## Autosomal Dominant Diseases:

**Locus beta, 1 gene**

<table>
<thead>
<tr>
<th>2 Alleles</th>
<th>A (dominant)</th>
<th>a (recessive)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>AA</th>
<th>#</th>
<th>Aa</th>
<th>#</th>
<th>aa</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Affected</th>
<th>#</th>
<th>Healthy</th>
</tr>
</thead>
</table>
**Haploinsufficiency**

Insufficient **protein** production as a result of **hemizygous** or **haploid gene** when the normal **phenotype** requires two **alleles**. The single copy of a **gene** does not provide enough potential for normal **protein** production.

The situation in which an individual who is heterozygous for a certain gene mutation or hemizygous at a particular locus, often due to a deletion of the corresponding allele, is clinically affected because a single copy of the normal gene is incapable of providing sufficient protein production as to assure normal function.
**Dominant negative mutation**

A mutation whose gene product adversely affects the normal, wild-type gene product within the same cell, usually by dimerizing (combining) with it.

Mutation resulting in a gene product that can interfere with the function of the normal gene product in heterozygotes.
In cases of polymeric molecules, such as collagen, dominant negative mutations are often more deleterious than mutations causing the production of no gene product (null mutations or null alleles).
Definition of gain-of-function dominant:

A **mutation** in which dominance is caused by changing the specificity or **expression** pattern of a **gene** or **gene product**, rather than simply by reducing or eliminating the normal activity of that **gene** or **gene product**.

**Dominant, Gain-of-Function Mutant Produced by Truncation of RPGR**

*Hong et al.*


In this study, we used the transgenic approach to demonstrate that a truncated RPGR acts as a dominant gain-of-function mutant, causing rapid photoreceptor loss, regardless of whether normal RPGR is present.

**RPGR** retinitis pigmentosa GTPase regulator
A couple in which one parent is heterozygous for a dominant allele (Aa) and the other is homozygous for the recessive allele (aa) will have 50% of children carrying the dominant allele, and thus showing the related phenotype.
Autosomal Dominant Inheritance

- The disease is observed in each generation
- Both males and females affected
- Each affected subject has inherited the disease from one parent
- 50% of children of an affected subject are expected to be similarly affected
In pedigrees showing dominant diseases,

every affected individual has an affected biological parent. Usually there is no skipping of generations.

Males and females have an equally likely chance of inheriting the mutant allele and being affected. The recurrence risk of each child of an affected parent is 1/2.

Normal siblings of affected individuals do not transmit the trait to their offspring.

The defective product of the gene is usually a structural protein, not an enzyme.
Achondroplasia

Homozygosity for the dominant allele is lethal

Aa x Aa

AA  Aa  aa

1  :  2  :  1
Dominant disorders:

What happens for a double dose of the dominant allele?
Pedigree 1. An idealized pedigree of a family with hypercholesterolemia, an autosomal dominant disease where the heterozygote has a reduced number of functional low density lipoprotein receptors.
# OMIM 143100  HUNTINGTON DISEASE; HD

Gene map locus 4p16.3

A number sign (#) is used with this entry because Huntington disease (HD) is caused by an expanded trinucleotide repeat in the gene encoding huntingtin (HTT; 613004) on chromosome 4p16.3.
Disease characteristics. Huntington disease (HD) is a progressive disorder of motor, cognitive, and psychiatric disturbances. The mean age of onset is 35 to 44 years and the median survival time is 15 to 18 years after onset.

Homozygotes for HD appear to have a similar age of onset to heterozygotes, but may exhibit an accelerated rate of disease progression [Squitieri et al 2003].

The age at onset of symptoms in the homozygote cases was within the range expected for heterozygotes with the same CAG repeat lengths, whereas homozygotes had a more severe clinical course. Our analysis suggests that although homozygosity for the Huntington disease mutation does not lower the age at onset of symptoms, it affects the phenotype and the rate of disease progression. These data, once confirmed in a larger series of patients, point to the possibility that the mechanisms underlying age at onset and disease progression in Huntington disease may differ.
When studying the relationships between genotype and phenotype, it is important to examine the statistical occurrence of phenotypes in a group of known genotypes. You might be surprised to learn that, for some traits, the phenotype might not occur as often as the genotype. For example, say everyone in population W carries the same allele combinations for a certain trait, yet only 85% of the population actually shows the phenotype expected from those allele combinations.

