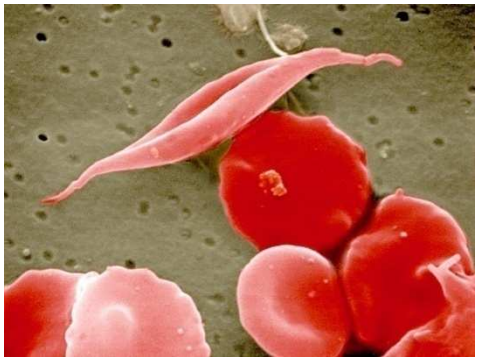
Researching SNPs

Master practical
Protein Structure and Function Analysis

Laura Schiller

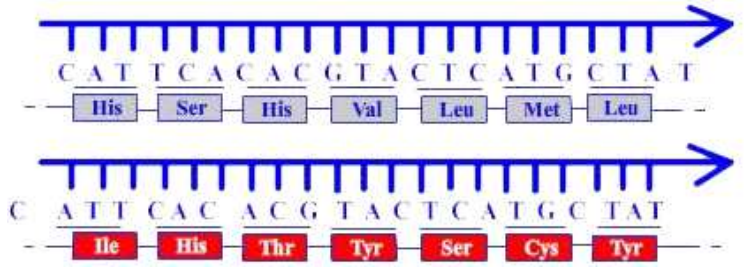
Mutations

- point mutations (if persistent: SNPs)



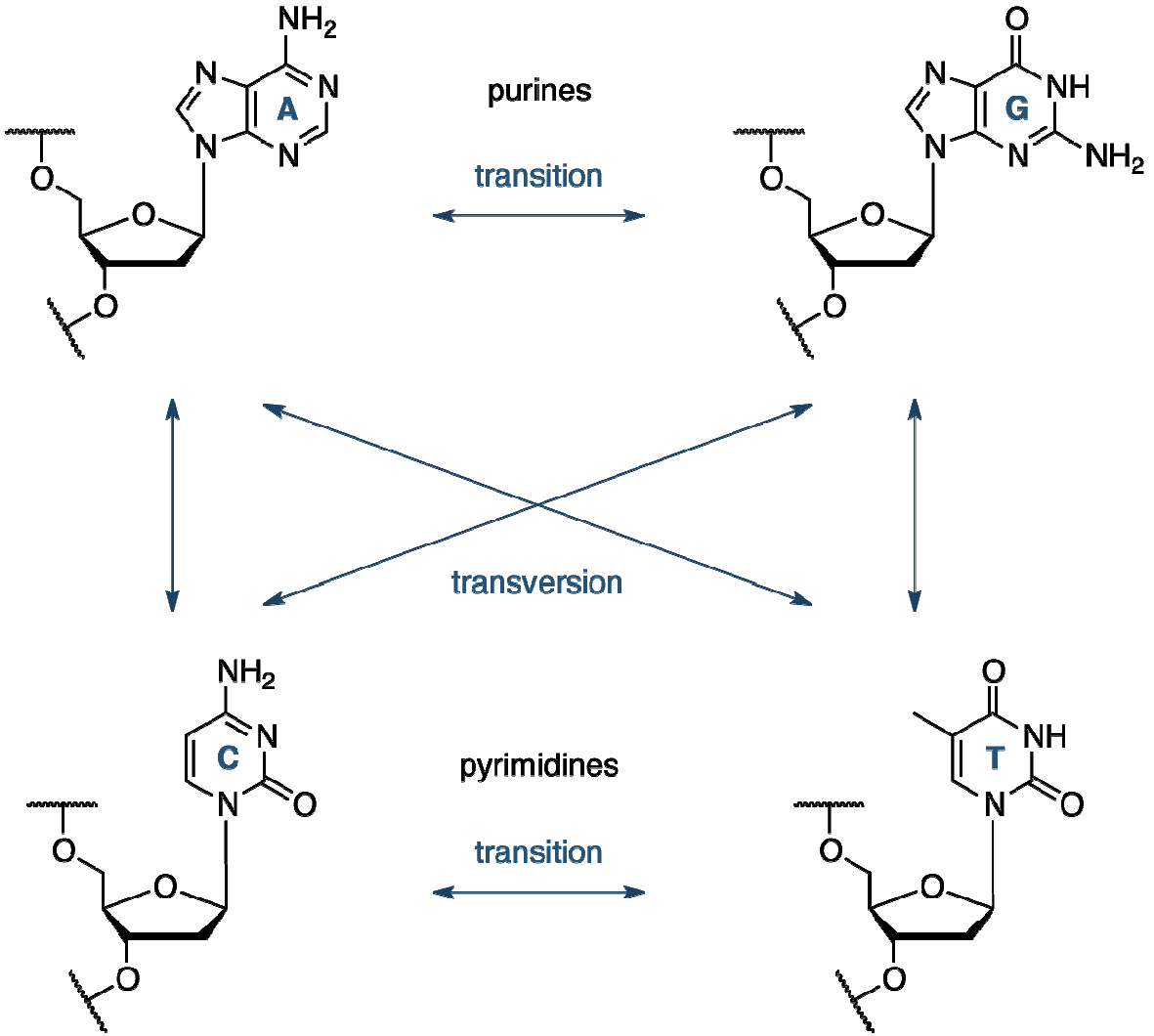
sickle cell anemia:

