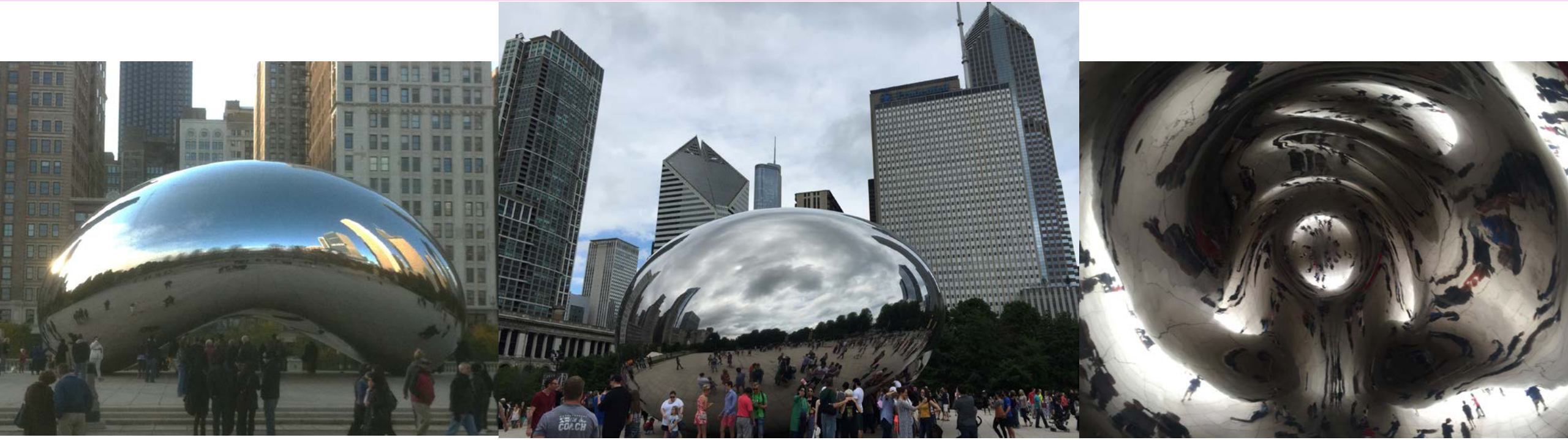
2017 Society of Hematopathology Workshop
Session 1: Germline Predisposition Cases



Cloud Gate aka "The Bean", Millenium Park, Chicago

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Hematolymphoid Neoplasms with Germline Predisposition

Key points

- **Most neoplasias result from acquired somatic mutations/genetic alterations**
- **Increased recognition that a subset is associated with germline mutations**
- **Inherited mutations: variable penetrance may cloud recognition of familial disease**
- ***de novo* germline mutations:**
  - **Absence of family history, not inherited**
  - **But can be passed on to future generations**

Therapy related MDS/AML may occur in patients with germline predisposition

Why is this so important?

Donor selection for BMT/HSCT

- Multiple cases of donor derived leukemia or failed engraftment s/p HSCT when healthy family member with mutation used as donor (e.g. GATA2, CEBPA, RUNX1)
  - Late onset of disease
  - Incomplete penetrance
  - => need to screen all family donors for mutation regardless of phenotype

Optimal treatment and conditioning regimens

May differ from non-germline hematolymphoid neoplasia (e.g. FA, GATA2, etc.)

Genetic counseling

Getting the right diagnosis – Hematopathologists play a critical role

Germline Predisposition Considerations

Inheritance patterns:	**Autosomal Recessive, Autosomal Dominant, X-linked recessive**
Penetrance:	**High, incomplete, variable**
Mutations:	**Missense, Nonsense, Deletions, Insertions, Null** **Synonymous vs. Non-synonymous** **Genotype/phenotype correlations**
Gene Functions:	**Tumor suppressor, oncogene, regulator of hematopoiesis, DNA repair**
Mechanisms:	**Gain of function, Loss of function,** **Dominant negative, Haploinsufficiency**

Challenges and Pitfalls for Germline Diagnosis

NGS Targeted sequencing panels:

- **May not include all relevant genes**
- **Capture targets vary**
  - **May not include regulatory regions**
  - **Somatic "hot spots" do not necessarily equal germline hotspots**
- **Advantage: depth of coverage may be helpful for deletions**

Whole Exome Sequencing:

- **Intronic regulatory regions excluded – mutations missed**

Variants of Unknown significance (VUS) vs. known pathogenic mutations

Analysis and interpretation errors

Sample for sequencing

- **BM/PB: High variant allele frequency (VAF) suggestive of germline but may also be somatic**
- **Buccal swab or saliva: contamination with blood cells can be problematic**
- **Cultured fibroblasts ideal. Hair or nails also germline DNA sources.**

New WHO Chapter:
Myeloid Neoplasia with Germline predisposition

Without a preexisting disorder/organ function:

