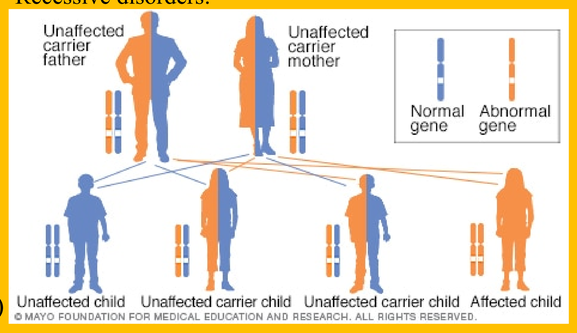
Genetic Variation of the Metabolic Disorder Homocystinuria

By: Alexandra Norton

Homocystinuria (HCU) – a genetic disease:

- ❖Autosomal recessive inheritance
- ❖ Impacts metabolism
- ❖Common cause: functional defects in the enzyme, or protein, cystathionine-beta-synthase (CBS)
  - ❖Leads to elevated levels of homocysteine

Recessive disorders:



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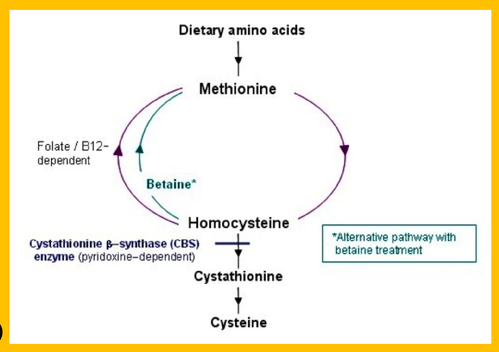
Importance of homocysteine:

- ❖CBS defects cause inability to utilize homocysteine, a form of the amino acid, cysteine
- ❖Amino acids are critical nutrients, and can be acquired from protein in foods or synthesized
  - ❖But excess levels of amino acids can cause many health defects



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HCU Incidence:

- ❖Globally: rare disease
- ❖But clinical studies show some regions have higher rates of disease (2)
  - ❖Qatar (1:1800)
  - ❖Norway (1:6,400)
  - ❖Germany (1:17,800)
  - ❖Ireland (1:65,000)
- ❖Symptoms variable, with some individuals asymptomatic

Genetic basis of HCU:

- ❖CBS gene codes for enzyme
  - ❖Gene mutations may lead to defective enzymes which cannot break down homocysteine
- ❖Complex genetic basis: many different mutations can lead to this disease
- ❖Our work explores variation in CBS which will be informative for disease risk assessments, and for identification of other mutations that may affect disease manifestation

Country	Nucleotide Change	Protein Change	Exon	Mutation Type
Spain	c.869 C>T	p.P290L	8	Missense
	c.572C>T	p.T191M	5	Missense
	c.833T<G	p.I278S	8	Missense
Portugal	c.572C>T	p.T191M	5	Missense
Venezuela	c.700G>A	p.D234N	8	Missense
France	1150 A>G	p.K384E	11	Missense
	1616 T>C	p.L539S	16	Missense
UK	c.374G>A	p.R125Q	3	Missense
	c.430G>A	p.E144K	3	Missense
	c.833T>C	p.I278T	8	Missense
	c.919G>A	p.G307S	8	Missense
USA	c.341C>T	p.A114V	3	Missense
	c.374G>A	p.R125Q	3	Missense
	c.785C>T	p.T262M	7	Missense
	c.797G>A	p.R266K	7	Missense
	c.833T>C	p.I278T	8	Missense
	c.919G>A	p.G307S	8	Missense
	g.13217A>C	(del ex 12)	Intron 11	Deletion
	c.1330G>A	p.D444N	12	Missense
India	c.518delTGA	p.M173del	4	Deletion
Argentina	c.676G<A	p.A226T	6	Missense
	c.962A<T	p.D321V	9	Missense
	c.1336G<T	p. A446S	12	Missense
Australia	c.833T>C	p.I278T	8	Missense

(3)

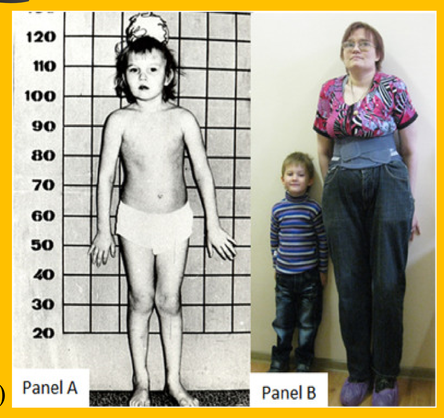
(4)

(5)

Potential effects on health:

Wide array of effects including:

- ❖Skeletal, nervous and vascular system issues (2)
  - ❖Osteoporosis
  - ❖Stroke
  - ❖Heart attack
  - ❖Megaloblastic anemia
- ❖Nearsightedness and displacement of the lenses (2)
- ❖Blood clotting issues (2)
- ❖Heterozygotes (having a copy of the mutation from only one parent) may be at increased risk for vascular disease



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Age 5 Age 28

Importance in awareness of genetic disorders:

- ❖Mutations are common and some are harmless, but others are detrimental
- ❖If two carriers of disease alleles have offspring, may cause lethal fetal anomalies
  - ❖Dependent on type of disease
- ❖Genetic testing can determine the presence of disorders
- ❖ Some diseases are late-onset, like many cases of HCU
- ❖Certain treatments and lifestyle changes are useful
  - ❖Can delay or reduce intensity of symptoms

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References:

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