, the second mutation is a new mutation
If this is a pedigree for a recessive trait,

what is the chance for III,1 to be a carrier, provided that a carrier test is not available?

if she is a carrier, does she have a chance of an affected child?

what is her the chance to marry a carrier?
Figure 19-1. Examples of autosomal recessive pedigrees commonly seen in Kuwait. a. Cerebellar ataxia with progressive external ophthalmoplegia. b. Autosomal recessive microcephaly. c. Trover's syndrome. d. Richner-Hanhart syndrome (Tyrosinemia type II).
Founder effect:

Original population
Aa: 1/32

New population
Aa: 11/33

Carriers and population
What is the chance in the original population and in the new population of random mating between two carriers?

Original population:

\[ \frac{1}{32} \times \frac{1}{32} \times \frac{1}{4} \quad \Rightarrow \quad \frac{1}{4096} \]

New population:

\[ \frac{1}{3} \times \frac{1}{3} \times \frac{1}{4} \quad \Rightarrow \quad \frac{1}{36} \]
**Founder effect**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th><strong>Andermann syndrome</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synonym</strong></td>
<td>Charlevoix disease</td>
</tr>
<tr>
<td><strong>Personalia</strong></td>
<td>Andermann, Frederick (Canadian physician)</td>
</tr>
<tr>
<td><strong>MeSH</strong></td>
<td><strong>Corpus Callosum / abnormalities</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Mental Retardation</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Hereditary Motor and Sensory Neuropathies</strong></td>
</tr>
<tr>
<td><strong>OMIM</strong></td>
<td>218000</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td>Agenesis of the corpus callosum with mental retardation and progressive sensorimotor neuropathy. The syndrome was first observed in children in a family from Charlevoix County in the province of Quebec in Canada and was traced to a couple married in 1637. It was later reported in other parts</td>
</tr>
</tbody>
</table>
Andermann Syndrome

Figure 1. A.B. Later in the first decade the primary chiasmal and midline septo-optic pseudo hypoplasia appears.

Figure 4. A. At age 4, C.G. is able to stand alone. B. The first patients described: J.B. and P.B. C. Older affected siblings confined to a wheelchair. D. An older patient showing pronounced digital wasting.
N. Dupré et al., Annals of Neurology 2003
Figure 6. Extended pedigree showing consanguinity (bold lines) and a common ancestral couple.
ALLELIC VARIANTS
(selected examples)

AGENESIS OF THE CORPUS CALLOSUM WITH PERIPHERAL NEUROPATHY [SLC12A6, 1-BP DEL, 2436G]

