JOURNAL OF NURSING SCHOLARSHIP

An Update of Childhood Genetic Disorders

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http://www.genome.gov/27552093

Presentation By: Cynthia A. Prows, MSN, CNS, FAAN

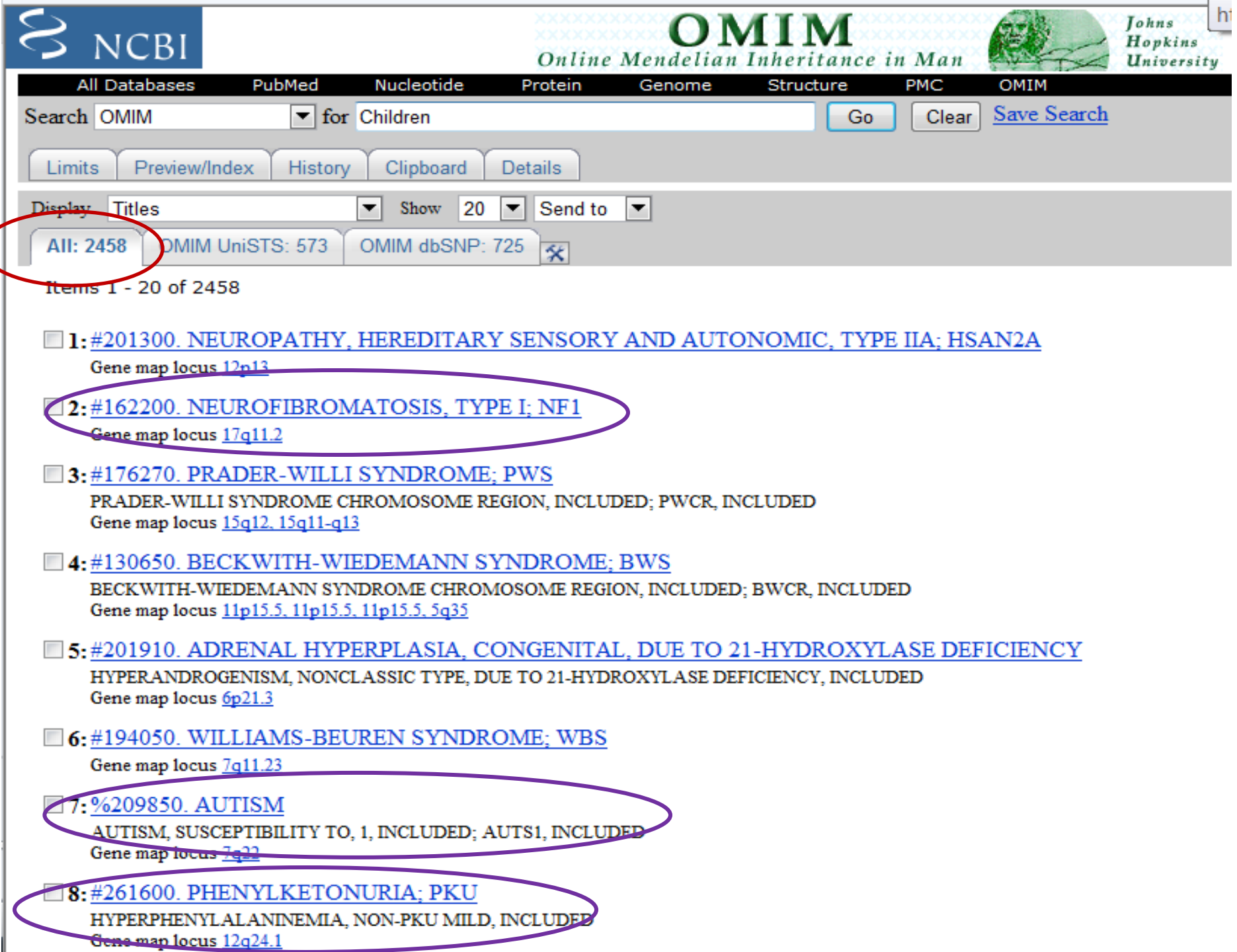
Cincinnati Children's
change the outcome

Webinar Outline

- Incorporate key points from article but not repeat content
- Use case example to illustrate ways nurses can incorporate genetics / genomics information into practice.
- Briefly discuss impact of new technology and national recommendations on our definition of childhood genetic disorders.