The proportion of genotypes that actually show expected phenotypes is called penetrance.

Thus, in the preceding example, the penetrance is 85%. This value is calculated from looking at populations whose genotypes we know.

Studies of penetrance help us predict how likely it is that a trait will be evident in those who carry the underlying alleles. In general, when we know that the genotype is present but the phenotype is not observable, the trait shows incomplete penetrance.

Basically, anything that shows less than 100% penetrance is an example of incomplete penetrance. Therefore, the penetrance of a trait is a statistically calculated value based on the appearance of a phenotype among known genotypes.
Age Related Penetrance

Penetrance

- Likelihood that the effect of the mutation will become clinically apparent
- 85% of women who carry a BRCA 1 mutation will develop breast cancer in their lifetime
- Therefore, the penetrance in women is 85%
- Penetrance for men with a BRCA 1 mutation is <1%
Lip pits

Donna

Bilateral cleft lip and palate

William

Normal examination

Bill

Lip pits

Dave
Dominant disease with reduced (80%) penetrance

Parent  Aa >> abnormal phenotype caused by the A allele

Child, of course 50% chance of inheriting the A allele

But the chance of demonstrating the abnormal phenotype will be

80% of 50% >> 40% only

The shaded individuals (red and pink) all have a genetic variant. Due to reduced penetrance, only the individuals in pink actually have the disease associated with the variant.
What is the difference between *penetrance* and *variable expressivity*?

*Penetrance* is the proportion of individuals with a disease-causing mutation who have clinical evidence of the disorder. *Penetrance* usually applies to autosomal dominant disorders.

*Variable expressivity* refers to the range of clinical features observed in individuals with a particular disorder. *Variable expressivity* applies to disorders following all patterns of inheritance.

**How is penetrance influenced by variable expressivity?**

*Penetrance* depends upon the disease manifestations used to determine if an individual is affected. For example, individuals with mild manifestations of an autosomal dominant disorder may be thought to be unaffected, resulting in apparent reduced *penetrance* for the disorder. Consider the following:

- An individual is known to have a *FBN1* mutation causing Marfan syndrome because she has an affected father and an affected child. She has a normal physical examination and is thought to have no manifestations of Marfan syndrome. Echocardiogram, however, reveals a dilated aortic root, a major clinical feature of Marfan syndrome. Studies based on both physical examination and echocardiogram will reveal a higher *penetrance* for Marfan syndrome than studies based on physical examination alone.
Treacher Collins Syndrome as an Example of **Variable Expressivity**

**Inheritance pattern:** *Autosomal dominant*

**Gene:** *TCOF1*  **Locus:** 5q32-q33.1

**Major clinical features:**
- Down-sloping palpebral fissures
- Eyelid colobomas
- Partial to total absence of lower eyelashes
- Malar hypoplasia
- Cleft palate
- Mandibular hypoplasia
- Ear deformities
- Hearing loss
Genotype-phenotype correlation

+162200
NEUROFIBROMATOSIS, TYPE I; NF1

- Six or more café au lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Freckling in the axillary or inguinal regions
- Optic glioma
- Two or more Lisch nodules (iris hamartomas)
- A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudarthrosis
- A first-degree relative (parent, sib, or offspring) with NF1 as defined by the above criteria
Genotype-Phenotype Correlations

NF1 is characterized by extreme clinical variability, not only between unrelated patients but also among affected individuals within a single family. Some investigators interpret this variability as evidence that most complications of NF1 result from the effects of additional random events in individual patients.

Evidence in support of this interpretation is provided by the occurrence of acquired "second hit" mutations and loss of heterozigosity at the \textit{NF1} locus in some neurofibromas, malignant peripheral nerve sheath tumors, pheochromocytomas, pilocytic astrocytomas, and juvenile chronic myelogenous leukemia cells from patients with NF1.
Genetic heterogeneity in AD diseases

