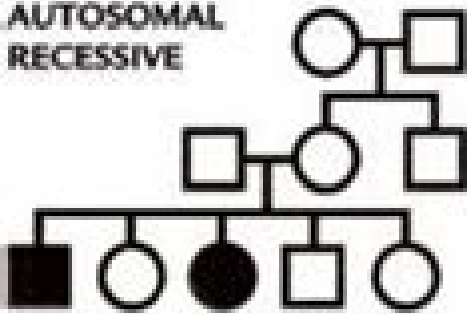
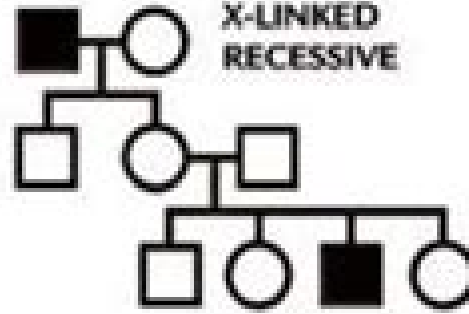


Pedigree charts

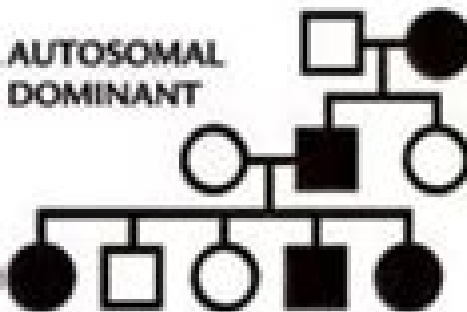
**AUTOSOMAL
RECESSIVE**



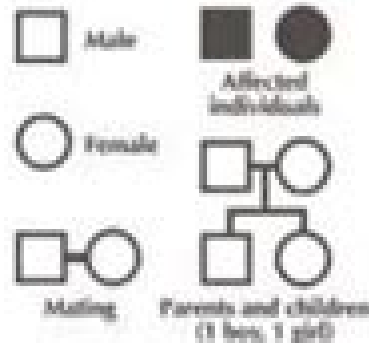
**X-LINKED
RECESSIVE**



**AUTOSOMAL
DOMINANT**



**PEDIGREE ANALYSIS
SYMBOLS**



Autosomal recessive:
Involves a recessive allele on a non-sex chromosome

Autosomal dominant:
Involves a dominant allele on a non-sex chromosome

X-linked recessive:
Involves a recessive allele on the X-chromosome

X-linked dominant:
Involves a dominant allele on the X-chromosome

Y-linked: Involves an allele on the Y-chromosome

CHALLENGE: Match these disorders to an appropriate pedigree pattern above, if possible.

- | | |
|-----------------------|---|
| a. Cystic fibrosis | g. Familial adenomatous polyposis (FAP) |
| b. Down syndrome | h. Huntington disease |
| c. Hemophilia | i. Duchenne muscular dystrophy |
| d. Lyme disease | j. Red-green color blindness |
| e. Sickle cell anemia | k. Spinocerebellar ataxia type 1 (SCA1) |
| f. Tay-Sachs disease | |

Human Pedigrees Biology Lf8765

Laurence Hasbrouck Snyder



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The Human Pedigree Anthony Smith, 1975 **Some Extensions of the Gene Frequency Analysis of Human Pedigrees** Charles William Cotterman, 1937 **Modern Analysis of Human Pedigrees** Laurence Hasbrouck Snyder, 1934

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The Mendelian Collection of Human Pedigrees George P. Mudge, 1911* **Symbols for Human Pedigree Charts** Lee Raymond Dice, 1946 Methods for Fine Mapping Complex Traits in Human Pedigrees Gonçalo Rocha Abecasis, William Cookson, 2001 *Dealing with Relatives* Dominic Nelson, 2021 All of humanity and indeed all living things are connected by a complex web of ancestral relationships. How much of this shared pedigree is known, how much can be inferred, and how completely it can be described are important factors in interpreting present-day genetic diversity and discovering genetic contributions to disease. The challenges of using pedigree information are twofold. First, in human populations, genealogical data is often unavailable or incomplete. Second, when such datasets are available, there are significant computational challenges to using them. In both cases, the response has often been to use approximate models of pedigree structure which removes the need for complete historical data and simplifies analysis. But genetic cohorts are growing, and increased sample sizes necessitate more detailed models of relatedness. The work presented here represents a first step in explicitly modeling the relatedness of millions of individuals and using it to understand the fine-scale diversity of whole populations as well as the genetic architecture of rare diseases. First, we developed a software package ISGen: Importance Sampling in Genealogies, for inferring the ancestral origin of rare alleles in population-scale pedigrees as well as their distribution among present-day individuals in a fully Bayesian framework. Similar analysis had never been possible before at that scale, and as a proof of concept, we analyzed the distribution of the allele causing Chronic Atrial and Intestinal Dysrhythmia (CAID) within the province of Quebec. Using observations of only 11 patients and 4 heterozygous carriers of the allele, we estimated the allele frequency in 26 geographic regions of the province, finding the highest expected frequency in Charlevoix where no carriers had yet been observed. Despite its value for supporting the design of screening programs for rare diseases, ISGen is limited to rare alleles and a single locus. Extending to whole-genome inference is a daunting challenge and can be aided significantly by high-quality data with a known transmission history. Simulations are a natural source of such data, yet the most efficient simulation frameworks were based on coalescent models with known biases for long genomic regions and large sample sizes. We developed two tools to address this issue. One is an extension to the state-of-the-art msprime coalescent simulator which

allows simulations under a Wright Fisher model This extension makes use of the highly efficient algorithms and data structures of msprime and we showed more realistic relatedness among simulated individuals as well as improved performance over coalescent simulations at whole genome scale We then continued to develop this extension to allow simulations to be performed within a predefined pedigree and when used with the population scale genealogy of Quebec Canada we showed that simulated cohorts captured much of the structure of a real dataset from the same population and significantly more than comparable simulations of a randomly mating population To show the potential of large scale pedigree simulations more generally we further described how pedigree simulations can aid in the design of sequencing cohorts for imputation and be used to detect rare variant associations while explicitly accounting for relatedness among cohort members

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