Childhood Genetic Disorders

- Diseases or syndromes caused by
  - Variants affecting nuclear or mitochondrial genes, or
  - Combinations of variant genes and environmental factors, or
  - Changes in the number or structure of one or more chromosomes or chromosomal regions
- Manifest prenatally or before 18 years of age


NCBI
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Display Titles Show 20 Send to
All: 2458 OMIM UniSTS: 573 OMIM dbSNP: 725
Items 1 - 20 of 2458
1: #201300. NEUROPATHY, HEREDITARY SENSORY AND AUTONOMIC, TYPE IIA; HSAN2A
Gene map locus 12p13
2: #162200. NEUROFIBROMATOSIS, TYPE I; NF1
Gene map locus 17q11.2
3: #176270. PRADER-WILLI SYNDROME; PWS
PRADER-WILLI SYNDROME CHROMOSOME REGION, INCLUDED; PWCR, INCLUDED
Gene map locus 15q12, 15q11-q13
4: #130650. BECKWITH-WIEDEMANN SYNDROME; BWS
BECKWITH-WIEDEMANN SYNDROME CHROMOSOME REGION, INCLUDED; BWCR, INCLUDED
Gene map locus 11p15.5, 11p15.5, 11p15.5, 5q35
5: #201910. ADRENAL HYPERPLASIA, CONGENITAL, DUE TO 21-HYDROXYLASE DEFICIENCY
HYPERANDROGENISM, NONCLASSIC TYPE, DUE TO 21-HYDROXYLASE DEFICIENCY, INCLUDED
Gene map locus 6p21.3
6: #194050. WILLIAMS-BEUREN SYNDROME; WBS
Gene map locus 7q11.23
7: %209850. AUTISM
AUTISM, SUSCEPTIBILITY TO, 1, INCLUDED; AUTS1, INCLUDED
Gene map locus 7q22
8: #261600. PHENYLKETONURIA; PKU
HYPERPHENYLALANINEMIA, NON-PKU MILD, INCLUDED
Gene map locus 12q24.1

Clinical Features

Early diagnosis of phenylketonuria, a cause of mental retardation, is important because it is treatable by dietary means. Features other than mental retardation in untreated patients include a 'mousy' odor; light pigmentation; peculiarities of gait, stance, and sitting posture; eczema; and epilepsy (Paine, 1957). Kawashima et al. (1988) suggested that cataracts and brain calcification may be frequently overlooked manifestations of classic untreated PKU. Brain calcification has been reported in dihydropteridine reductase (DHPR) deficiency (261630). Pitt and O'Day (1991) found only 3 persons with cataracts among 46 adults, aged 28 to 71 years, with untreated PKU. They concluded that PKU is not a cause of cataracts. Levy et al. (1970) screened the serum of 280,919 'normal' teenagers and adults whose blood had been submitted for syphilis testing. Only 3 adults with the biochemical findings of PKU were found. Each was mentally subnormal. Normal mentality is very rare among patients with phenylketonuria who have not received dietary therapy.

Evidence of heterogeneity in phenylketonuria was presented by Auerbach et al. (1967) and by Woolf et al. (1968).

Coskun et al. (1990) observed scleroderma in 2 infants with PKU. Improvement in the skin lesions after commencement of a low phenylalanine diet supported the possibility of a causal relationship.