<table>
<thead>
<tr>
<th>Retinitis Pigmentosa, Autosomal Dominant</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIPL1-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>CA4-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>CRX-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>FSCN2-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>GUCA1B-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>NRL-Related Retinitis Pigmentosa</td>
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<tr>
<td>PRPF 3-Related Retinitis Pigmentosa</td>
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<tr>
<td>PRPF 8-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>PRPF31-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>PRPH2-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>RHO-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>ROM1-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>RP1-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>RP9-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>IMDPH1-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>SEMA4A-Related Retinitis Pigmentosa</td>
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<tr>
<td>TOPORS-Related Retinitis Pigmentosa</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Retinitis Pigmentosa, Autosomal Recessive</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCA4-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>CNGA1-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>CNGB1-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>CRB1-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>FXYD-Related Retinitis Pigmentosa</td>
</tr>
<tr>
<td>Locus Name</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>RP18</td>
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<tr>
<td>RP4</td>
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<td>RP7</td>
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<td>RP9</td>
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<td>RP10</td>
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<td>RP27</td>
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<td>RP17</td>
</tr>
<tr>
<td>RP30</td>
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</tbody>
</table>

**Fig. 13.** ERG recordings in a normal patient and one with retinitis pigmentosa.
Clinical Diagnosis

The diagnosis of hereditary hemorrhagic telangiectasia (HHT) is based on the presence of arteriovenous malformations (AVMs), which may be cutaneous or mucocutaneous telangiectases or large visceral AVMs.

[Marchuk et al. 1998]
Diagnostic criteria include

• *Epistaxis*: spontaneous and recurrent -night-time nosebleeds heighten the concern for HHT

• *Mucocutaneous telangiectases, multiple*: small blanchable red spots that are focal dilatations of post-capillary venules or delicate, lacy red vessels with markedly dilated and convoluted venules at characteristic sites, as lips, oral cavity, fingers, and nose

• *Visceral arteriovenous malformation (AVM)*: an arteriovenous malformation lacks capillaries and consists of direct connections between arteries and veins. AVMs may be: # Pulmonary # Cerebral # Hepatic # Spinal # Gastrointestinal

• *Family history*: a first-degree relative with a definite HHT diagnosis
• Vascular dysplasia
• OMIM#187300
• Autosomal Dominant
• Penetrance complete > 40 yrs
• Incidence?
  - Haut Jura (Lyon, France) 53/1000 (Plauchu et al. 1980)
  - Vermont (USA) 1/8000-1/50000 (Shovlin et al. 1997)
  - Fyn (Denmark) 15.6/100 000 (Kjeldsen et al. 2001)
  - Bergamo (Italy) population 1,021,700 – 40 pts (Olivieri et.al 2007)
AVM LIVER (60%)

AVM LUNG (17-18%)

AVM BRAIN (6%)

AVM SPINAL (11%)
## HHT -- Known genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome Location</th>
<th>Description</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENG</strong> (MIM # 131195)</td>
<td>9q 34</td>
<td>Endoglin</td>
<td>HHT1</td>
</tr>
<tr>
<td><strong>ACVRL1</strong> (MIM # 601284)</td>
<td>12q11-14</td>
<td>Activin A Receptor, Type II-like1</td>
<td>HHT2</td>
</tr>
<tr>
<td><strong>MADH4</strong> (MIM # 600993)</td>
<td>18q21.1</td>
<td>Mothers against decapentaplegic, Drosophila, homolog of, 4</td>
<td>JP/HHT</td>
</tr>
</tbody>
</table>
Kaplan-Meier survival curve showing probability of remaining free of epistaxis.

Lesca et al., 2006
Genotype-Phenotype Correlations

<table>
<thead>
<tr>
<th>Clinical involvement</th>
<th>HHT1+2 (N = 343)</th>
<th>HHT1 (N = 93)</th>
<th>HHT2 (N = 250)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>313 (91.2%)</td>
<td>90 (96.8%)</td>
<td>223 (89.2%)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary</th>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Brain abscess</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Central nervous system</td>
<td></td>
<td></td>
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</table>

**Table 1**
Frequency of the symptomatic clinical manifestations according to the mutated gene

<table>
<thead>
<tr>
<th>Visceral involvement</th>
<th>HHT1+2</th>
<th>HHT1</th>
<th>HHT2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAVM</td>
<td>46/199 (23.1%)</td>
<td>27/50 (54%)</td>
<td>19/149 (12.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HAVM</td>
<td>107/197 (54.3%)</td>
<td>20/46 (43.5%)</td>
<td>87/151 (57.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>CAVM</td>
<td>4/72 (5.6%)</td>
<td>2/22 (9.1%)</td>
<td>2/50 (4%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Numbers in denominator refers to the patients who underwent screening for each organ.
NS, Not significant.
Families with a known mutation

- # families with a common ENG mutation
- # families with a common ACVRL1 mutation

