Pallister-Killian Syndrome (PKS)

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GGDL Case Conference

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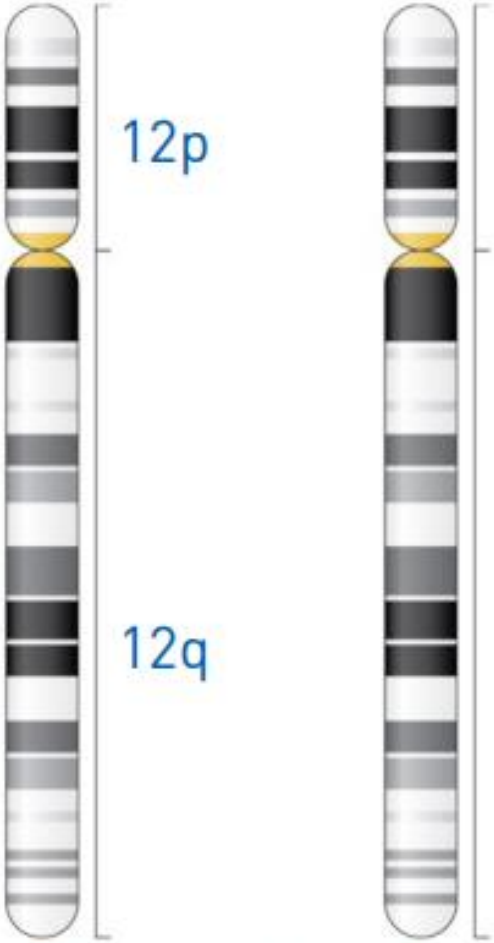
Summary

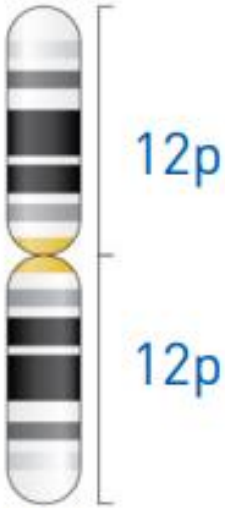
- Overview of PKS
- Mosaicism in PKS
- Case Example

Overview of PKS

- Aneuploidy syndrome characterized by coarse facial features, pigmentary skin lesions, localized alopecia, and severe developmental delay
- Mosaic tetrasomy 12p
  - Tissue-limited mosaicism
  - Mosaic hexasomy 12p also possible
- First described by Pallister et al. (1977) and Teschler-Nicola & Killian (1981)
- Incidence: 1 in 20,000
- *De novo* condition