Widespread screening of neonates for phenylketonuria brought to light a class of patients with a disorder of phenylalanine metabolism milder than that in PKU. These patients show serum phenylalanine concentrations well below those in PKU, but still several times the normal. PKU and hyperphenylalaninemia breed true in families (Kaufman et al., 1975), each behaving as an autosomal recessive. Kaufman et al. (1975) studied liver biopsies from patients with HPA and their parents. The patients with HPA had levels of phenylalanine hydroxylase about 5% of normal.

Burgard et al. (1996) found that all patients but one who had predicted in vitro residual enzyme activity greater than 20% had mild PKU, while those with predicted in vitro residual enzyme activity less than 20% were identified as having classical PKU. The authors stated that 'the difficulties of some patients to adjust their blood Phe level according to their target value although they comply with the dietary recommendations might be caused by low residual enzyme activity.' In addition, when considering the R261Q (612349.0006) mutation (a mutation with a considerable amount of residual enzyme activity, which produced higher Phe levels than expected), they hypothesized a negative intraallelic complementation effect as an explanation for higher than expected diagnostic Phe values.

Mildly depressed IQ is common in treated PKU. Griffiths et al. (2000) analyzed IQ scores collected from 57 British children with early-treated classic PKU using variants of the Wechsler intelligence scale for children (WISC) in relation to indicators of dietary control such as serum phenylalanine levels and socioeconomic factors. The authors found that, after correcting for socioeconomic status, phenylalanine control at age 2 was predictive of overall IQ, although early and continuous treatment did not necessarily lead to normalization of

http://omim.org/entry/261600

http://ghr.nlm.nih.gov

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Genetics Home Reference provides consumer-friendly information about the effects of genetic variations on human health.

The resources on this site should not be used as a substitute for professional medical care or advice. Users seeking information about a personal genetic disease, syndrome, or condition should consult with a qualified healthcare professional. See How can I find a genetics professional in my area? in the Handbook.

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Phenylketonuria

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Reviewed February 2012

What is phenylketonuria?

Phenylketonuria (commonly known as PKU) is an inherited disorder that increases the levels of a substance called phenylalanine in the blood. Phenylalanine is a building block of proteins (an amino acid) that is obtained through the diet. It is found in all proteins and in some artificial sweeteners. If PKU is not treated, phenylalanine can build up to harmful levels in the body, causing intellectual disability and other serious health problems.

The signs and symptoms of PKU vary from mild to severe. The most severe form of this disorder is known as classic PKU. Infants with classic PKU appear normal until they are a few months old. Without treatment, these children develop permanent intellectual disability. Seizures, delayed development, behavioral problems, and psychiatric disorders are also common. Untreated individuals may have a musty or mouse-like odor as a side effect of excess phenylalanine in the body. Children with classic PKU tend to have lighter skin and hair than unaffected family members and are also likely to have skin disorders such as eczema.

Less severe forms of this condition, sometimes called variant PKU and non-PKU hyperphenylalaninemia, have a smaller risk of brain damage. People with very mild cases may not require treatment with a low-phenylalanine diet.

Babies born to mothers with PKU and uncontrolled phenylalanine levels (women who no longer follow a low-phenylalanine diet) have a significant risk of intellectual disability because they are exposed to very high levels of phenylalanine before birth. These infants may also have a low birth weight and grow more slowly than other children. Other characteristic medical problems include heart defects or other heart problems, an abnormally small head size (microcephaly), and behavioral problems. Women with PKU and uncontrolled phenylalanine levels also have an increased risk of pregnancy loss.

Bookshelf ID: NBK1504 PMID: 20301677

Phenylalanine Hydroxylase Deficiency

Synonym: PAH Deficiency. Includes: Hyperphenylalaninemia (HPA), Phenylketonuria (PKU), Variant PKU

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Summary

Go to:

Disease characteristics. Phenylalanine hydroxylase (PAH) deficiency results in intolerance to the dietary intake of the essential amino acid phenylalanine and produces a spectrum of disorders including phenylketonuria (PKU), non-PKU hyperphenylalaninemia (non-PKU HPA), and variant PKU. Classic PKU is caused by a complete or near-complete deficiency of phenylalanine hydroxylase activity; without dietary restriction of phenylalanine, most children with PKU develop profound and irreversible intellectual disability. Non-PKU HPA is associated with a much lower risk of impaired cognitive development in the absence of treatment.

