

# Microdélétion 22q11 : connaissances génétiques en 2018

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# Chromosomes humains



[illegible]

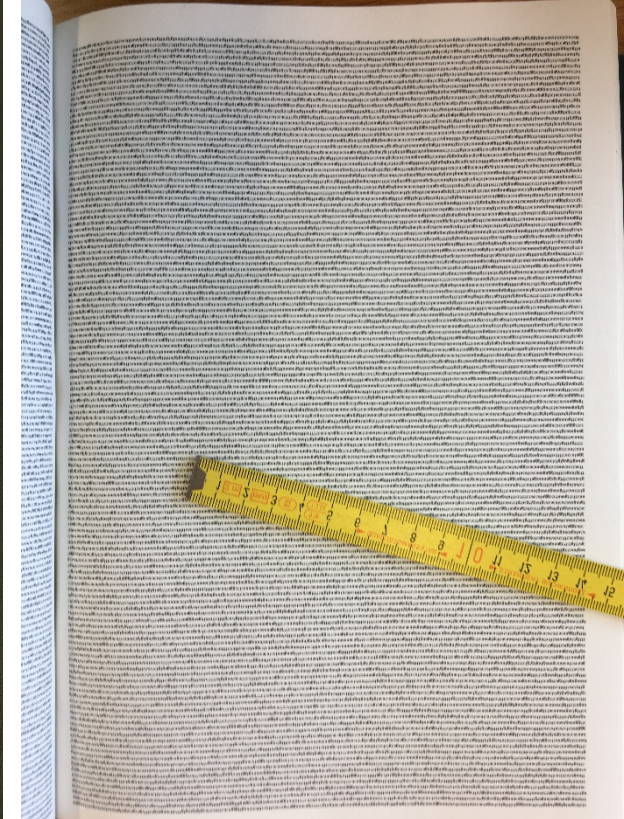
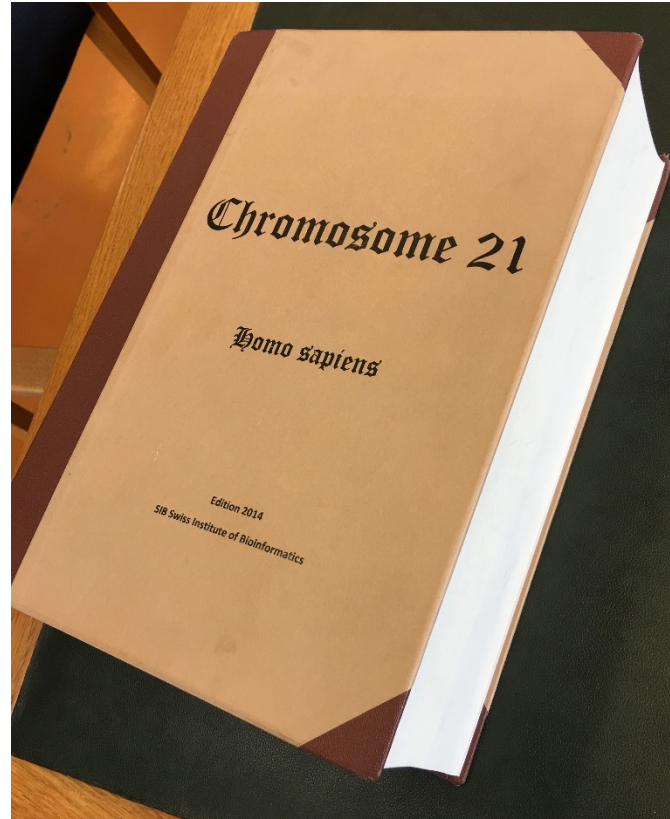
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GGGC TCTC G  
AGCT CGCA C  
GCTC CTCT C  
CACA GATA T  
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TCCT CTCGA  
CAGA TATA T  
GCTC GCACA  
CTCC TCTC G  
ACAG ATAT A  
ACAC CGCT C  
TCGA GACGT  
TCGA CGAGA  
GATA TATAG  
CCGC TCGA G  
AGAC GTAG G  
TAGC GCTC C  
TATA TAGC G  
ACAC GTGC T  
ACAC GTGCT  
ATAT AGCT C  
TCGC ACACC  
TCGC ACACC  
GCTC CTCT C  
GCTC CCTGA  
GCTC CCTGA  
AGAC CTGA C  
GCTC GCGA C  
CTCG ACGA G  
AGAT ATAT A  
GACC TGACA  
TGCT AGCT A  
GCTC GCGA C  
CACC GCTC G  
ACAG CTCG C  
TAGG GCTCT  
ACGT AGGG C  
GCGC TCCCT  
CGTG CTAG C  
CGTG CTAG C  
ACCT GACA C  
CTCC GACA C  
TGCT AGCT A  
CGCG ACACA  
CACA GCTC G  
CTAG CTCT T  
ACACACAGA