Two copies of Chromosome 12



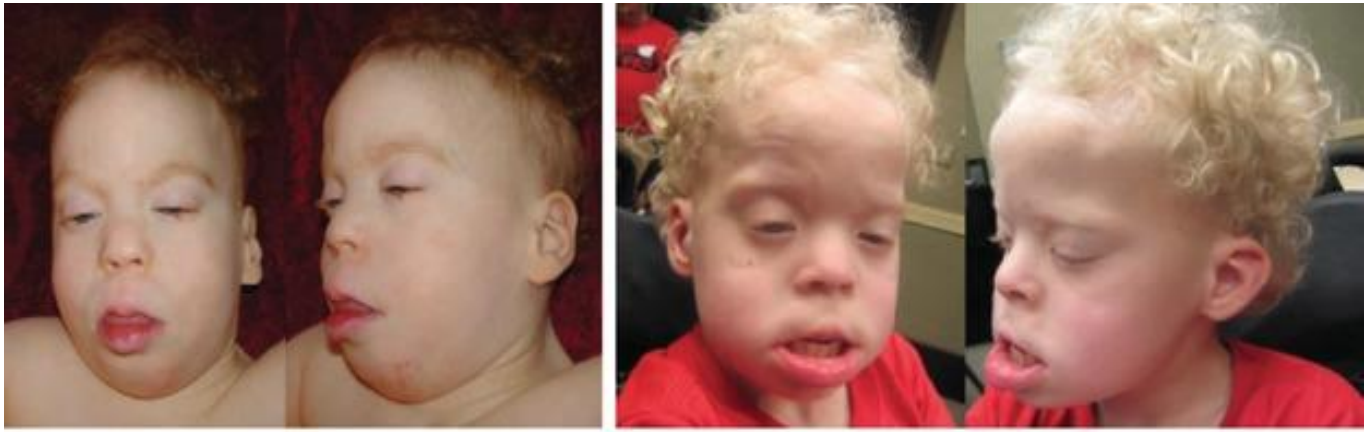
12p Isochromosome

Clinical Features

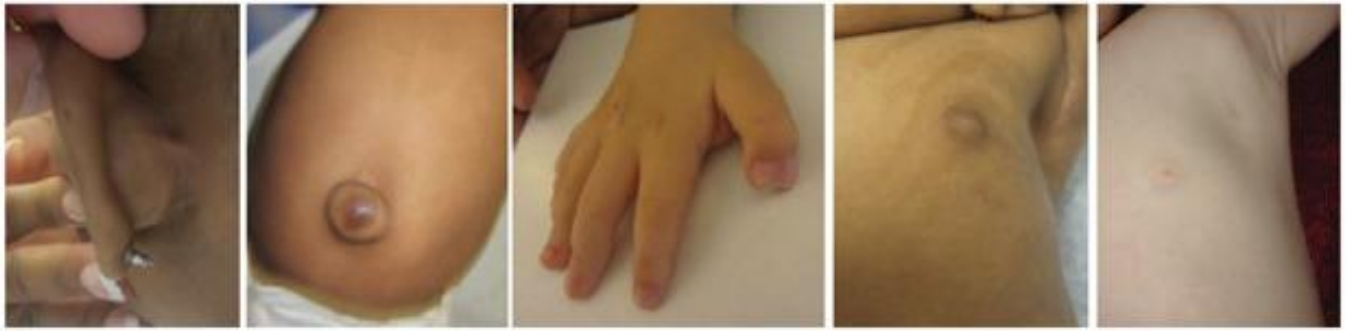
- Dysmorphic features
  - Prominent forehead, hypertelorism
  - Sparse anterior scalp hair/temporal alopecia
  - Flat occiput
  - Short neck
- **Developmental delay/Severe ID**
- Pigmentary skin lesions
- Accessory nipples
- Seizures
- Limb anomalies

Clinical Features

- Congenital heart defects, cardiomyopathy
- Hearing loss
- Eyes: cataracts, nystagmus, myopia, others
- Risk for cancer?
  - i(12p) as a cytogenetic marker