Diagnosis/testing. PAH deficiency can be diagnosed by newborn screening in virtually 100% of cases based on detection of the presence of hyperphenylalaninemia using the Guthrie microbial or other assays on a blood spot obtained from a heel prick. PKU is diagnosed in individuals with plasma phenylalanine (Phe) concentrations higher than 1000 µmol/L in the untreated state; non-PKU HPA is diagnosed in individuals with plasma Phe concentrations consistently above normal (i.e., >120 µmol/L), but lower than 1000 µmol/L when on a normal diet. Molecular genetic testing of *PAH* is used primarily for genetic counseling purposes to determine carrier status of at-risk relatives and for prenatal testing.

Management. *Treatment of manifestations:* Classic PKU: a low-protein diet and use of a Phe-free medical formula as soon as possible after birth to achieve plasma Phe concentrations of 120-360 µmol/L (2-6 mg/dL). A significant proportion of individuals with PKU may benefit from adjuvant therapy with 6R-BH_4 stereoisomer. Non-PKU HPA: It is debated whether those with plasma Phe concentrations consistently below 600 µmol/L (10 mg/dL) require dietary treatment

GeneReviews™ [Internet].
Pagon RA, Bird TD, Dolan CR, et al., editors.
Seattle (WA): University of Washington, Seattle; 1993-.

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Fictitious Case Example

- 5 year old female, evaluation of hypernasal speech in a multidisciplinary velo-pharyngeal insufficiency clinic
- Clinic nurse obtains brief history.
  - Ventricular septal defect – closed on its own
  - <5th percentile height & weight
  - Chronic otitis media – 4 sets of PE tubes
- Clinic nurse finishes by saying the child “looks different” & doesn’t seem to understand personal boundaries