…GAG…	…GTG…	DNA
…Glu…	…Val…	Protein



- insertions, deletions
- inversions
- chromosome abberations

Transitions and transversions



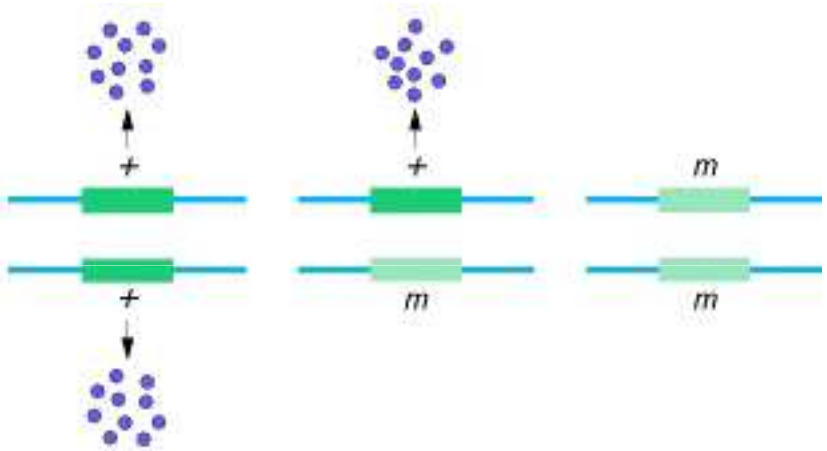
Single nucleotide polymorphisms (SNPs)

- where they occur: coding region (cSNP)
  intron (iSNP)
  regulatory region (rSNP)
  intergenic region
- in coding regions: synonymous (sSNP)
  non-synonymous (nsSNP)
- non-synonymous: missense mutation
  nonsense mutation

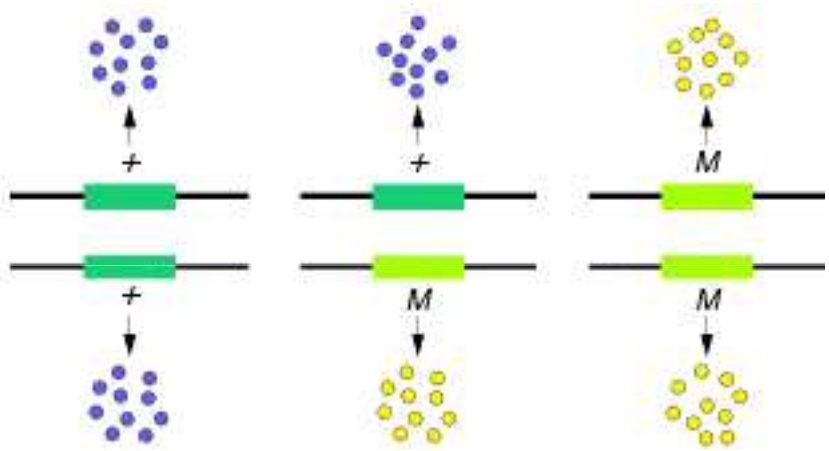
Impact of amino acid substitutions on protein structure / function

- destroy hydrogen bonds, ionic bonds
- size changes (hydrophobic core)
- disrupt protein-protein interactions, quarternary structure
- change Cys: break disulphide bonds
- catalytic residues
- metal-binding residues

Mutations



loss of function



gain of function

Online Mendelian Inheritance in Man (OMIM)

- daily updated
- 21 844 entries (updated 11 June 2013)
- gene entries → allelic variants (only selected mutations)
- disease entries
- relationship between genotype and phenotype (diseases)