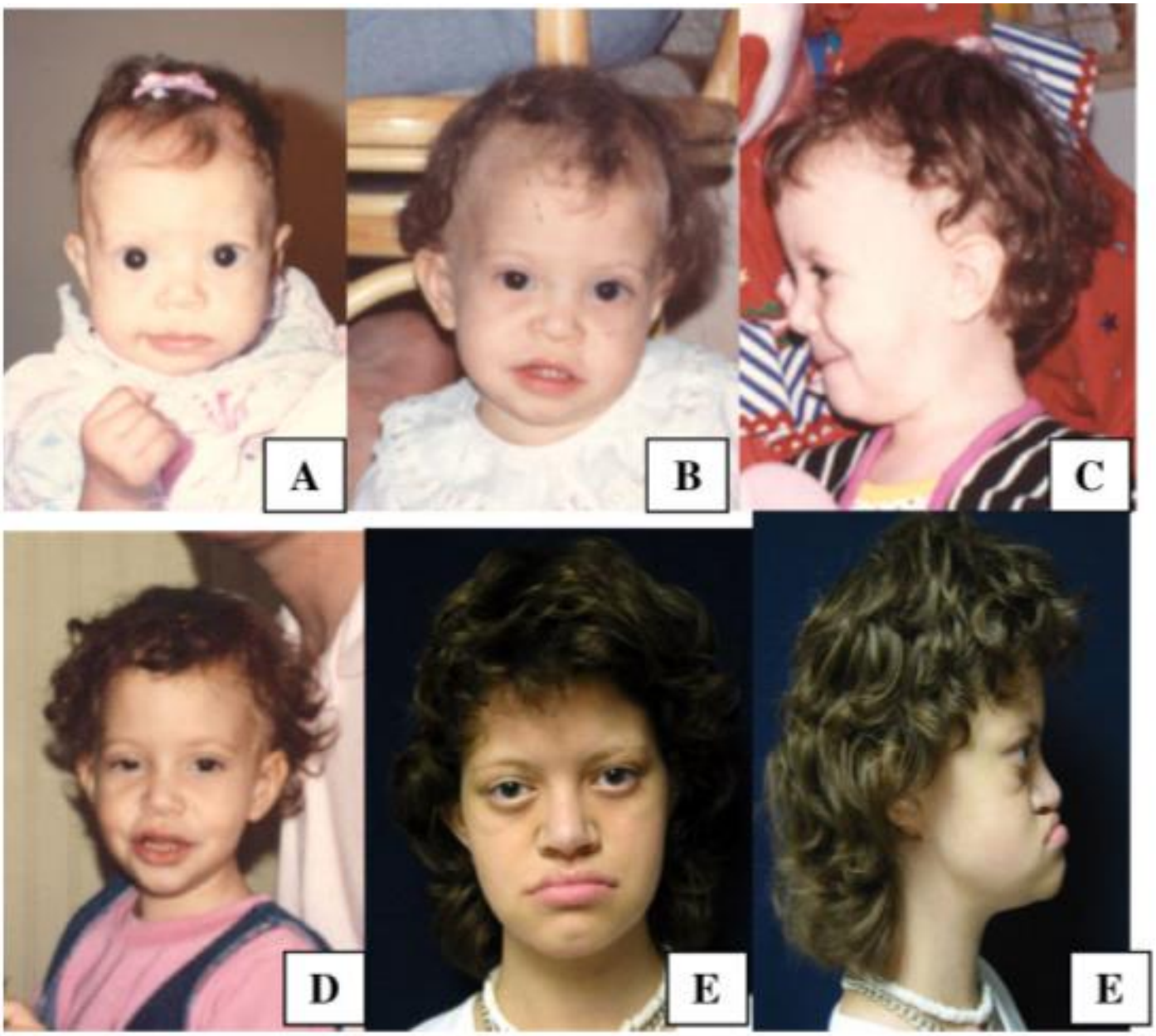
A



B

C

Izumi & Krantz 2014

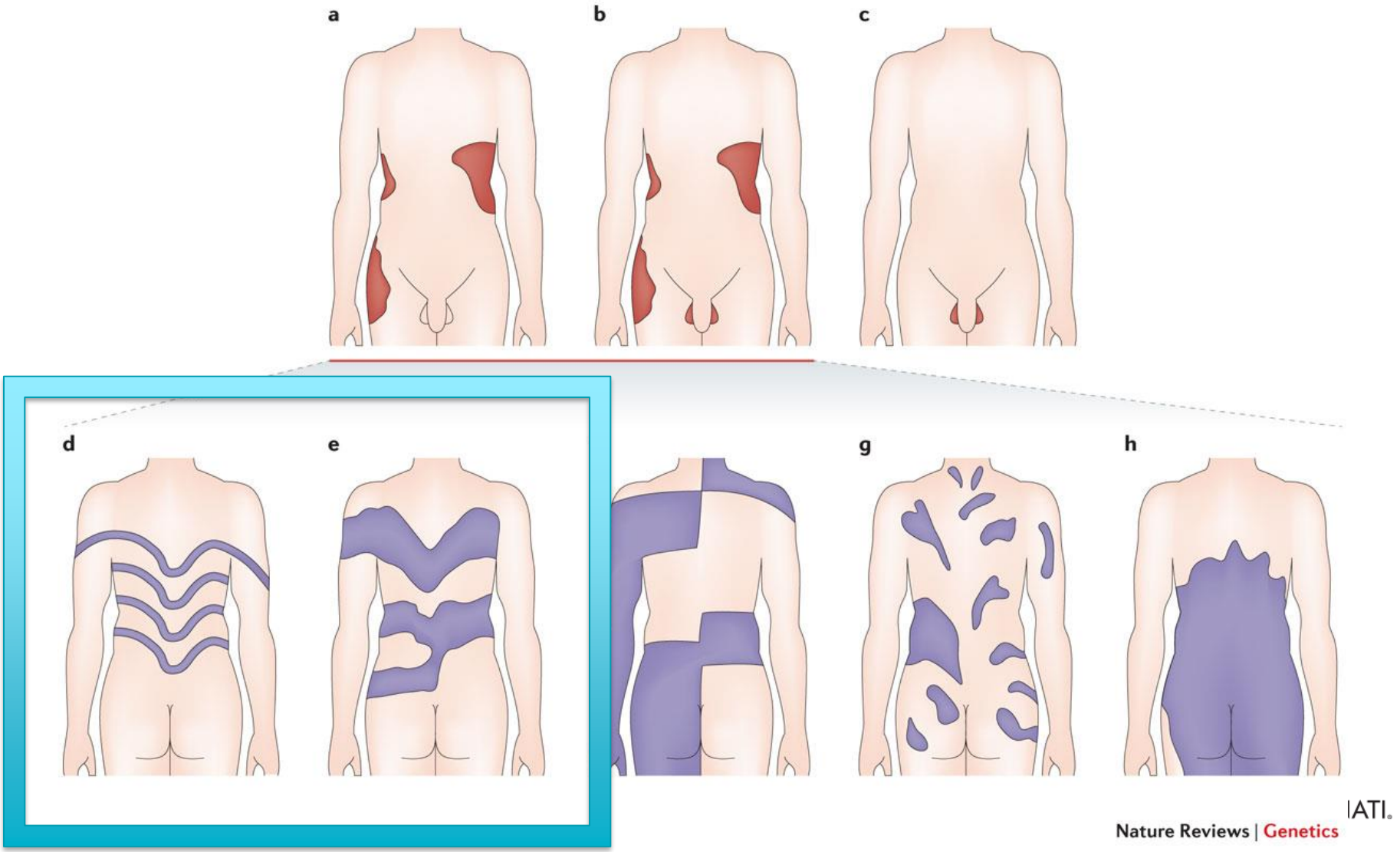


Stalker et al. 2006

Common Prenatal Indications

- Rhizomelic limb shortening
- Congenital diaphragmatic hernia
- Postaxial polydactyly
- Increased nuchal translucency
- Polyhydramnios
- Intrauterine growth restriction
- CHD

Mosaicism



Mosaicism in PKS

- Prezygotic maternal meiosis II nondisjunction event
  - rare paternal nondisjunction
  - rare postzygotic mitotic error
- Origin of mosaicism hypotheses:
  - WT outcompetes mosaic cells
  - Rescue via loss of i(12p)
- Phenotypic variation based on mosaicism of different tissue types
  - Vs percentage of mosaic cells or gene-dosage effects

PKS Testing

- Karyotype
- FISH
- CMA
- Sample types
  - Skin fibroblasts
  - Bone marrow
  - Amnio/CVS
  - Not routinely detected in blood leukocytes

