Improved Recognition of the Genetic Aspects of Childhood Cancers

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Outline/Objectives

• Case presentation
• Review syndromes that present with pediatric cancers
• Recognize hereditary predisposition to cancer in pediatric patients
• Understand genetic testing options and surveillance for at-risk children
• Recognize other syndromes that predispose to malignancy

Case Presentation

• Birth History-
  – CD was born full term to a G1P0 mother via vaginal delivery.
  – There were no delivery complications.
  – Pregnancy was uncomplicated except for a prenatal ultrasound that showed left sided hydronephrosis.
  – Amniocentesis was performed and showed a normal karyotype.
  – Newborn examination was normal.

• Follow up
  – At 8 months of age he had a follow up ultrasound which again showed left hydronephrosis.
  – In addition, he was found to have a right suprarenal mass.
  – Physical examination:
    • Height: 25th centile
    • Weight: 5th centile
    • OFC: 90th centile
    • No abnormal findings

• Diagnostic Work-up
  – CT chest/abdomen/pelvis revealed an adrenal mass and a right paraspinal mass.
  – Bone scan was normal
  – MIBG scan showed no increased uptake within the tumor or elsewhere
  – Urine catecholamines were normal
• Surgical Intervention
  – He underwent a VATS procedure to resect the paraspinal mass.
  – Adrenalectomy was performed 2 weeks later.
  – Bone Marrow aspirate and biopsies were performed.

Pathology
– Right Paraspinal Mass- Unfavorable histology, MCYN non amplified Neuroblastoma

- Adrenal Mass- Adrenal Cortical Carcinoma

- Bone Marrow- normal

• Therapy
  – Surgical excision, no chemotherapy
  – Genetics consult

Family History

HEREDITARY CANCER SYNDROMES IN CHILDREN
LAURA ANDOLINA, MS, CGC
Genetic Testing

- TP53 sequence analysis disclosed a heterozygous missense mutation at nucleotide 13163 (A>T), resulting in a change from an isoleucine to a phenylalanine at codon 162 (ile162phe) in exon 5 of the TP53 gene.
- This mutation has not been previously reported in Li Fraumeni syndrome families but has been reported several times as a somatic mutation in tumors.
- Conserved across 13 of 13 mammalian species.
- Conformation of the protein is likely affected, as the isoleucine is aliphatic while the phenylalanine is a more bulky, aromatic residue.
- Patient’s mother is heterozygous for the mutation, while his younger brother tested negative.
**LI-FRAUMENI SYNDROME**

**Li-Fraumeni Syndrome (LFS)**
- "Rare" to 1/20,000
- Autosomal dominant
- % of de novo mutations is unknown (~25%?)
- Early onset of soft tissue sarcoma, osteosarcoma, breast cancer, brain tumors, adrenocortical carcinoma (ACC)
- Multiple primary tumors
- Most “classic” LFS families have a mutation in TP53

**LFS Tumors**
- Sarcoma
  - Soft tissue (median age 14 yrs)
  - Bone (median age 15 yrs)*
- Both types can also occur in adulthood, most before age 50 years
- Ewing sarcoma is not associated with LFS
- Rhabdomyosarcoma*
- Breast cancer
  - Median age 33 years
- Adrenocortical carcinomas (ACC)*
- Median age 3 years
- Brain tumors
  - Multiple types
  - Choroid plexus carcinoma (CPC) *
  - Childhood or adulthood; median age 16 years

**Other LFS-Associated Cancers**
- Colorectal cancer
- Endometrial cancer
- Esophageal cancer
- Gonadal germ cell tumor
- Hematopoietic malignancies (leukemias and lymphomas)
- Lung cancer
- Melanoma and non-melanoma skin cancer
- Neuroblastoma
- Ovarian cancer
- Pancreatic cancer
- Prostate cancer
- Stomach cancer
- Thyroid cancer
- Wilms' tumor and other kidney cancers