In 20 French Canadians with ACCPN (218000) from the Charlevoix and Saguenay-Lac-St-Jean regions of the province of Quebec in Canada, Howard et al. (2002) found homozygosity for a guanine deletion in exon 18 at nucleotide 2436 (2436delG) of the KCC3A open reading frame. The deletion converted GT at the splice donor site of exon 18 to TA, suggesting an effect on RNA splicing. Furthermore, a premature stop codon was predicted to occur at amino acid 813, removing the last 338 amino acids from the KCC3 protein (2436delG, thr813fsX813).
### TABLE 2. Biochemical-Genetic Delineation of Patients affected with Pompe’s disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>α-Glucosidase* Activity</th>
<th>Genotype</th>
<th>Amino Acid Substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.6</td>
<td>G1799A/del exon 18</td>
<td>R600H/del55AA</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>A1115T/delT525</td>
<td>H372L/−</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>delT525/delT525</td>
<td>−/−</td>
</tr>
<tr>
<td>4</td>
<td>0.7</td>
<td>G1913T/silent</td>
<td>G638V/−</td>
</tr>
<tr>
<td>Contr.</td>
<td>40–160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td>Name</td>
<td>OMIM</td>
<td>Heredity</td>
</tr>
<tr>
<td>------</td>
<td>-------------------------------------------</td>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>FC</td>
<td>ARSACS</td>
<td>270550</td>
<td>AR</td>
</tr>
<tr>
<td>FC</td>
<td>ACCPN</td>
<td>218000</td>
<td>AR</td>
</tr>
<tr>
<td>FC</td>
<td>Leigh syndrome (French Canadian type)</td>
<td>220111</td>
<td>AR</td>
</tr>
<tr>
<td>FC</td>
<td>Hereditary multiple intestinal atresia</td>
<td>243160</td>
<td>AR</td>
</tr>
<tr>
<td>FC</td>
<td>Jumping Frenchman of Maine</td>
<td>244100</td>
<td>AD</td>
</tr>
<tr>
<td>FN</td>
<td>Cree encephalopathy</td>
<td>603896</td>
<td>AR</td>
</tr>
<tr>
<td>FN</td>
<td>Cree encephalitis</td>
<td>608505</td>
<td>AR</td>
</tr>
<tr>
<td>FN</td>
<td>North American Indian Childhood Cirrhosis</td>
<td>604901</td>
<td>AR</td>
</tr>
<tr>
<td>R</td>
<td>Tyrosinaemia type I</td>
<td>276700</td>
<td>AR</td>
</tr>
<tr>
<td>R</td>
<td>Tay Sachs</td>
<td>272800</td>
<td>AR</td>
</tr>
<tr>
<td>R</td>
<td>Pseudovitamin D deficiency rickets</td>
<td>254700</td>
<td>AR</td>
</tr>
</tbody>
</table>
Recessive disorders:

The patient who is homozygous for the recessive \((a)\) allele, may in fact be carrier: of two \textbf{identical} mutations, or of two \textbf{different} mutations. When two different mutations are present, compound heterozygous is a more appropriate, but not commonly used definition.
Genotype-phenotype correlation in recessive diseases:

Beta thalassemia

Shwachman syndrome

Pompe’s disease
Beta thalassemia
The genotypes: [AA, Aa healthy] [aa affected]

Old books refers to

Healthy subjects >>> AA
Thalassemia maior >>> aa

Thalassemia minor
Thalassemia minima

The genotype Aa is associated with different level of clinical expression

There is a good correlation between the presence of two mutated alleles and a severe phenotype
Shwachman syndrome

Diagnóstico de criterios de Kuijpers et al. (Blood, 2005)
1—Insuficiencia exocrina de la páncreas
2—Crecimiento corto y 3—fallo de crecimiento
4—Dysfunción del bazo
Dos criterios >>>probables
Tres criterios >>>definitivos
(irrespeto de análisis genético del gen SBDS)


Fifteen patients (mean age 9.7 years) with documented SBDS gene mutations were included.

The skeletal changes were variable, even in patients with identical genotypes.
Pompe’s disease

Some alleles (mutations) are specific for each type
CLINICAL HETEROGENEITY


   “Patients with the same c.-32-13T-->G haplotype (c.q. GAA genotype) may manifest first symptoms at different ages, indicating that secondary factors may substantially influence the clinical course of patients with this mutation”.

• *Neuromuscul Disord*. 2007 Oct;17(9-10):698-706. Late onset Pompe disease: clinical and neurophysiological spectrum of 38 patients including long-term follow-up in 18 patients. Muller-Felber W et al

   “There was no correlation between the clinical phenotype and the genetic findings”.
CLINICAL VARIATION AMONG SIBLINGS