Mosaicism in PKS

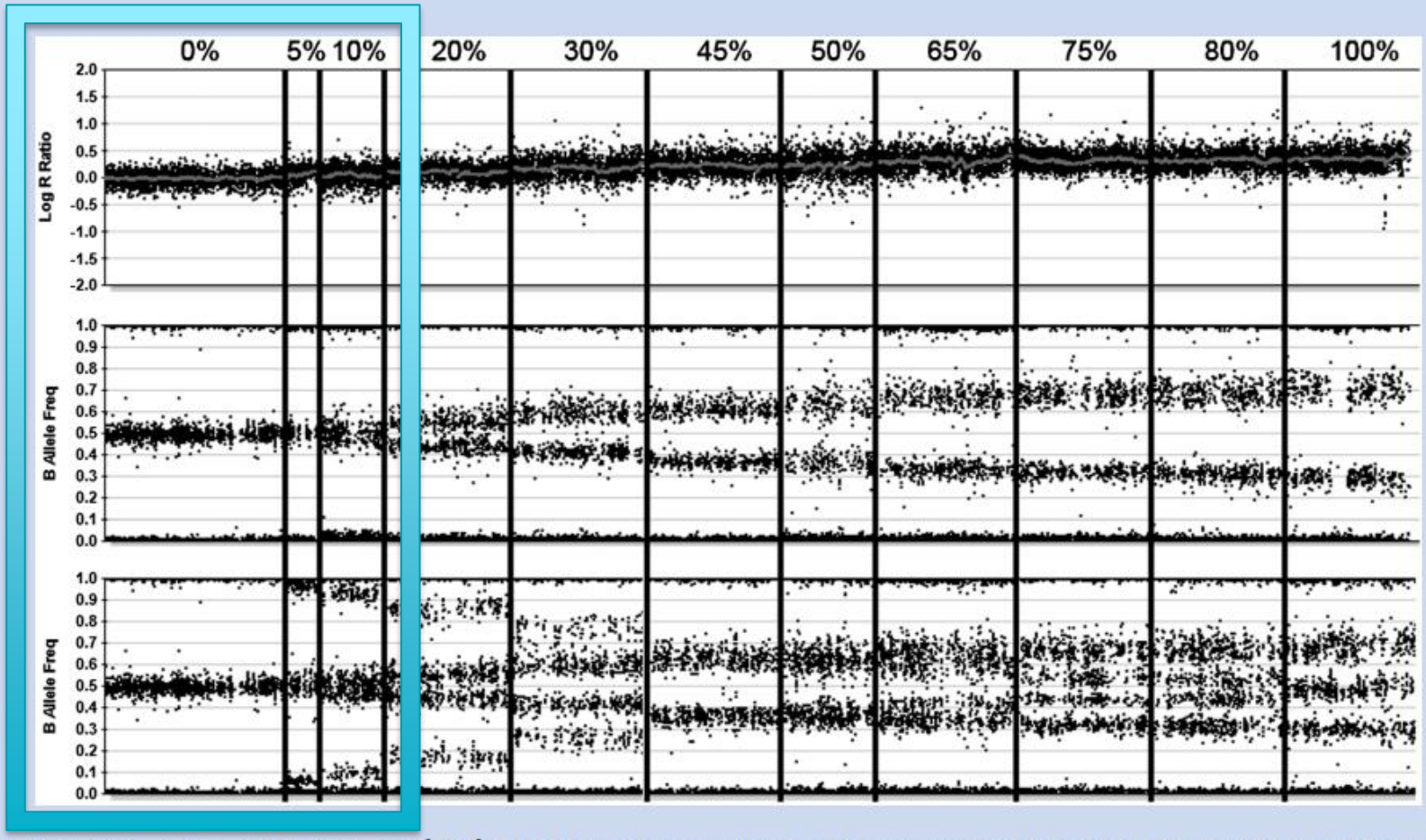


FIG. 2. Composite array results for mosaic i(12p). This figure shows chromosomal segments from11 patients illustrating mosaicism for isochromosome 12p from 0% to 100%. For all figure parts, the percentages above the data indicate the level of mosaicism, with 0% representing a region of 12p with normal copy number, and 100% representing a nonmosaic i(12p). Top: Log R Ratio. Middle: B allele frequency for i(12p) mosaicism from regions of 12p with genotypes indicating two haplotypes at a ratio of three copies to one copy. Bottom: B allele frequency for i(12p) mosaicism from regions of 12p from the same patients with genotypes indicating three haplotypes at a ratio of two copies to one copy to one copy.