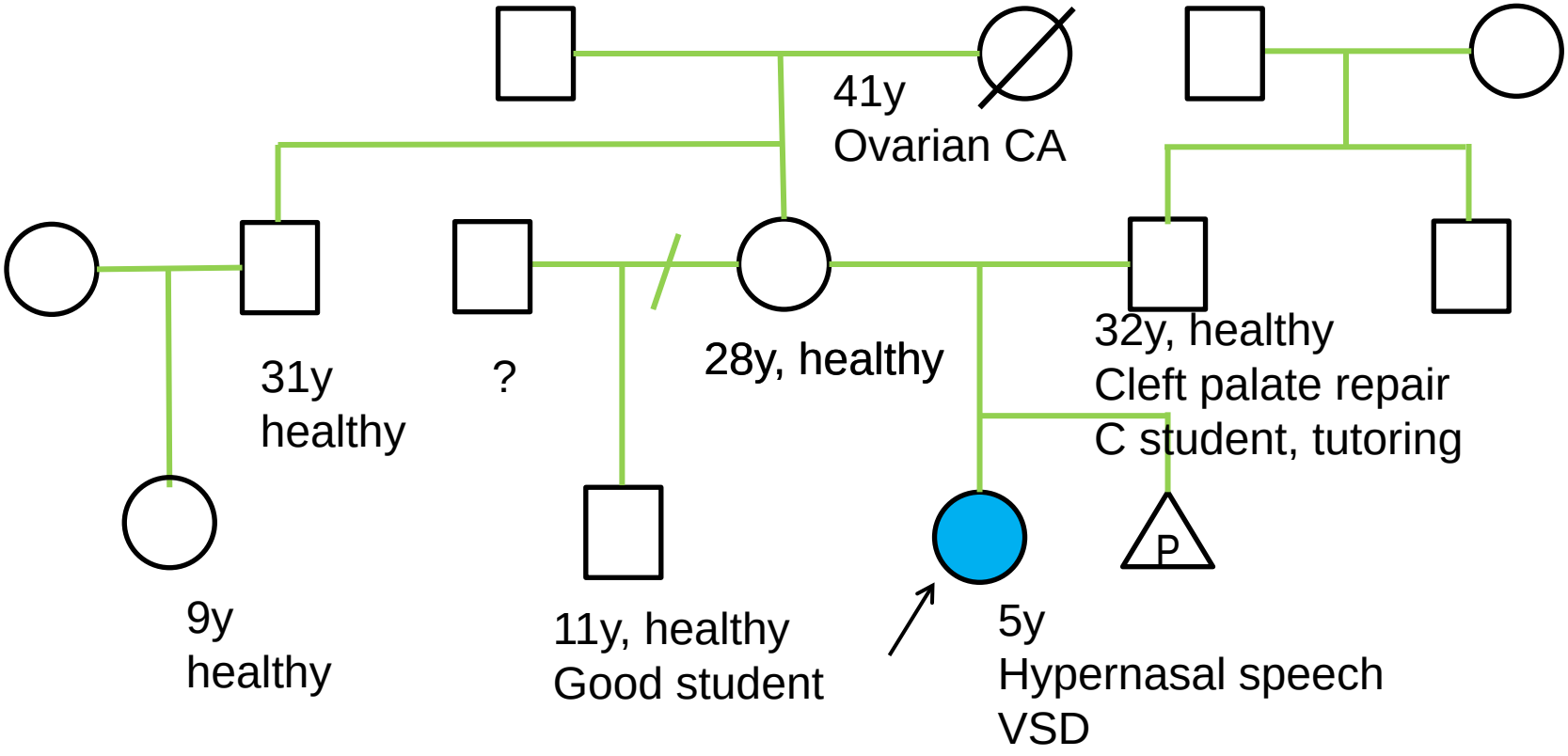
Clinical Nurse Specialist Findings

- Dysmorphology: mildly upward slanting palpebral fissures, rectangular nose, downward turned upper lip, somewhat prominent simplified ears, long slender fingers. No palatal notch nor bifid uvula. (http://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.v149a:1/issuetoc)
- Development: walked at 15 months, single words at 2 years, full sentences ~ 4 years but difficult to understand, difficulty following sequential instructions