<table>
<thead>
<tr>
<th>Fam.</th>
<th>Onset/age</th>
<th>Walton/Resp</th>
<th>Allele 1</th>
<th>Allele 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Va**</td>
<td>Val</td>
<td>20/45</td>
<td>2 /-</td>
<td>IVS1(-13T&gt;G)</td>
</tr>
<tr>
<td></td>
<td>VaR</td>
<td>23/50</td>
<td>3 /+++</td>
<td>IVS1(-13T&gt;G)</td>
</tr>
<tr>
<td>Ta**</td>
<td>TaMG</td>
<td>25/62</td>
<td>4 /+++</td>
<td>IVS1(-13T&gt;G)</td>
</tr>
<tr>
<td></td>
<td>TaE</td>
<td>--/70</td>
<td>0 /-</td>
<td>IVS1(-13T&gt;G)</td>
</tr>
<tr>
<td>Fe</td>
<td>FeR</td>
<td>35/50</td>
<td>1 /-</td>
<td>IVS1(-13T&gt;G)</td>
</tr>
<tr>
<td></td>
<td>FeB</td>
<td>44/51</td>
<td>0 /</td>
<td>IVS1(-13T&gt;G)</td>
</tr>
<tr>
<td>Me</td>
<td>MeN</td>
<td>36/46</td>
<td>2 /+</td>
<td>IVS1(-13T&gt;G)</td>
</tr>
<tr>
<td></td>
<td>MeS</td>
<td>48/54</td>
<td>3 /+</td>
<td>IVS1(-13T&gt;G)</td>
</tr>
<tr>
<td>Sa</td>
<td>SaMB</td>
<td>42/57</td>
<td>2 /+</td>
<td>IVS1(-13T&gt;G)</td>
</tr>
<tr>
<td></td>
<td>SaL</td>
<td>50/58</td>
<td>2 /+</td>
<td>IVS1(-13T&gt;G)</td>
</tr>
<tr>
<td>Gh**</td>
<td>GhSg</td>
<td>60/72</td>
<td>3 /-</td>
<td>IVS1(-13T&gt;G)</td>
</tr>
<tr>
<td></td>
<td>GhSc</td>
<td>67/83</td>
<td>8 /+++</td>
<td>IVS1(-13T&gt;G)</td>
</tr>
</tbody>
</table>
ACE I/D POLYMORPHISM

- insertion/deletion (I/D) of a 287-base-pair DNA fragment within the intron 16
- It accounts approximately for 40% of the total variance of plasma ACE
- The I allele seems to be associated with enhanced endurance in elite distance runners, rowers, and mountaineers
- The D allele is associated with higher percentage
ACE FUNCTION

ACE is part of the renin-angiotensin system. The inactive form of the angiotensin hormone, angiotensinogen, is cleaved by renin to produce angiotensin I. ACE then catalyzes the conversion of angiotensin I to produce angiotensin II, which is the physiologically active form of the hormone. Along with several other effects, angiotensin II causes vasoconstriction and regulates salt and water homeostasis through the release of the hormone aldosterone. ACE also degrades the potent vasodilator bradykinin.

  “...we found a highly significant (p<0.01) association between ACE genotype and clinical severity, with strong correlation between severe phenotype and number of D alleles....”


  “...Significant correlation was observed (exact two-sided P<0.0001) between the number of D alleles of the ACE gene and the disease severity...”
<table>
<thead>
<tr>
<th></th>
<th>DD</th>
<th>ID</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients (tot.124); N (%)</strong></td>
<td>38 (30.6)</td>
<td>64 (51.6)</td>
<td>22 (17.7)</td>
</tr>
<tr>
<td><strong>Controls (tot.224); N (%)</strong></td>
<td>79 (35.2)</td>
<td>106 (47.3)</td>
<td>39 (17.4)</td>
</tr>
</tbody>
</table>

\[ X^2 = 0.66 \]
ACE and predicted risk of disease onset for the “average” patient

DD have higher hazard curve because they have a greater potential to earlier disease onset.
ACE and risk of disease severity at a given age

DD has higher hazard curve because it has a greater potential to more severe disease at any age.
- **ACE**: genotype II increase in % of type 1 muscle fiber
- **ACTN3**: genotype XX increase in % type 1 muscle fiber

- Better response to enzyme replacement therapy of type 1 muscle fiber in mice.