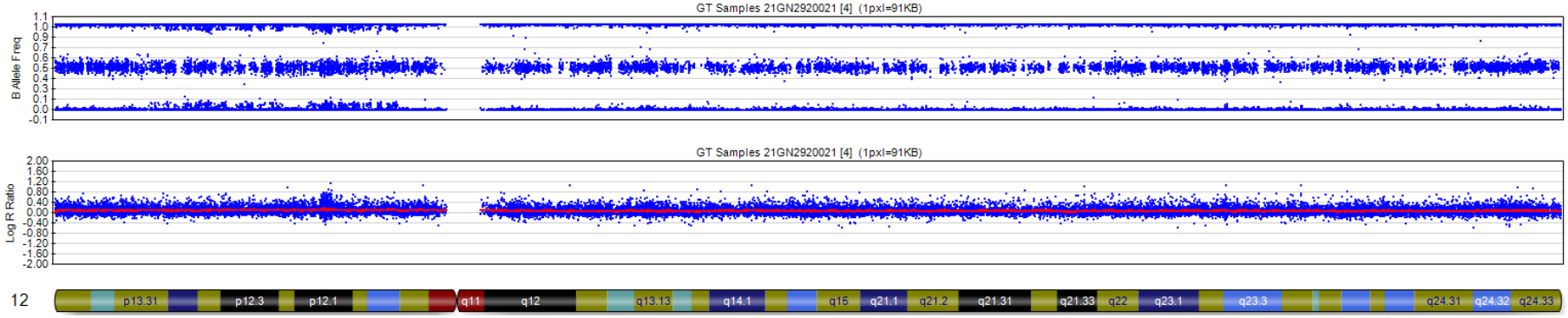
Case Example

- 8 mo male
  - **Hypomelanosis along lines of Blaschko**
  - **Corneal opacities/sclerocornea**
  - Small kidneys
  - Redundant nuchal tissue
  - Possible cryptorchidism
  - **Normal development**
- Suspicion for mosaic syndrome, anterior segment dysgenesis condition

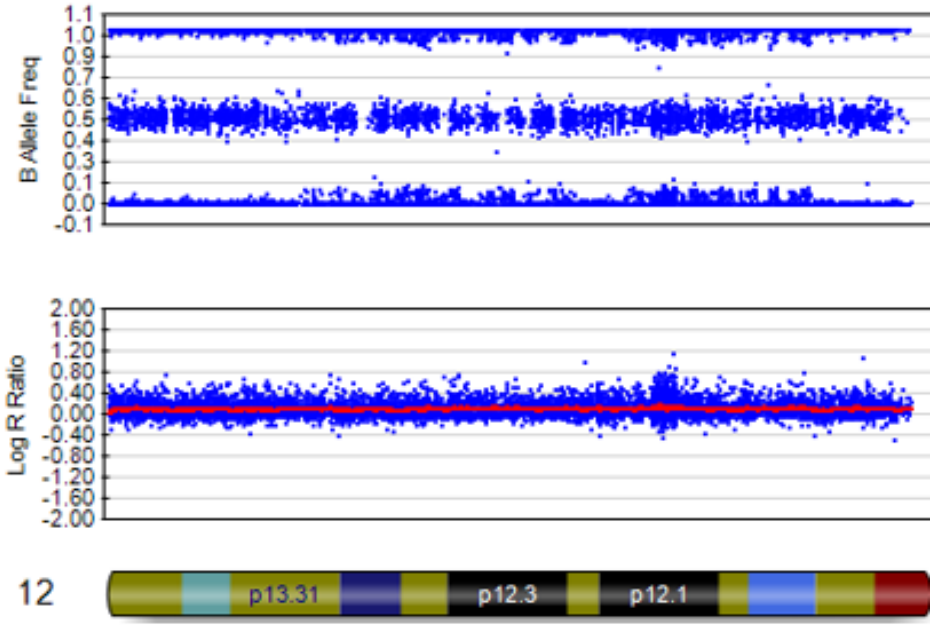
Testing Strategy

- Microphthalmia, Anophthalmia and Anterior Segment Dysgenesis Panel, Blueprint Genetics (61 genes)
  - Result: negative
- Reflex to microarray due to hypermelanosis vs WES
  - Sample: blood
  - Result: tetrasomy 12p