OMIM numbering system

1….., 2…..	autosomal loci or phenotypes (entries created before May 15, 1994)
3…..	X-linked loci or phenotypes
4…..	Y-linked loci or phenotypes
5…..	mitochondrial loci or phenotypes
6…..	autosomal loci or phenotypes (entries created after May 15, 1994)
*	gene
+	gene and phenotype
#	phenotype, molecular basis known
%	phenotype, molecular basis unknown

OMIM

#248600

MAPLE SYRUP URINE DISEASE; MSUD

Alternative titles; symbols

BRANCHED-CHAIN KETOACIDURIA
BRANCHED-CHAIN ALPHA-KETO ACID DEHYDROGENASE DEFICIENCY
BCKD DEFICIENCY
KETO ACID DECARBOXYLASE DEFICIENCY

*608348

BRANCHED-CHAIN KETO ACID DEHYDROGENASE E1, ALPHA POLYPEPTIDE; BCKDHA

Alternative titles; symbols

BCKD, E1-ALPHA SUBUNIT; BCKDE1A

HGNC Approved Gene Symbol: *BCKDHA*

Cytogenetic location: *19q13.2* ***Genomic coordinates (GRCh37):*** *19:41,903,693 - 41,930,909* (from NCBI)

Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
19q13.2	Maple syrup urine disease, type Ia	248600

Human Gene Mutation Database (HGMD)

- publicly available: 3 years old version
- 99 869 entries (11 June 2013)
- mutations of human nuclear genes

  in coding, splicing, regulatory regions

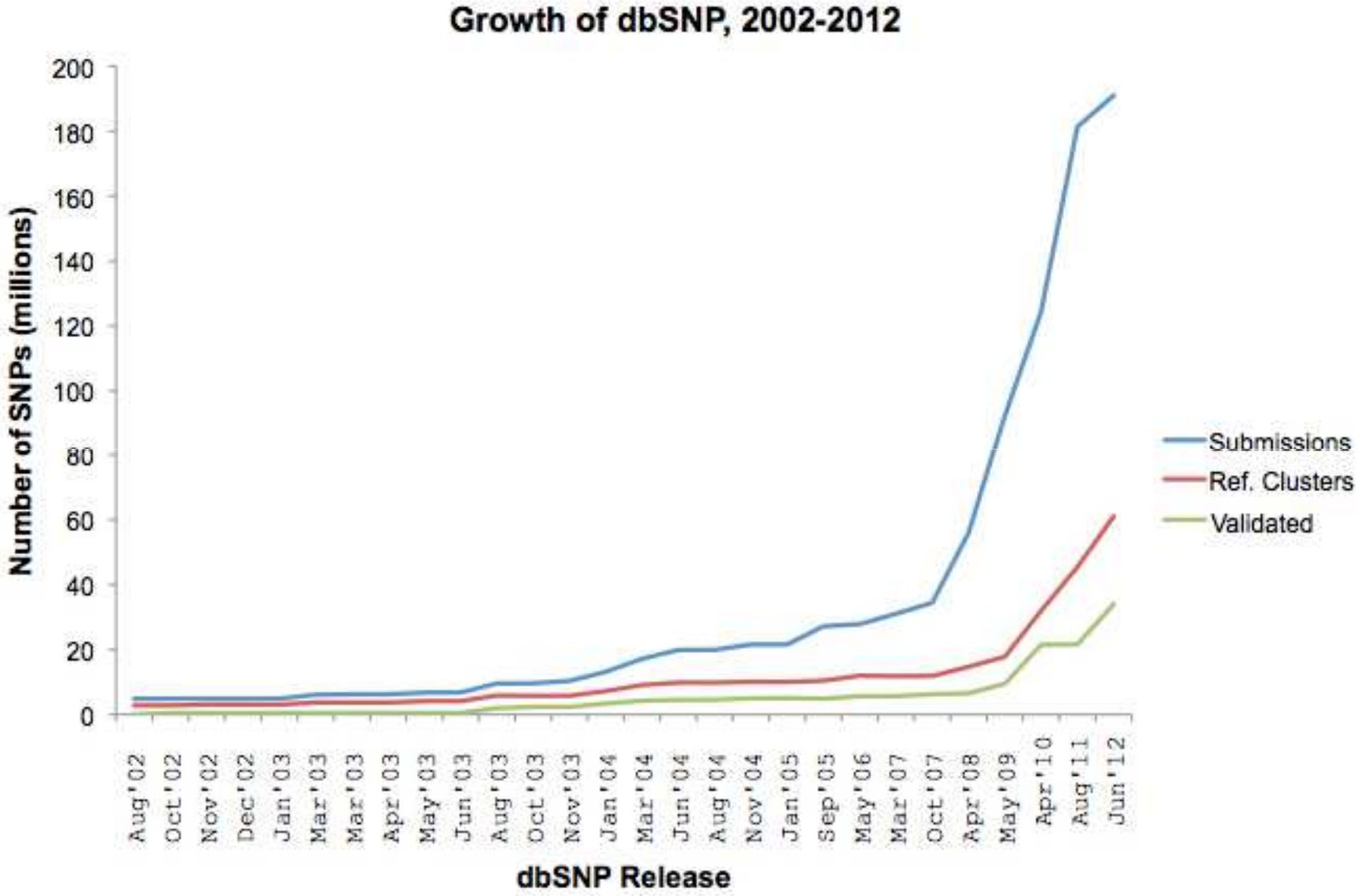
  associated with inherited diseases
- data collection: manual + automated (scanning of journals)