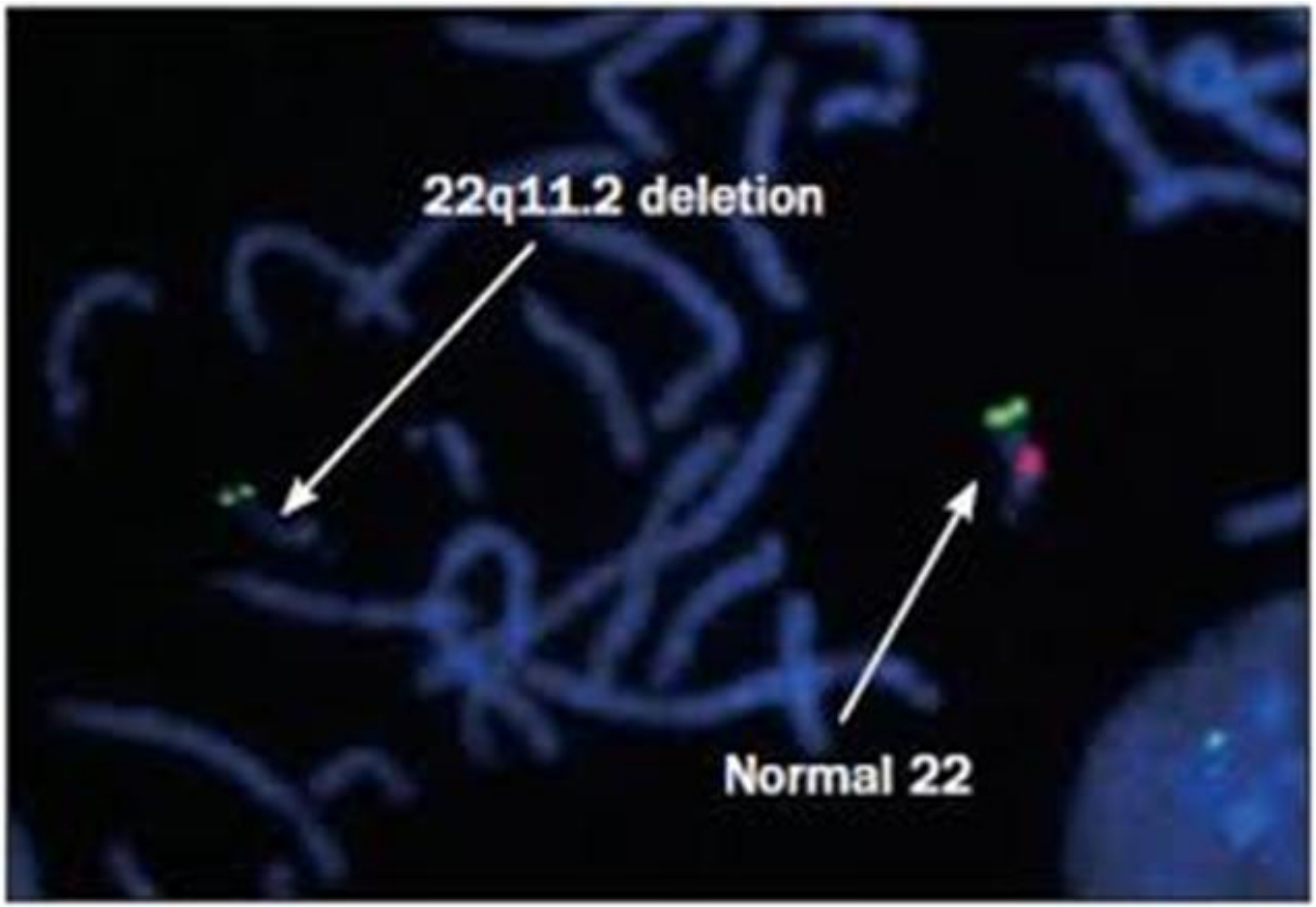
Nasopharyngoscopy Findings

- Short palate
- Poor lateral wall movement
- Medially displaced internal carotid arteries