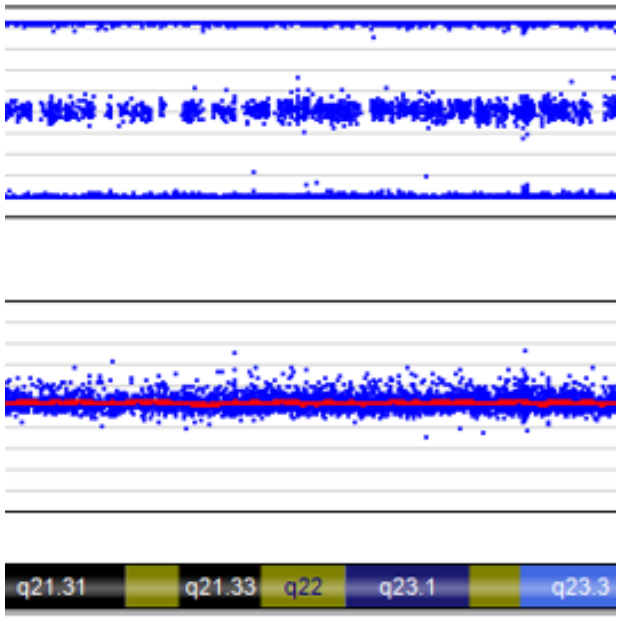
Results



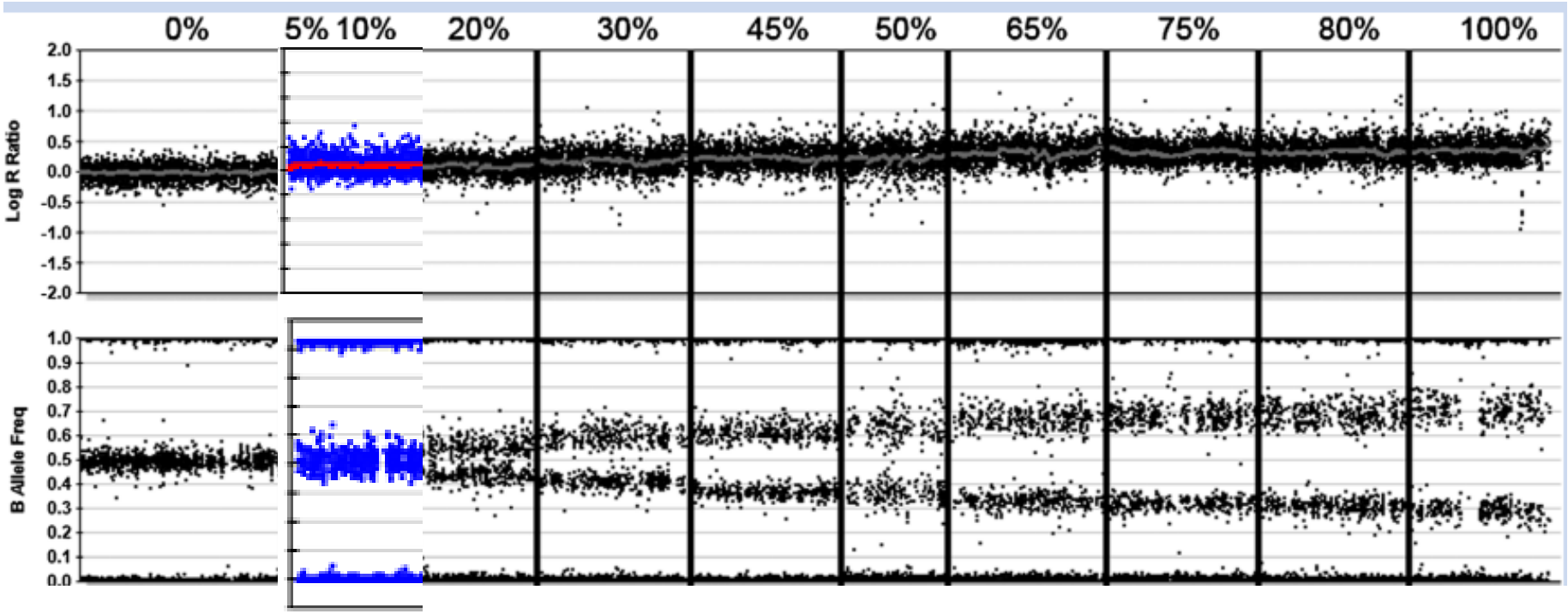
Mosaic 12p



Normal 12q



Results



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Conclusions

- Low-mosaicism PKS can be difficult to detect on CMA
- Syndromes are a spectrum with high clinical variability

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Questions?