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# Bayesian inference of parental allele inheritance in fetus for noninvasive prenatal diagnosis

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## More info

Publication [1]



<https://hal.science/hal-03716132>

Source code



<https://github.com/gdurif/nipd>

Contact



<https://gdurif.perso.math.cnrs.fr>

## The problem (c.f. figure 1)

Noninvasive prenatal diagnosis (NIPD) [2] used to detect pathogenic genetic variation potentially transmitted to the fetus by a parent at risk without a hazardous invasive prenatal diagnosis (PND), i.e. risk of miscarriage

NIPD successfully applied for single-gene disorders [3] but still challenging for triplet-repeat expansion diseases, a.k.a. trinucleotide repeat disorder (e.g., myotonic dystrophy type 1, Huntington's disease, fragile X syndrome)

Fetal genotyping using circulating cell-free fetal DNA (cff-DNA) from maternal blood may not be able to detect complex genetic patterns in the fetal DNA that could have been inherited from a parent at risk

## The proposed method (c.f. figure 1)

Directly infer which haplotypes among the pair of parental homologous chromosomes have been inherited by the fetus

→ to determine if the haplotype region carrying the pathogenic variation was transmitted to the fetus or not

## The data (c.f. figure 2)

- parental phased haplotypes for the targeted chromosomal region
- maternal plasma cell-free DNA (cf-DNA) genotype for the targeted chromosomal region

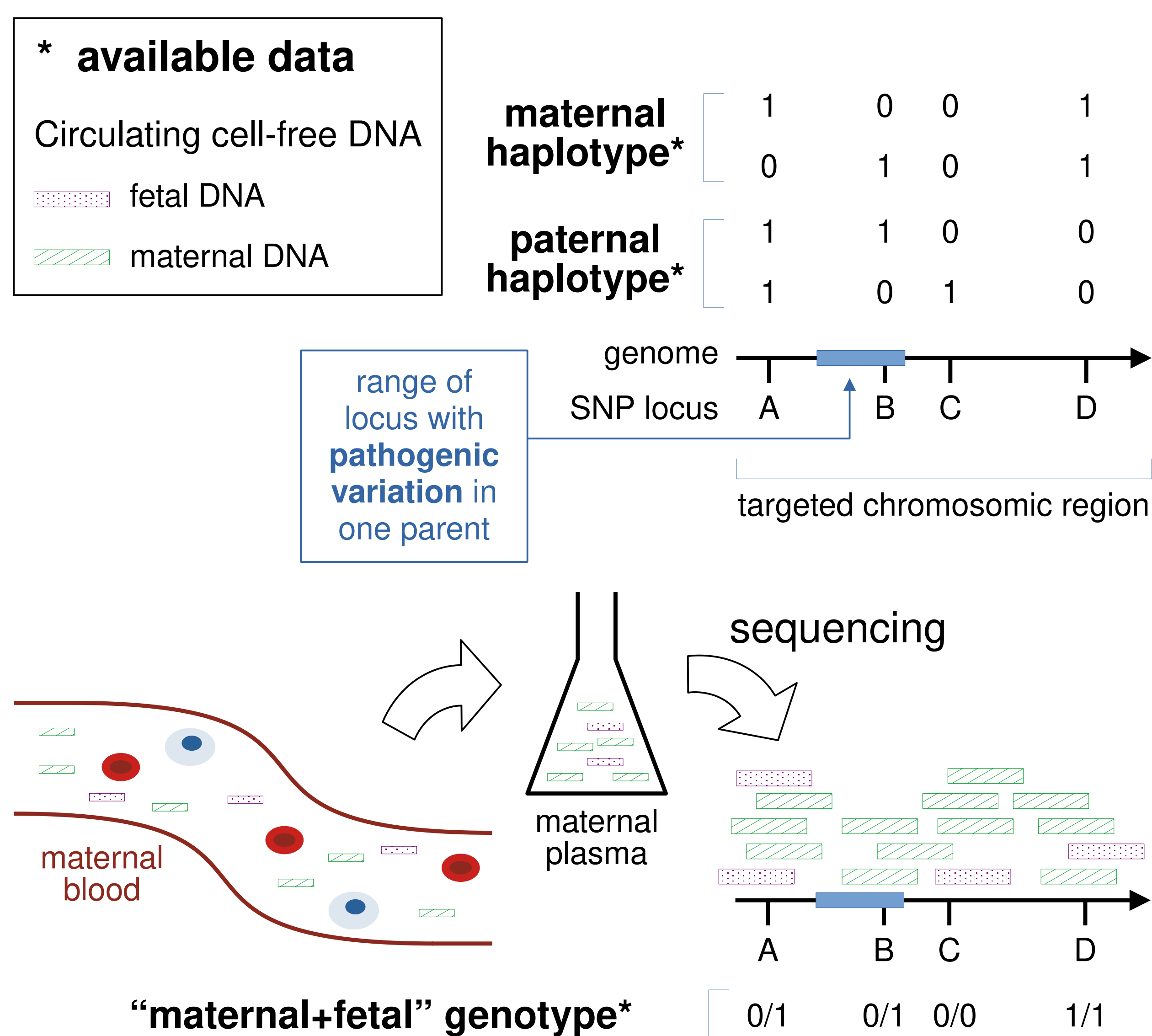


Figure 2. Available data to infer the parental allele origin in the fetus

## The perspectives

- Integrate the fetal fraction (=proportion of fetal DNA in sampled maternal plasma DNA) estimation [4] in the Bayesian model
- Run a larger-scale study with a different phasing protocol