dbSNP

- simple genetic polymorphisms
- submitted SNPs: ss#
- reference SNPs (refSNPs): rs#
- build cycle (synchronized with release of new genome assembly):

  cluster submitted SNPs

  → non-redundant set of refSNPs
- human: 38 072 522 validated refSNP clusters (build 137)



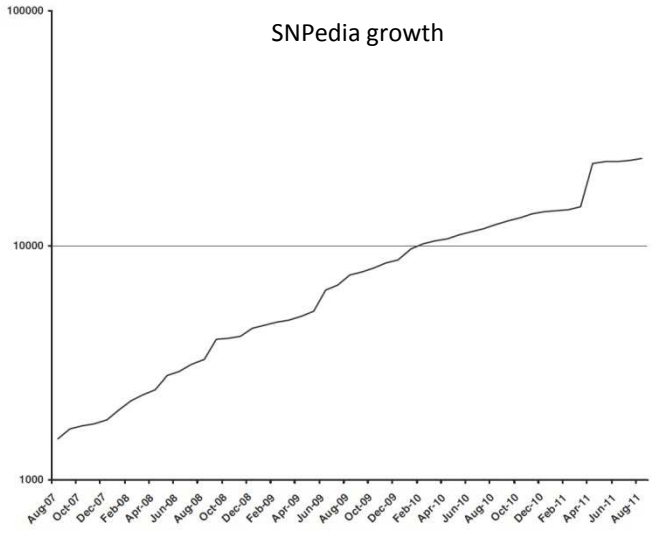
SNPdbe

- SNP database of effects
- nsSNPs: from dbSNP, 1000 Genomes, UniProt, PMD
- functional impacts of single amino acid substitutions (SAAS): predicted (SNAP, SIFT) + experimentally derived

  → neutral/non-neutral
- human: 967 879 SAASs, 31 979 sequences (updated 2012/03/05)

SNPedia

- wiki
- effects of DNA variations
- 39 167 SNPs (14 June 2013)
- selected SNPs: medical / genealogical significance, common, reproducible



Cariaso and Lennon, 2011

- convert information from literature to machine-readable form
- assignment of associations to single genotypes or sets of genotypes (genosets)

Thank you.

Questions?

References

- Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), 2013. http://omim.org/
- Stenson et al (2003). The Human Gene Mutation Database (HGMD®): 2003 Update. *Hum Mutat*(2003) 21:577-581
- http://www.hgmd.org/
- Kitts A, Sherry S. The Single Nucleotide Polymorphism Database (dbSNP) of Nucleotide Sequence Variation. 2002 Oct 9 [Updated 2011 Feb 2]. In: McEntyre J, Ostell J, editors. The NCBI Handbook [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2002-. Chapter 5.
- http://www.ncbi.nlm.nih.gov/SNP/
- Schaefer C, Meier A, Rost B, Bromberg Y (2012). SNPdbe: Constructing an nsSNP functional impacts database. *Bioinformatics*; 28(4):601-602
- http://www.rostlab.org/services/snpdbe/
- Cariaso M, Lennon G. SNPedia: a wiki supporting personal genome annotation, interpretation and analysis. Nucleic Acids Research 2011; doi: 10.1093/nar/gkr798
- http://www.snpedia.com/index.php/SNPedia
- Methoden der Genomanalyse, lecture by Prof. D. Frishman, summer semester 2012
- Campbell NA, Reece JB: Biologie. Spektrum Akademischer Verlag
- Griffiths AJF, Miller JH, Suzuki DT, et al. An Introduction to Genetic Analysis. 7th edition. New York: W. H. Freeman; 2000. Mutant types.