<table>
<thead>
<tr>
<th>ACE Genotype (N. pts.)</th>
<th>DD (3)</th>
<th>ID (9)</th>
<th>II (4)</th>
<th>* P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle mass (thigh)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean variation (95% CI)</td>
<td>-4.9%</td>
<td>+5.9%</td>
<td>+12.0%</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td>(-26.3% to 15.5%)</td>
<td>(-1.0% to 12.8%)</td>
<td>(7.1% to 16.9%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACTN3 genotype (N. pts.)</th>
<th>RR (4)</th>
<th>RX (10)</th>
<th>XX (2)</th>
<th>* P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle mass (thigh)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean variation (95% CI)</td>
<td>+4.7%</td>
<td>+2.5%</td>
<td>+20.6%</td>
<td>0.075</td>
</tr>
<tr>
<td></td>
<td>(-4.4% to 13.9%)</td>
<td>(-3.8% to 8.7%)</td>
<td>(3.9% to 37.2%)</td>
<td></td>
</tr>
</tbody>
</table>

*P value obtained with Kruskal Wallis test
Genetic heterogeneity:
Same phenotype/different genes.

Usher Syndrome (US)

US is characterized by the association of sensorineural deafness (usually congenital) with retinitis pigmentosa and progressive vision loss. Prevalence is estimated at 1/30,000. Onset usually occurs during childhood. Transmission is autosomal recessive.

Thee clinical entities have been defined:
- type 1 (around 40% of cases), hearing loss is congenital, profound, nonprogressive, and associated with vestibular areflexia leading to delayed acquisitions (delayed head control and unassisted sitting and walking);
- type 2 (around 60% of cases), hearing loss is prelingual, moderate/severe, slowly progressive, and not associated with vestibular disorders;
- type 3 (< 3% of cases, but more frequent in the Finnish and Ashkenazi Jewish populations), hearing loss is rapidly progressive, often diagnosed during the 1st decade; vestibular disorders in half the cases. Retinitis pigmentosa, generally diagnosed after the deafness, first manifests by visual discomfort at low light levels, followed by total blindness within a few decades.

So far, mutations in **five** genes (MYO7A, USH1C, CDH23, PCDH15, USH1G) and one locus (USH1E) have been implicated in US type 1. Mutations in **threee** genes (USH2A, GPR98 and DFNB31) and one possible locus (15q) have been implicated in US type 2. Mutations in only **one** gene (CLRN1) have been identified for US type 3.
The inner ear houses the sensory organs for hearing and balance. Wavelengths of sound are sensed in the cochlea by specialized receptor neurons called hair cells, while acceleration and gravity are detected by similar hair cells in the vestibular apparatus. Although all hair cells share the same basic properties, different subtypes of hair cells have unique features that allow them to subserve distinct functions in hearing or balance. In the organ of Corti of the cochlea, for example, inner hair cells are directly responsible for detecting sound stimuli, while outer hair cells serve primarily to amplify the signal. Similar diversities can be seen in the hair cells of the vestibular system, which vary in morphology, in their physiological properties and in the kinds of synaptic inputs they receive.
Table 1. Molecular Genetic Testing Used in Usher Syndrome Type I (USH1)