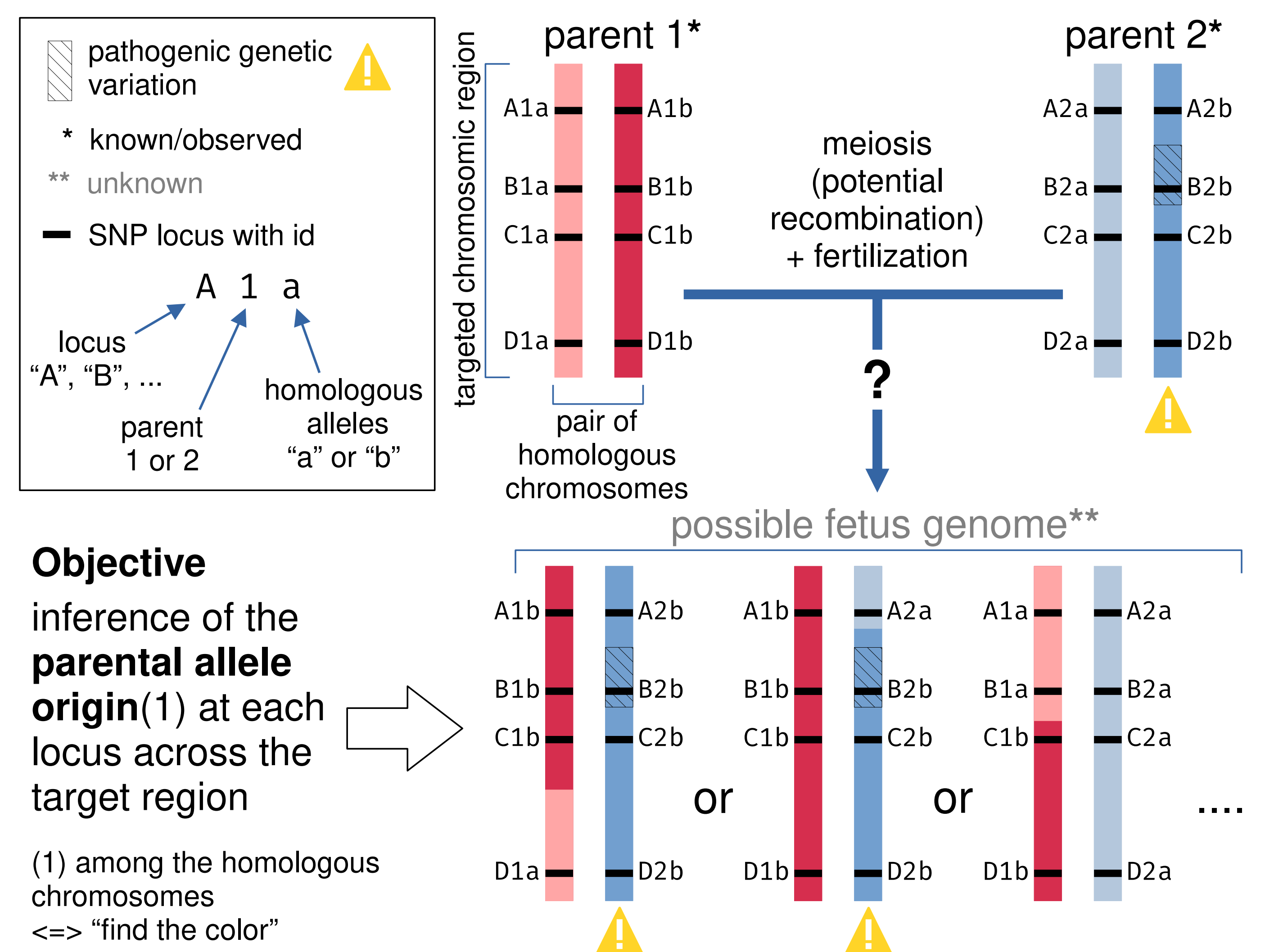


Figure 1. Inheritance pattern of the pathogenic genetic variation

## The Bayesian model

Output:  $O_\ell = (\text{mat}X, \text{pat}Y)$  fetal allele origin among the pair of homologous haplotypes from each parent ( $\text{mat} = \text{maternal}$ ,  $\text{pat} = \text{paternal}$  and  $X, Y \in \{1, 2\}$ ) at locus  $\ell$

Objective: infer  $(O_1, \dots, O_\ell, \dots, O_L)$  over all locus inside the targeted region

Tool: estimate the full posterior jointly over all locus

$$P(O_1, \dots, O_\ell, \dots, O_L | \text{data})$$

Issue: impossible because of combinatorial cost (no independence between locus)

Workaround: use a Markov chain Monte Carlo (MCMC) algorithm to estimate the full posterior, specifically a Gibbs sampler based on iterative sampling from the conditional marginal posterior

$$P(O_\ell | \text{data}, O_{\ell-1}) \sim P(\text{data at locus } \ell | O_\ell) \times P(O_\ell | O_{\ell-1})$$

- $P(O_\ell | O_{\ell-1}) = \text{transition probability}$  (depending on recombination probability and potential phasing error in both parents between locus  $\ell$  and  $\ell - 1$ )
- $P(\text{data at locus } \ell | O_\ell) = \text{conditional likelihood}$  that can be explicitly derived from fetal genotype model using read counts and fetal fraction estimation (as in the locus-independent fetal genotyping Hoobari model [3])

## The results

Analysis: a cohort of 14 families, each including one parent with a pathogenic genetic variation	Non conclusive <sup>(2)</sup> 9/14
Comparison between Bayesian NIPD and invasive PND results (=ground truth)	Accordance 4/14
	Error 1/14

(2) because of either poor polymorphism or phasing quality

## References

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