**Classic LFS Diagnostic Criteria**
- A proband with a sarcoma diagnosed before age 45 years AND
- A first-degree relative with any cancer before age 45 years AND
- A first- or second-degree relative with any cancer before age 45 years or a sarcoma at any age
Li-Fraumeni-Like Syndrome

- Birch definition of LFL syndrome [Birch et al 1994]:
  - A proband with any childhood cancer or sarcoma, brain tumor, or ACC diagnosed before age 45 years AND
  - A first- or second-degree relative with a typical LFS cancer (sarcoma, breast cancer, brain tumor, ACC, or leukemia) at any age AND
  - A first- or second-degree relative with any cancer before age 60 years
- Eeles definition of LFL syndrome [Eeles 1995]:
  - Two first- or second-degree relatives with LFS-related malignancies at any age

Why is it important to recognize LFS?

- High lifetime cancer risk
  - 30-40% by age 20 years
  - 50% by age 30 years
  - 90% by age 60 years
- Risk of multiple primary cancers
  - Younger age at 1st cancer, higher risk of multiple primaries
- Genotype-phenotype correlations
  - Missense mutations → earlier onset
- Risks to relatives

LFS Surveillance – Children

- Adrenocortical carcinoma
  - Ultrasound of abdomen and pelvis every 3–4 months
  - Complete urinalysis every 3–4 months
  - Blood tests every 4 months: ß-human chorionic gonadotropin, alpha-fetoprotein, 17-DH-progesterone, testosterone, dehydroepiandrosterone sulfate, androstenedione
- Brain tumor
  - Annual brain MRI
- Soft tissue and bone sarcoma
  - Annual rapid total body MRI
- Leukemia or lymphoma
  - Blood test every 4 months: complete blood count, erythrocyte sedimentation rate, lactate dehydrogenase

LFS Surveillance – Adults

- Breast cancer
  - Monthly breast self-examination starting at age 18 years
  - Clinical breast examination once a year, starting at age 20–24 years, or 5–10 years before the earliest known breast cancer in the family
  - Annual mammography (?) and breast tomoscanning starting at age 20–25 years, or at earliest age of onset in the family
  - Consider risk reducing bilateral mastectomy
- Brain tumor
  - Annual brain MRI
- Soft tissue and bone sarcoma
  - Annual rapid total body MRI
  - Ultrasound of abdomen and pelvis every 6 months
- Colon cancer
  - Colonoscopy every 3 years, beginning at age 45 years, or 5 years before the earliest known colon cancer in the family
- Melanoma
  - Annual dermatological examination
- Leukemia or lymphoma
  - Complete blood count every 6 months
  - Erythrocyte sedimentation rate, lactate dehydrogenase every 4 months

Retinoblastoma (RB)

- Malignant tumor of the developing retina that occurs in children, usually before age five years
- 1/15,000-1/20,000
- May be unilateral, bilateral or “trilateral” when RB co-occurs with a pinealoma
  - 60% unilateral, mean age of dx 24 mo
  - 40% bilateral, mean age of dx 15 mo
**Sporadic vs. Hereditary RB**

- RB is caused by mutations in the tumor suppressor RB1
- Probands present with either:
  1. Chromosome deletion involving band 13q14
     - Up to 5% of all index cases with unifocal RB and 7.5% of all index cases with multifocal RB have a chromosomal deletion of 13q14
     - Often associated with developmental delay and birth defects
  2. Normal cytogenetic study and one of the following
     - Positive family history and unilateral or bilateral RB: ~10% of index cases
     - Negative family history and bilateral RB: 30% of index cases
     - Negative family history and unilateral RB: 60% of index cases

**Molecular Testing**

- In simplex cases of unilateral RB, molecular analysis should begin in tumor tissue
- In familial or bilateral cases of RB, molecular analysis should begin in peripheral blood
- Various methodologies (sequencing, MLPA, mutation scanning, methylation, etc) will detect a mutation in 90-95% of individuals with hereditary predisposition to RB