<table>
<thead>
<tr>
<th>Percent of All USH1</th>
<th>Gene Symbol (Locus Name)</th>
<th>Test Method</th>
<th>Mutations Detected</th>
<th>Mutation Detection Frequency by Gene and Test Method</th>
<th>Test Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>39%-55%</td>
<td>MYO7A (USH1B)</td>
<td>Sequence analysis</td>
<td>Sequence variants</td>
<td>~90% (^1,^2)</td>
<td>Clinical Testing</td>
</tr>
<tr>
<td>6%-7% (^3)</td>
<td>USH1C (USH1C)</td>
<td>Sequence analysis</td>
<td>Sequence variants</td>
<td>Unknown</td>
<td>Clinical Testing</td>
</tr>
<tr>
<td>19%-35%</td>
<td>CDH23 (USH1D)</td>
<td>Sequence analysis</td>
<td>Sequence variants</td>
<td>~90% (^1)</td>
<td>Clinical Testing</td>
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<tr>
<td>Rare</td>
<td>Unknown (USH1E)</td>
<td>Linkage analysis</td>
<td>N/A</td>
<td>N/A</td>
<td>Research only</td>
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<tr>
<td>11%-19%</td>
<td>PCDH15 (USH1F)</td>
<td>Targeted mutation analysis</td>
<td>p.Arg245X</td>
<td>See footnote 4</td>
<td>Clinical Testing</td>
</tr>
<tr>
<td>Rare (7%)</td>
<td>USH1G (USH1G)</td>
<td>Direct DNA (^3)</td>
<td>Sequence variants; other abnormalities</td>
<td>Unknown</td>
<td>Research only 6</td>
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<tr>
<td>Rare</td>
<td>Unknown (USH1H)</td>
<td>Linkage analysis</td>
<td>N/A</td>
<td>N/A</td>
<td>Research only</td>
</tr>
</tbody>
</table>
Digenic inheritance in Usher Syndrome

**OMIM 605514**, PROTOCADHERIN 15; PCDH15
Gene map locus 10q21-q22

**OMIM 605516** CADHERIN 23; CDH23
Gene map locus 10q21-q22
**Figure 3.3**

**Complementation: parents with autosomal recessive profound hearing loss often have children with normal hearing**

II₆ and II₇ are offspring of unaffected but consanguineous parents, and each has affected sibs, making it likely that each has autosomal recessive hearing loss. All their children are unaffected, showing that II₆ and II₇ have nonallelic mutations.
Figure 3
Classical complementation assay by cell fusion for nucleotide excision repair defects. The fibroblast strains used as partners in the fusion are grown for three days in medium containing latex beads of different sizes that are incorporated into the cytoplasm as a marker. The cells are fused using polyethylene glycol and, two days later, analyzed for their ability to perform UV-induced DNA repair synthesis (UDS) by autoradiography. The two cell strains are classified in the same complementation group if the heterodikaryons (identified as binuclear cells containing beads of different sizes) fail to recover normal UDS levels. Conversely, the recovery of normal UDS levels in the heterodikaryons indicates that the cell strains used as partners in the fusion are carrier of genetically different defects.
Fanconi’s Anemia

Genetics

Autosomal and X-linked recessive

Incidence <1:100,000 live births

Genetic heterogeneity
Cellular phenotype

• Spontaneous chromosomal instability

• Hypersensitivity to:
  - crosslinking agents (MMC, DEB)
  - oxygen radicals
  - tumor necrosis factor (TNF)
  - interferon-gamma

• G2 phase prolongation and/or arrest

Diagnosis

DEB test

Flow cytometry
Chromosomal rearrangements reflect a loss of fidelity in repairing double strand DNA breaks. These lesions are corrected normally by 2 primary pathways:

- NHEJ (non homologous end joining)
- HRR (homologous recombinational repair)