1 Belgium
1 France
1 Germany
1 India
**152427**

**POTASSIUM CHANNEL, VOLTAGE-GATED, SUBFAMILY H, MEMBER 2; KCNH2**

*Alternative titles; symbols*

HUMAN ETHER-A-GO-GO-RELATED GENE; HERG
ETHER-A-GO-GO-RELATED GENE, HUMAN
ERG1

*HGNC Approved Gene Symbol: KCNH2*

*Cytogenetic location: 7q36.1  Genomic coordinates (GRCh37): 7:150,642,043 - 150,675,401  (from NCBI)*

<table>
<thead>
<tr>
<th>Location</th>
<th>Phenotype</th>
<th>Phenotype MIM number</th>
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<tbody>
<tr>
<td>7q36.1</td>
<td>Long QT syndrome-2</td>
<td>613688</td>
</tr>
<tr>
<td></td>
<td>Short QT syndrome-1</td>
<td>609620</td>
</tr>
<tr>
<td></td>
<td>[Long QT syndrome-2, acquired, susceptibility to]</td>
<td>613688</td>
</tr>
</tbody>
</table>
The higher the number of SNPs, the higher the risk.

Schwartz PJ, unpublished
The higher the number of SNPs, the higher the risk.

Schwartz PJ, unpublished
Disease characteristics. Myotonic dystrophy type 1 (DM1) is a multisystem disorder that affects skeletal and smooth muscle as well as the eye, heart, endocrine system, and central nervous system. The clinical findings, which span a continuum from mild to severe, have been categorized into three somewhat overlapping phenotypes: mild, classic, and congenital. Mild DM1 is characterized by cataract and mild myotonia (sustained muscle contraction); life span is normal. Classic DM1 is characterized by muscle weakness and wasting, myotonia, cataract, and often cardiac conduction abnormalities; adults may become physically disabled and may have a shortened life span. Congenital DM1 is characterized by hypotonia and severe generalized weakness at birth, often with respiratory insufficiency and early death; mental retardation is common.
Typical appearance in myotonic dystrophy (ie, Steinert disease) includes frontal baldness, temporal atrophy, and narrow facies.
If we know that the child is affected with an AD disease, than we can deduct the genotypes.

Be aware of exceptions!
The phenomenon of dominant and recessive mutations in the same gene is well described and associated with a range of molecular etiologies.

This is exemplified by mutations in RET gene. Heterozygous gain of function are associated with thyroid carcinoma and multiple endocrine neoplasia types 2A and 2B versus homozygous loss of function mutations in Hirschsprung disease.
Thrombocytopenia–absent radius (TAR) syndrome is characterized by hypomegakaryocytic thrombocytopenia and bilateral radial aplasia in the presence of both thumbs.

Evidence for autosomal recessive inheritance comes from families with several affected individuals born to unaffected parents, but several other observations argue for a more complex pattern of inheritance.
Figure 2. A, Adult patient (patient 1) with moderate upper-limb involvement. Note the radial deviation of both hands. B, Patient 9, showing mild upper-limb involvement with slightly reduced length...

Complex Inheritance Pattern Resembling Autosomal Recessive Inheritance Involving a Microdeletion in Thrombocytopenia?Absent Radius Syndrome

The American Journal of Human Genetics Volume 80, Issue 2 2007 232 - 240
Pedigrees of TAR-affected families. Arrow indicates index patients. A dot inside a symbol indicates presence of microdeletion (i.e., a carrier). A bar on top of a symbol indicates that the individual was tested for the presence of the deletion.
Kloppoki et al. (2007) found that carriers of a 200-kb microdeletion (i.e., clinically inconspicuous parents and grandparents) are not affected and implied that haploinsufficiency of the deleted region is not sufficient to cause TAR syndrome. They remarked that TAR syndrome does not appear to follow a standard autosomal dominant or complex pattern of inheritance. The possibility of genomic imprinting was excluded by the detection of maternal as well as paternal transmission of the deletion among the unaffected carrier parents.
Given the unclear inheritance and frequently sporadic nature of TAR syndrome, Klopacki et al. (2007) searched for genomic aberrations in 30 patients with TAR syndrome and their families, using high-resolution microarray-based comparative genomic hybridization (rearray CGH). They identified a common 200-kb deletion on the long arm of chromosome 1 in all the affected individuals and in 25 (32%) of 78 unaffected family members. The results indicated that TAR syndrome is associated with a microdeletion on 1q21.1 that is necessary but not sufficient to cause the phenotype. They postulated that the phenotype develops only in the presence of an additional modifier (mTAR). The TAR deletion does not overlap with the deletion on 1q21.1 identified in another syndrome of mental retardation and congenital anomalies (see 612474).
A: Array CGH profile of chromosome 1 (patient 1). Note the microdeletion in 1q21.1.