**Prevalence of RB1 Germline Mutation**

<table>
<thead>
<tr>
<th>Family History</th>
<th>Retinoblastoma Presentation</th>
<th>Probability that an RB1 Germline Mutation is Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative 1</td>
<td>Unilateral</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Multifocal</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Unifocal</td>
<td>100%</td>
</tr>
<tr>
<td>Positive 1</td>
<td>Unilateral</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Multifocal</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Unifocal</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>100%</td>
</tr>
<tr>
<td>Negative 2</td>
<td>Unilateral</td>
<td>~14%</td>
</tr>
<tr>
<td></td>
<td>Multifocal</td>
<td>~14%</td>
</tr>
<tr>
<td></td>
<td>Unifocal</td>
<td>~14%</td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>74%</td>
</tr>
</tbody>
</table>

**Empiric Recurrence Risks**

<table>
<thead>
<tr>
<th>Tumor Presentation in Index Case</th>
<th>Bilateral</th>
<th>Unilateral</th>
<th>Family History</th>
<th>Risk to Sibs of an Index Case</th>
<th>Risk to Offspring of an Index Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Negative</td>
<td>2% 1</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>Negative</td>
<td>1% - 2% 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>Negative</td>
<td>~1%</td>
</tr>
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<td></td>
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<td></td>
<td>X</td>
<td>Positive</td>
<td>Variable 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>Positive</td>
<td>50%</td>
</tr>
</tbody>
</table>

1. If there is no unaffected sibling (Draper et al 1982)
2. In families with unilateral retinoblastoma, penetrance varies wildly

**Why is it important to distinguish between sporadic and hereditary RB?**

- Surveillance of at-risk relatives
  - Fundus examination every three to four weeks until age one year and then less frequently until age three years
- Some families (<10%) show a "low penetrance" phenotype
  - Reduced expressivity (increased prevalence of unilateral retinoblastoma)
  - Incomplete penetrance (25% or lower)
**Why is it important to distinguish between sporadic and hereditary RB?**

- Risk of second primary extra-ocular tumors in adolescence or adulthood
  - Osteosarcomas, soft tissue sarcomas and melanomas
  - Greater than 50% risk for patients who have received external beam radiation therapy

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**NEUROENDOCRINE TUMORS**

**Neuroendocrine Tumors**

- Neoplasms that arise from cells of the endocrine and nervous systems
- May be benign or malignant
- May or may not secrete hormones

**Cancer Syndromes That May Present with Neuroendocrine Tumors**

- Multiple endocrine neoplasia type 1 (MEN1)
- Multiple endocrine neoplasia type 2 (MEN2)
- von Hippel-Lindau (VHL) syndrome
- Hereditary paraganglioma/pheochromocytoma syndrome (PGL-PCC)
- Neurofibromatosis type 1
- Neurofibromatosis type 2
- Tuberous sclerosis complex
- Carney complex

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**MEN1**

- ~1/30,000
- Autosomal dominant
- 10% of cases occur as the result of a *de novo* mutation
- Caused by mutations in the *MEN1* (*menin*) gene
- Endocrine and non-endocrine tumors

**MEN1 – Endocrine Tumors**

- Parathyroid tumors
- Pituitary tumors
- Well-differentiated endocrine tumors of the gastro-entero-pancreatic (GEP) tract (including tumors of the stomach, duodenum, pancreas, and intestinal tract)
  - Gastrinoma
  - Insulinoma
  - Glucagonoma
  - Vasoactive intestinal peptide (VIP)-secreting tumor (VIPoma)
MEN1 – Non-Endocrine Tumors

- Facial angiofibromas
- Collagenomas
- Lipomas
- Meningiomas
- Ependymomas
- Leiomyomas