Absence of either pathway results in genomic instability and increased radiosensitivity
<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal (radial ray, hip, vertebral scoliosis, rib)</td>
<td>71</td>
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<tr>
<td>Skin pigmentation (café au lait, hyper- and hypopigmentation)</td>
<td>64</td>
</tr>
<tr>
<td>Short stature</td>
<td>63</td>
</tr>
<tr>
<td>Eyes (microphthalmia)</td>
<td>38</td>
</tr>
<tr>
<td>Renal and urinary tract</td>
<td>34</td>
</tr>
<tr>
<td>Male genital</td>
<td>20</td>
</tr>
<tr>
<td>Mental retardification</td>
<td>16</td>
</tr>
<tr>
<td>Gastrointestinal (e.g., anorectal, duodenal atresia)</td>
<td>14</td>
</tr>
<tr>
<td>Cardiac abnormalities</td>
<td>13</td>
</tr>
<tr>
<td>Hearing</td>
<td>11</td>
</tr>
<tr>
<td>Central nervous system (e.g., hydrocephalus, septum pellucidum)</td>
<td>8</td>
</tr>
<tr>
<td>No abnormalities</td>
<td>30</td>
</tr>
<tr>
<td>Complementation Groups</td>
<td>Genes</td>
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<td>-------------------------</td>
<td>-------------</td>
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<tr>
<td>FA-A</td>
<td>FANCA</td>
</tr>
<tr>
<td>FA-B</td>
<td>FANCB</td>
</tr>
<tr>
<td>FA-C</td>
<td>FANCC</td>
</tr>
<tr>
<td>FA-D1</td>
<td>FANCD1</td>
</tr>
<tr>
<td>FA-D2</td>
<td>FANCD2</td>
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<tr>
<td>FA-E</td>
<td>FANCE</td>
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<td>FA-F</td>
<td>FANCF</td>
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<td>FA-G</td>
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<td>FA-H</td>
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<tr>
<td>FA-J</td>
<td>BACH1</td>
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<tr>
<td>FA-L</td>
<td>FANCL</td>
</tr>
<tr>
<td>FA-M</td>
<td>FANCM</td>
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</tbody>
</table>
Molecular Diagnosis

Phenotype

FA-?

FANCA
FANCB
FANCC
D1-BRCA2
FANCD2
FANCE
FANCF
FANCG
FANCJ
FANCL
FANCM

Positive DEB test

Complementation

PROTEIN

Linkage

Mutated gene

Screening for mutations
FA/BRCA pathway: a network of processes
**Uniparental disomy (UPD)** refers to a condition in which both homologues of a chromosomal region/segment are inherited from only one parent [Engel, 1980].

The extent of the UPD can range from a small segment to the entire chromosome. Isodisomy describes the inheritance of two copies of a single parental homologue with associated reduction to homozygosity in the offspring, whereas heterodisomy refers to the inheritance of both homologues from one parent.

The incidence of UPD of any chromosome is estimated to be about 1:3,500 live births.

UPD for some chromosomes does not exert any adverse effect on an individual. However, for other chromosomes, it can result in abnormality through aberrant genomic imprinting, defined as differential gene expression dependent on parent of origin.

Additionally, in the case of isodisomy, homozygosity of autosomal recessively inherited mutations is possible. Indeed, more than 50 patients with recessive disorders due to isodisomy have been reported thus far [Engel, 2006].
In the case of isodisomy, homozygosity of autosomal recessively inherited mutations is possible: more than 50 patients with recessive disorders due to isodisomy have been reported thus far [Engel, 2006].

A fascination with chromosome rescue in uniparental disomy: Mendelian recessive outlaws and imprinting