B: Confirmation of the microdeletion by FISH. Deletion of RP11-698N18

Klopopki et al.

Complex Inheritance Pattern Resembling Autosomal Recessive Inheritance Involving a Microdeletion in Thrombocytopenia Absent Radius Syndrome

The American Journal of Human Genetics, 2007, Vol 80, p 2232 - 240
Pedigrees of TAR-affected families. Arrow indicates index patients. A dot inside a symbol indicates presence of microdeletion (i.e., a carrier). A bar on top of a symbol indicates that the individual was tested for the presence of the deletion.
Albers et al. (2012) reported that 51 of 55 cases of TAR syndrome had a 200-kb deletion on 1q21 while 2 had a truncation or frameshift (null) mutation in the RBM8A gene on 1 allele.

Of these 53 cases, all had 1 of 2 low-frequency SNPs in regulatory regions of RBM8A on the other allele. Klopocki et al. (2007) had demonstrated that an inherited or de novo deletion on chromosome 1q21.1 is found in the majority of individuals with TAR syndrome, but the apparent autosomal recessive nature of this syndrome required the existence of an additional causative allele. Sequencing of all of their exomes, did not identify TAR-associated coding mutations in any gene.

However, 4 of the cases carried the minor allele of a low-frequency SNP in the 5-prime UTR of the RBM8A gene (rs139428292; 605313.0001), while the remaining case carried a previously unknown SNP in the first intron of the same gene (605313.0002). Genotyping by Sanger sequencing of another 48 cases of European ancestry identified the 2 SNPs in 35 and 11 samples, respectively.

In the 25 trios where the deletion in the child was not a de novo event, Albers et al. (2012) confirmed that the deletion and the newly identified SNPs were inherited from different parents.
**rs139428292 SNP**

**Original source**
Variants (including SNPs and Indels) imported from dbSNP (release 137) | [View in dbSNP](#)

**Alleles**
Reference/Alternative: **G/A** | Ancestral: **G** | Ambiguity code: **R** | MAF: **0.02 (A)**

**Location**
Chromosome **1:145507646** (forward strand) | [View in location tab](#)

**Validation status**
This variation is validated by **1000 Genomes** and also frequency

**Synonyms**
None currently in the database

**HGVS names**
This feature has 8 HGVS names - click the plus to show
1g.145507646G>A
ENST00000412239.1:n.456C>T
ENST00000484825.1:n.49G>A
ENST00000488663.1:n.49G>A
ENST00000447688.1:n.500C>T
ENST00000369307.3:x.-21G>A
ENST00000457797.1:n.343C>T
ENST00000330165.7:x.-21G>A

---

**1000 Genomes allele frequencies**

**ALL**
- G: 98%
- A: 2%

**AFR**
- G: 100%

**AMR**
- G: 98%
- A: 2%

**ASN**
- G: 100%

**EUR**
- G: 97%
- A: 3%

---

**EUR sub-populations**

**CEU**
- G: 98%
- A: 2%

**FIN**
- G: 98%
- A: 4%

**GBR**
- G: 97%
- A: 3%

**IBS**
- G: 86%
- A: 14%

**TSI**
- G: 98%
- A: 2%
The minor allele frequency of the 5-prime UTR and intronic SNPs were 3.05% and 0.42%, respectively, in 7,504 healthy individuals of the Cambridge BioResource, and the deletion was absent from 5,919 shared healthy controls of the Wellcome Trust Case Control Consortium.

*Albers et al. (2012)* concluded that in the vast majority of cases, compound inheritance of a rare null allele (containing a deletion, frameshift mutation, or encoded premature stop codon) and 1 of 2 low-frequency noncoding SNPs in RBM8A causes TAR syndrome. *Albers et al. (2012)* showed that the 2 regulatory SNPs result in diminished RBM8A transcription in vitro and that expression of Y14 (a subunit of the exon junction complex (EJC) encoded by the RBM8A gene) is reduced in platelets from individuals with TAR.