Why is it important to diagnose MEN1 in childhood? Tumor risk

- 90% of individuals with parathyroid tumors and hypercalcemia by age 20-25 years
- Hypercortisolism occurs in ACTH-secreting tumors and has been reported in children with MEN1 with Cushing’s disease as the first manifestation of MEN1
- Gigantism occurs in children with growth hormone (GH)-secreting tumors

Why is it important to diagnose MEN1 in childhood? Surveillance

- Biochemical investigations
  - Yearly:
    - Serum concentration of prolactin from age five years
    - Fasting total serum calcium concentration (corrected for albumin) and/or ionized serum calcium concentration from age eight years
    - Fasting serum gastrin concentration from age 20 years
  - To be considered: fasting serum concentration of intact (full-length) PTH
- Imaging
  - Every three to five years:
    - Head MRI from age five years
    - Abdominal CT or MRI from age 20 years
  - To be considered: yearly chest CT, somatostatin receptor scintigraphy (SRS) octreotide scan

Who should be tested for MEN1?

- Child of a parent with MEN1
- All cases of “classical” MEN1
- Familial hyperparathyroidism
- Sporadic hyperparathyroidism with one other MEN1 related tumor or condition
- Patients <30 years old with sporadic hyperparathyroidism and multigland hyperplasia

MEN2

- ~1/35,000
- Autosomal dominant
- Caused by mutations in the RET proto-oncogene
- Classified into three subtypes
  - MEN2A (<5% de novo)
  - MEN2B (50% de novo)
  - Familial medullary thyroid cancer

MEN2 Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Medullary Thyroid Carcinoma</th>
<th>Pheochromocytoma</th>
<th>Parathyroid Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN2A</td>
<td>95%</td>
<td>50%</td>
<td>20%-30%</td>
</tr>
<tr>
<td>FMTC</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>MEN2B</td>
<td>100%</td>
<td>50%</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
MEN2B

- Mucosal neuromas of the lips and tongue
- Distinctive facies with enlarged lips
- Ganglioneuromatosis of the gastrointestinal tract
- 'Marfanoid' body habitus

Genetic Testing for MEN2

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Test Method</th>
<th>Mutations Detected</th>
<th>Mutation Detection Frequency by Test Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN 2A</td>
<td>Sequence analysis of select exons</td>
<td>Sequence variants in exons 10, 11, 13-16</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td>Sequence analysis of coding region</td>
<td>Sequence variants in exons &amp; splice junctions</td>
<td>&lt;98%</td>
</tr>
<tr>
<td>RMTC</td>
<td>Sequence analysis of select exons</td>
<td>Sequence variants in exons 10, 11, 13-16</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>Sequence analysis of coding region</td>
<td>Sequence variants in exons &amp; splice junctions</td>
<td>&lt;98%</td>
</tr>
</tbody>
</table>

MTC Screening and Timing of Thyroidectomy

<table>
<thead>
<tr>
<th>Mutation locations</th>
<th>Exons 13, 14, 15</th>
<th>Exon 10</th>
<th>Exon 11</th>
<th>MEN 2B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of pheochromic symptoms</td>
<td>5 years as stringent criteria are met</td>
<td>Before surgery</td>
<td>Before 5 years</td>
<td>Before 5 years</td>
</tr>
<tr>
<td>Screening for MTC</td>
<td>20 years</td>
<td>25 years</td>
<td>30 years</td>
<td>37 years</td>
</tr>
<tr>
<td>Screening for PHC</td>
<td>30 years</td>
<td>40 years</td>
<td>50 years</td>
<td>60 years</td>
</tr>
</tbody>
</table>

Who should be tested for RET mutations?