Abbreviated Family History



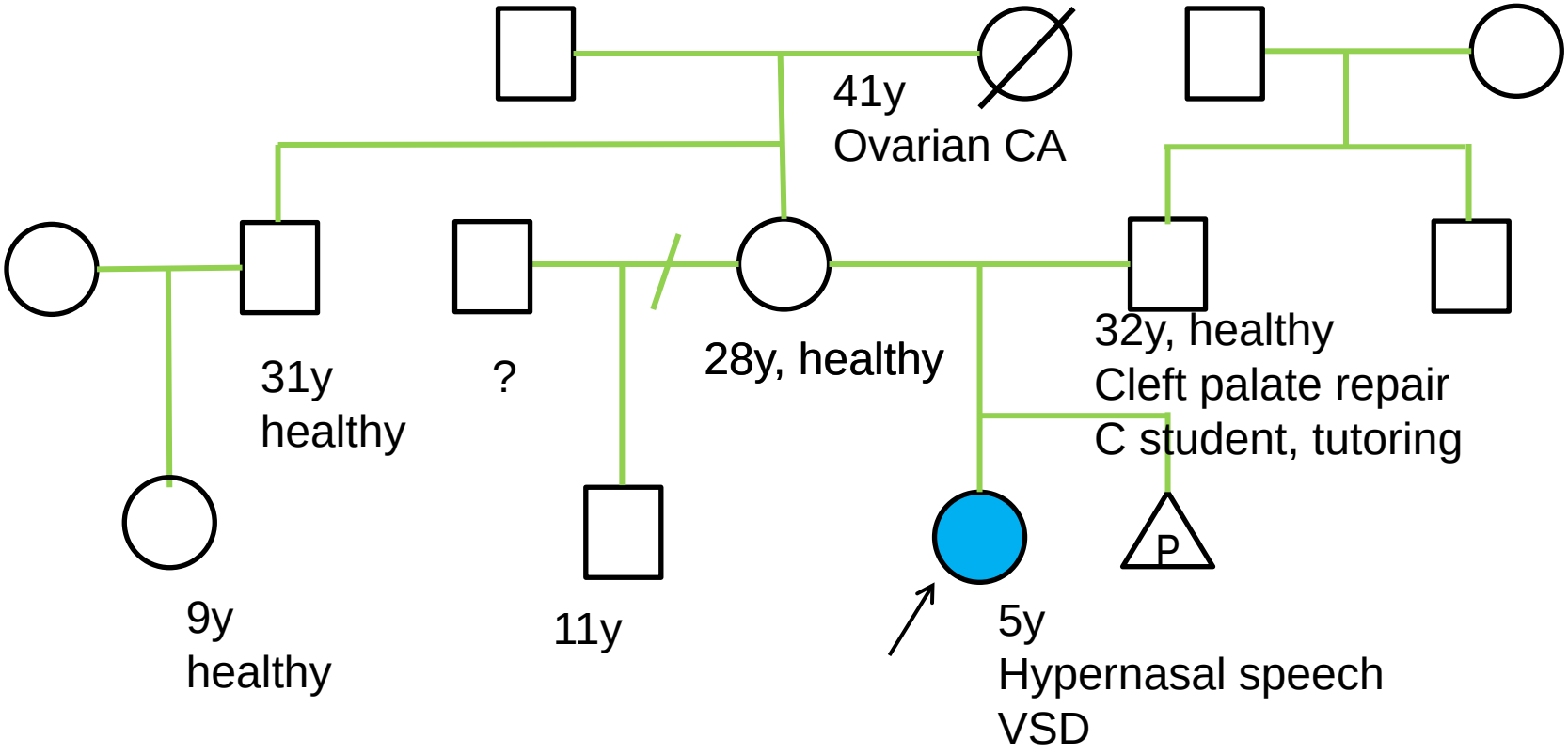
FISH for 22q11.2 Deletion Ordered



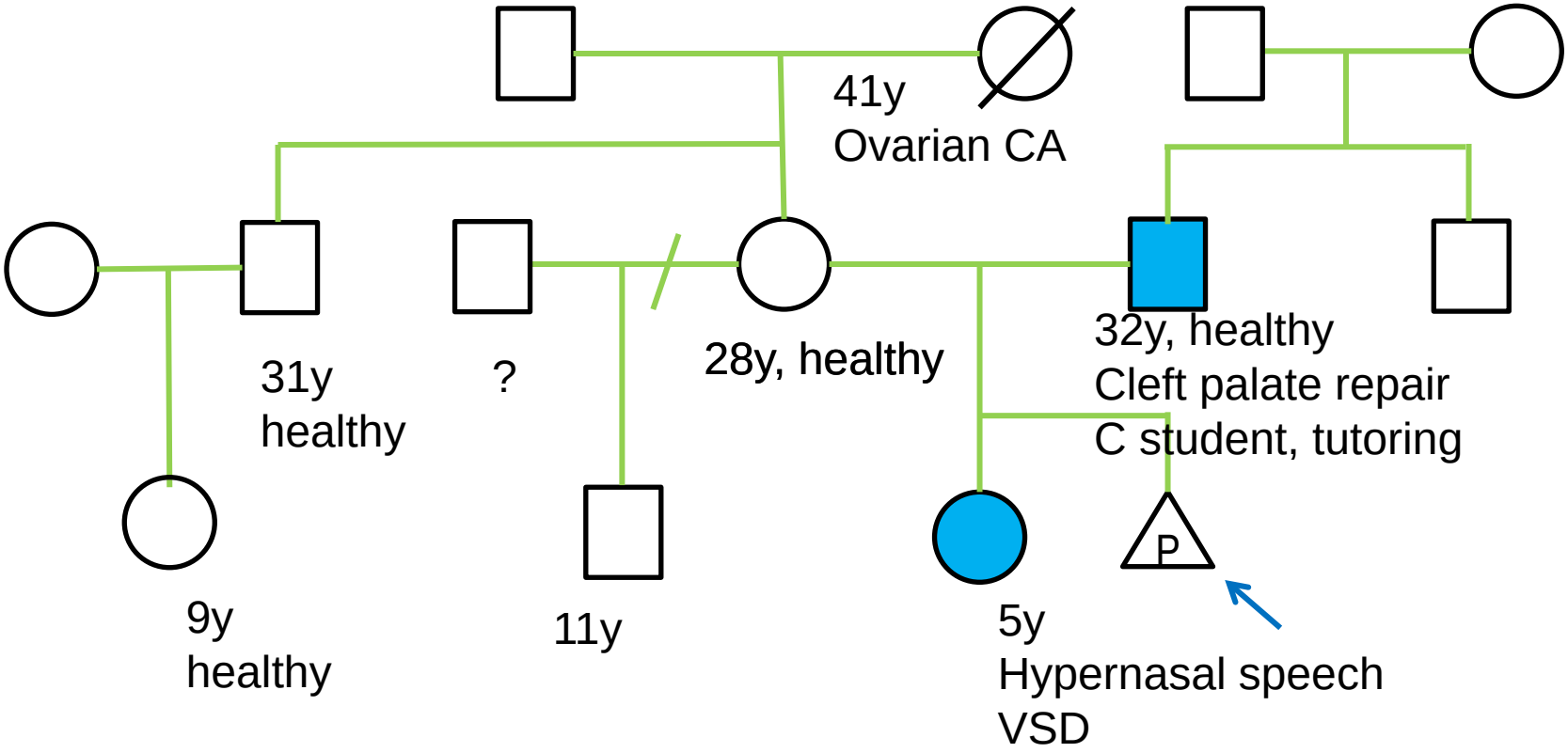
Velo-Cardio-Facial Syndrome

- Chromosome deletion syndrome
  - Typically submicroscopic so more accurate to call contiguous gene deletion
- Majority de novo but transmitted in autosomal dominant manner

De Novo or Inherited?



Consultation with Midwife



Variable Expressivity, 100% Penetrance

- 70% have congenital heart disease or palatal abnormalities or characteristic facial features or learning difficulties or immune deficiency or any combination of these.
- ~25% adults have psychiatric disorder
- List of additional findings possible is extensive

http://www.ncbi.nlm.nih.gov/books/NBK1523/
http://ghr.nlm.nih.gov/condition/22q112-deletion-syndrome

ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

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List of genes to be examined and reported regardless the indication and regardless the age of the patient

Finding Health Care Professionals Trained in Genetics / Genomics

- International Society of Nurses in Genetics
  - www.isong.org
- American College of Medical Genetics
  - www.acmg.net
- National Society of Genetic Counselors
  - www.nsgc.org
- Clinic Directory of Genetics Clinics
  - www.ncbi.nlm.nih.gov/sites/GeneTests/clinic?db=GeneTests

Tuesday, May 7, 2013, 3:30-4:30 p.m.

- *A Blueprint for Genomic Nursing Science*
- Drs. Kathleen Calzone, Jean Jenkins, and Ann Cashion, NIH, and Dr. Alexis Bakos HRSA, summarize recommendations from a 2012 Genomic Nursing State of Science Advisory Panel. This blueprint provides the framework for furthering genomic nursing science to improve health outcomes. Suggestions for targeted research to build the evidence base of the value of genomic information are offered.
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