



Optical Mapping of 22q11.2 Low Copy Repeats Reveals Structural Hypervariability

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Background: The 22q11.2 locus is structurally one of the most complex areas of the human genome due to the presence of low copy repeats. Despite the newest sequencing technologies, the human reference genome 38 still comprises three unresolved sequence gaps in LCR22-A. The recurrent deletion/duplication breakpoints of 22q11.2 deletion syndrome are embedded within these repeats. Despite extensive research, the exact location remains unclarified. **Methods:** To map those repeats, we performed a *de novo* assembly by using fiber-FISH. Long DNA molecules (>200 kb) were extracted from cells and stretched onto a coverslip with constant stretching factor. Long range PCR products were developed for charted subunits in these LCR22s, differentially labeled and hybridized to the DNA fibers. Following manual signal screening, alleles were *de novo* assembled by overlapping images based on matching colors and distances between the different probes. **Results:** Haplotyping the LCR22s of 36 individuals uncovered the presence of 20 different alleles for LCR22-A. These alleles range in size between 200 kb and 2 Mb. Subunits cluster in larger substructures. Substructure alleles vary in orientation and copy number, with some substructures present in some alleles but absent in others. We mapped the recombination between LCR22-A and LCR22-D in ten patients and identified differences in the location of the 22q11DS rearrangements between patients. **Conclusions:** The LCR22 hypervariability implicates interindividual gene dosage differences for the genes located within LCR22A. Genic copy number variations could influence gene expression profiles. Additionally, mapped rearrangement breakpoints vary among patients. We hypothesize this variability could provide a genetic explanation for some of the phenotypic variability characterizing the 22q11.2 deletion syndrome. Our LCR22 map paves the way towards unraveling this potential correlation.