- Child of a parent with a RET mutation
- All patients with MTC (25-30% will have a germline RET mutation)
- Patients with Hirschprung disease (50% of familial cases and 35% of simplex cases will have a germline RET mutation)
- Patients with mucosal neuromas on the anterior dorsal surface of the tongue, palate, or pharynx in infancy or childhood

Paraganglioma/Pheochromocytoma

- Tumors that arise from neuroendocrine tissues symmetrically distributed along the paravertebral axis from the base of the skull to the pelvis
- Pheochromocytomas: paragangliomas that are confined to the adrenal medulla
- Sympathetic paragangliomas hypersecrete catecholamines
- Parasympathetic paragangliomas are most often nonsecreting

Germline Mutations & Paragangliomas

- Regardless of family history, 1/3 of patients with a paraganglioma/pheo have a predisposing germline mutation in one of 6 genes
  - NF1
  - RET
  - VHL – von Hippel Lindau
  - SDHB – PGL-PCC
  - SDHC – PGL-PCC
  - SDHD – PGL-PCC
von Hippel Lindau (VHL)

- ~1/36,000
- Autosomal dominant
- Caused by mutations in the VHL gene
- 20% of cases occur as the result of a de novo mutation
- Hemangioblastomas of the brain, spinal cord, and retina
- Renal cysts and clear cell renal cell carcinoma;
- Pheochromocytoma
- Endolympathic sac tumors

VHL Tumor Screening

Ages 11-19
- Every six months:
  - Eye/retinal examination with indirect ophthalmoscope by ophthalmologist
- Annually:
  - Physical examination and neurological assessment by physician informed about VHL (physicals include scrotal examination in males)
  - Test for elevated catecholamines and metanephrines in 24-hour urine collection. Abdominal MRI or MIBG scan only if biochemical abnormalities found
  - Ultrasound of abdomen (kidneys, pancreas, and adrenals). If abnormal, MRI or CT of abdomen, except in pregnancy.
- Every 1-2 years and if symptoms:
  - MRI with gadolinium of brain and spine. Annually at onset of puberty or before and after pregnancy (not during pregnancy except in medical emergencies.)
  - Audiologist examination for abnormalities.

Who should be tested for VHL?

- Child of a parent with VHL
- Multiple hemangioblastomas (blood vessel tumors) of the brain, spinal cord, or eye
- One hemangioblastoma and kidney cysts, pancreatic cysts, pheochromocytoma, or kidney cancer
- Multifocal or bilateral clear cell renal cell carcinoma
- If a person has a family history of VHL, he or she is suspected of also having VHL if the person has any one symptom, such as hemangioblastoma, kidney or pancreatic cysts, pheochromocytoma, or kidney cancer

PGL-PCC

- Prevalence unknown
- Autosomal dominant
- Caused by mutations in SDHD, SDHB, SDHC
  - Mitochondrial enzyme succinate dehydrogenase (SDH), catalyzes the conversion of succinate to fumarate in the Krebs cycle and serves as complex II of the electron transport chain
- Parent-of-origin effect
  - SDH mutations generally cause disease only when inherited from the father
- % of de novo mutations is unknown

PGL-PCC

- Characterized by paragangliomas and pheochromocytomas
- Extra-adrenal parasympathetic paragangliomas are located predominantly in the head and neck; approximately 95% of such tumors are nonsecretory
- Sympathetic extra-adrenal paragangliomas are generally confined to the thorax, abdomen, and pelvis, and are typically secretory
- The risk of malignant transformation is greater for extra-adrenal sympathetic paragangliomas than for pheochromocytomas or head and neck paragangliomas
PGL-PCC Screening

- Screening should begin at age ten years or at least ten years before the earliest age at diagnosis in the family.
- Monitoring includes the following:
  - Twenty-four hour urinary excretion of fractionated metanephrines and catecholamines, and/or plasma fractionated metanephrines
  - Follow-up imaging by CT, MRI, 123I-MIBG, or FSG-PET
  - In persons with SDHD and SDHC mutations
    - Periodic (e.g., every 2 years) MRI or CT of the head and neck
    - Periodic (e.g., every 4 years) body MRI or CT and 123I-MIBG scintigraphy
  - In persons with SDHB mutations
    - Periodic (e.g., every 2 years) MRI or CT of the abdomen, thorax, and pelvis
    - Periodic (e.g., every 4 years) 123I-MIBG scintigraphy

Who should be tested for PGL-PCC?