CEBPA, DDX41

With pre-existing platelet disorders

RUNX1, ANKRD26, ETV6

With other organ dysfunction:

GATA2

BMF syndromes:

Fanconi Anemia: ***FANC genes***

Severe Congenital Neutropenia: ***ELANE, CSF3R, GFI1, HAX1, G6PC3, WAS***

Shwachman-Diamond syndrome: ***SBDS***

Diamond Blackfan anemia: ***RPS19, RPS17, RPS24, RPL35A, RPL5, RPL11, RPS7, RPS26, RPS10, GATA1***

Dyskeratosis Cong./Telomere Ds: ***DKC1, TERT, TERC, TINF2, RTEL1, NOP10, NHP2, WRAP53, CTC1***

JMML associated with neurofibromatosis, Noonan syndrome, or Noonan like syndromes

Myeloid neoplasms associated with Down Syndrome

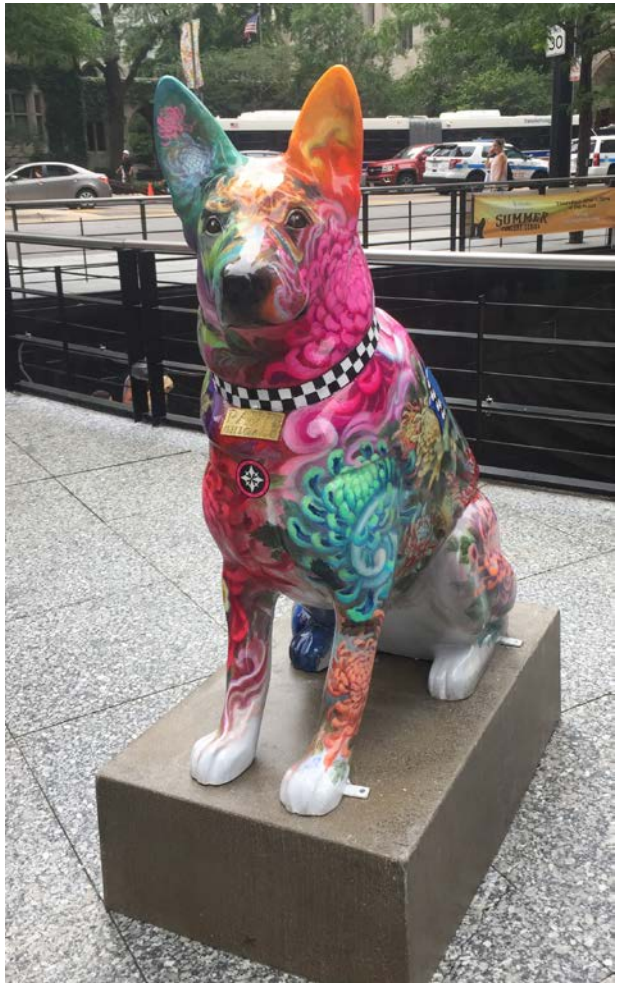
Session 1: SH Germline Predisposition Case Submissions Breakdown

	GENE	# cases	SH Case Disease(s)
Myeloid	GATA2	16	MDS-MLD, MDS-EB1, RCC, AML, BMID/monoMAC, HLH
	RUNX1	10	Thrombocytopenia, AML, TAFRO
	CEBPA	2	AML
	CSF3R	1	t-AML (donor)
	PTPN11	2	JMML, Transient MPD
	SAMD9	2	RCC, MDS-MPN (MIRAGE Syndrome)
	ANKRD26	1	Thrombocytopenia
	BLM	1	AML
	DDX41	1	AML
	G6P3	1	MDS-MLD
	IDH2	1	MDS-MLD
	MPL	1	Thrombocytosis
	NF1	1	AML
	RBM8A	1	MDS-EB2
	SH2B2	1	MPN
	PTCH TGRB1 del	1	t-AML (prior neuroblastoma)
	TP53	1	t-AML (prior FL)
Lymphoid	CSF3R	1	CHL (and SCN)
	CTLA4	1	T-LGL
	ELANE	1	B-ALL (and SCN)
	PAX-5	1	B-ALL
	SH2D1A	1	XLP and BL
	SHOC2	1	B-ALL
	TP53	1	FL

SH 2017 Session 1
Germline Predisposition to Hematolymphoid Neoplasia
Oral presentations

SH2017-0283:	Dr. Rena Xian
SH2017-0039:	Dr. Karen Chisholm
SH2017-0307:	Dr. Chollada Curry
SH2017-0042:	Dr. Craig Soderquist
SH2017-0106:	Dr. Sunita Park
SH2017-0167:	Dr. Chelsey Deel
SH2017-0275:	Dr. Cecilia Yeung

NOTE: Each case presentation is allotted 10 minutes with 2 minutes for questions



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