E. Engel

<table>
<thead>
<tr>
<th>Recessive disorders</th>
<th>UPD type</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Functional epidermolysis bullosa, herlitz type</td>
<td>1 mat</td>
<td>Pulkkinen et al.³¹</td>
</tr>
<tr>
<td>Diabetes mellitus, type I</td>
<td>1 mat</td>
<td>Field et al.⁴⁵</td>
</tr>
<tr>
<td>Chediak–Higashi syndrome</td>
<td>1 mat</td>
<td>Dufourcq–Lagelouse et al.⁴¹</td>
</tr>
<tr>
<td>Maple syrup disease, type 2</td>
<td>1 mat</td>
<td>Lebo et al.⁴²</td>
</tr>
<tr>
<td>MCA (multiple congenital anomaly)</td>
<td>1 mat</td>
<td>Rothlisberger et al.⁴²</td>
</tr>
<tr>
<td>Pyknodysostosis</td>
<td>1 pat</td>
<td>Gelb et al.⁴⁵</td>
</tr>
<tr>
<td>MICA</td>
<td>1 pat</td>
<td>Chen et al.⁴⁶</td>
</tr>
<tr>
<td>Functional epidermolysis bullosa, Herlitz type</td>
<td>1 pat</td>
<td>Takizawa et al.⁴⁵</td>
</tr>
<tr>
<td>Congenital insensitivity to pain anhidrosis (CIPA)</td>
<td>1 pat</td>
<td>Miura et al.⁴⁸</td>
</tr>
<tr>
<td>CIPA+pyruvate kinase deficiency</td>
<td>1 pat</td>
<td>Indo et al.⁴⁷</td>
</tr>
<tr>
<td>Junctional epidermolysis bullosa, Herlitz type</td>
<td>1 pat</td>
<td>Fassihi et al.⁴⁸</td>
</tr>
<tr>
<td>Retinal dystrophy</td>
<td>1 pat</td>
<td>Thomson et al.³⁶</td>
</tr>
<tr>
<td>Usher syndrome type A2</td>
<td>1 pat</td>
<td>Rivolta et al.⁴⁹</td>
</tr>
<tr>
<td>Trifunctional protein deficiency</td>
<td>2 mat</td>
<td>Speikerkoetter et al.⁵⁰</td>
</tr>
<tr>
<td>Pseudohypophosphatidism (5α reductase deficiency)</td>
<td>2 pat</td>
<td>Chavez et al.⁵¹</td>
</tr>
<tr>
<td>Retinal dystrophy</td>
<td>2 pat</td>
<td>Thomson et al.³⁶</td>
</tr>
<tr>
<td>Crigler–Najjar, type I</td>
<td>2 pat</td>
<td>Petit et al.⁵²</td>
</tr>
<tr>
<td>Congenital aærinogenaemia</td>
<td>4 mat</td>
<td>Spena et al.⁵³</td>
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<tr>
<td>Spinal muscular atrophy, type 3, Juvenile</td>
<td>5 pat</td>
<td>Brzustowicz et al.⁵²</td>
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<td>Congenital adrenal hyperplasia</td>
<td>6 mat</td>
<td>Spiro et al.⁵⁴</td>
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<tr>
<td>Cystic fibrosis</td>
<td>7 mat</td>
<td>Spence et al.⁷</td>
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<tr>
<td>Cystic fibrosis</td>
<td>7 mat</td>
<td>Voss et al.⁵⁵</td>
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<td>Osteogenesis imperfecta (COL1A2)</td>
<td>7 mat</td>
<td>Spotila et al.⁵⁶</td>
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<tr>
<td>Cystic fibrosis</td>
<td>7 mat</td>
<td>Hehr et al.⁵⁷</td>
</tr>
<tr>
<td>Congenital chloride diarrhoea</td>
<td>7 pat</td>
<td>Höglund et al.³²</td>
</tr>
<tr>
<td>Cystic fibrosis and kartagener syndrome</td>
<td>7 pat</td>
<td>Pan et al.⁵⁸</td>
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<tr>
<td>Chylomicronemia familial</td>
<td>8 mat</td>
<td>Benlian et al.⁵⁹</td>
</tr>
<tr>
<td>Hair–cartilage syndrome</td>
<td>9 mat</td>
<td>Sulisalo et al.⁵⁹</td>
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<tr>
<td>Leigh syndrome</td>
<td>9 mat</td>
<td>Tiranti et al.⁵⁹</td>
</tr>
<tr>
<td>Beta thalassemia major</td>
<td>11 pat</td>
<td>Beldjord et al.⁵⁵</td>
</tr>
<tr>
<td>Prelingual hearing impairment (Connexin26)</td>
<td>13 mat</td>
<td>Alvarez et al.⁵¹</td>
</tr>
<tr>
<td>Complete congenital achromatopsia (rod monochr.)</td>
<td>14 mat</td>
<td>Pentao et al.⁵²</td>
</tr>
</tbody>
</table>
Figure 1. Possible formation mechanisms of UPD. A mixture of red and blue colors on a chromosome in (3) represents somatic recombination between paternal and maternal homologous chromosomes, whereas each mixture of red and pink colors on each chromosome in (4)–(7) represents recombination between non-sister chromatids of a pair of homologous chromosomes.