- PGL/PCC syndromes should be considered in all individuals with paragangliomas and/or pheochromocytomas, particularly those with the following findings:
  - Tumors that are:
    - Multiple, including bilateral tumors
    - Multifocal with multiple synchronous or metachronous tumors
    - Recurrent
    - Early onset (i.e., age <40 years)
  - A family history of such tumors

CANCER IN CHILDREN: PEDESTRIAN PRESENTATIONS
LUTHER ROBINSON, MD

Neurofibromatosis

- Six or more café au lait macules
- Two or more neurofibromas or plexiform neurofibroma
- Axillary or inguinal freckling
- Optic glioma
- Two or more Lisch nodules
- A distinctive osseous lesion (sphehoid dysplasia, pseudoarthrosis)
- An affected first-degree relative


What Is the Best Tumor Surveillance?

- Clinical examination
- Regular CT/MRI scans
- Urinary VMA and catecholamines
- Ophthalmological examination
- All of the above


Case

- Macrocrania
- Hyperpigmented macules
- Raised skin lesions
- Your diagnosis?
- Next steps?
Disorders Associated with Hyperpigmented Macules

- Neurofibromatosis, type 1
- Noonan syndrome
  - Loose nuchal skin, pulmonic stenosis, PTPN11 mutation
- Ataxia-telangiectasia syndrome
  - CNS degeneration, bulbar telangiectases, ATM mutation
- Rothmund-Thomson syndrome
  - Poikiloderma, radial (thumb) defect, cataract, alopecia
- Russell-Silver syndrome
- McCune Albright syndrome

Case

- Tall stature
- S/p omphalocele
- Hemihyperplasia
- Prognathism
- Your diagnosis?
- Tumor risk?

Hemihyperplasia

- Known associations: Wilms tumor-hemihyperplasia association
- Beckwith syndrome
- Is there an increased risk of neoplasia in a child with isolated hemihyperplasia?
  - A. Yes, but minimal
  - B. No
  - C. Yes, 50%
  - D. Yes, 8% – 10%
  - E. Yes, 25%

Hemihyperplasia

- For what types of cancer should we screen?
  - A. Neuroblastoma, carcinoid, squamous cell Ca
  - B. Acute lymphoblastic leukemia
  - C. Hepatoblastoma, Wilms tumor, adrenal tumor
  - D. Basal cell Ca, osteogenic sarcoma, medulloblastoma
  - E. Leiomyoma, gonadoblastoma, arrhenoblastoma

Case

Boy with aniridia and congenital glaucoma, small genitalia, cryptorchidism. FH negative for aniridia, genital anomalies

What is his diagnosis, and how is it confirmed?
WAGR syndrome

- Multiple malformation syndrome with:
  - Wilms tumor of the kidney in ~40%; led to the localization of the WT1 gene at 11p13
  - Aniridia – deletion of PAX6 gene at 11p13
  - Genital anomalies – del of WT1 at 11p13
  - Retardation of growth and development

Case

- Infant with abnormal genitalia
- History: unremarkable
- Physical examination
  - What do you see?
  - What is the appearance of labioscrotal folds?
  - Other findings?
- Your diagnosis?

Indication for Chromosomal Analysis

- Gender of rearing
- Risk of gonadoblastoma
- Risk of intersex condition

Disorders Associated with Abnormal External Genitalia

- WAGR
  - Wilms tumor, aniridia, genital anomalies, retardation (11p-)
- 46,XY/45,X gonadal mosaicism syndrome
- Denys-Drash syndrome
Disorders Associated with Radial Defects (Abnormal Thumbs)

- Fanconi pancytopenia syndrome
  - Anemia, hematologic malignancies
- Rothmund-Thompson syndrome
  - Poikiloderma
  - Sparse hair
  - Increased risk of osteosarcoma

References