~10'000 nucléotides

~10'000 nucléotides

Le génome total est ~310,000 fois plus grand

# Chromosome 21



1470 pages  
248 nucléotides par ligne  
31'775 nucléotides par page  
46'709'983 nucléotides  
1.6% du génome



|                                                 |                                                 |
|-------------------------------------------------|-------------------------------------------------|
| ACGTG CTAG CTAG CTCCTCTC GAGA CGTA GGGC TCTC G  | ACGTG CTAG CTAG CTCCTCTC GAGA CGTA GGGC TCTC G  |
| ATATA GCTC GCGA CACA CACA GATA TATA GCGC TCCC T | ATATA GCTC GCGA CACA CACA GATA TATA GCGC TCCC T |
| GAAC AGCT CCGA CACA GC                          | GAAC AGCT CCGA CACA GC                          |
| TGACC TGAC ACGT GCTA GC                         | TGACC TGAC ACGT GCTA GC                         |
| GGGCT CTCG ATAG ATAG CG                         | GGGCT CTCG ATAG ATAG CG                         |
| CGCCT CCCT GAAA CAGC TC                         | CGCCT CCCT GAAA CAGC TC                         |
| CTCGA GACC TGAC CTGA CA                         | CTCGA GACC TGAC CTGA CA                         |
| CGAGA CGTA GGGC TCTC GA                         | CGAGA CGTA GGGC TCTC GA                         |
| AGATA TATA CGCG TCCC TG                         | AGATA TATA CGCG TCCC TG                         |
| CGCAC ACCG CTCG AGAC CT                         | CGCAC ACCG CTCG AGAC CT                         |
| AGCTC CTCT CGAG ACGT AG                         | AGCTC CTCT CGAG ACGT AG                         |
| GACAC ACAG AGAT ATAT AG                         | GACAC ACAG AGAT ATAT AG                         |
| GACAC AGCT CGCA CACC GC                         | GACAC AGCT CGCA CACC GC                         |
| GTGCT AGCT AGCT CCTC TC                         | GTGCT AGCT AGCT CCTC TC                         |
| ATAGC TCGC GACA CACA CA                         | ATAGC TCGC GACA CACA CA                         |
| AACAG CTCG GACA CAGC TC                         | AACAG CTCG GACA CAGC TC                         |
| ACCTG ACAC GTGC TAGC TA                         | ACCTG ACAC GTGC TAGC TA                         |
| GCTCT CGAT ATAG CTCG CG                         | GCTCT CGAT ATAG CTCG CG                         |
| GCTCC CTGA AACA GCTC CG                         | GCTCC CTGA AACA GCTC CG                         |
| CGAGA CTTG ACCT GACA CG                         | CGAGA CTTG ACCT GACA CG                         |
| AGACG TAGG GCTC TCGA TA                         | AGACG TAGG GCTC TCGA TA                         |
| ATATA TAGC GCTC CTTG AA                         | ATATA TAGC GCTC CTTG AA                         |
| CACAC CGCT CGAG ACCT GA                         | CACAC CGCT CGAG ACCT GA                         |
| CTCCT CTCG AGAC GTAG GG                         | CTCCT CTCG AGAC GTAG GG                         |
| CACAC ACAG ATAT ATAG CG                         | CACAC ACAG ATAT ATAG CG                         |
| CACAG CTCG GACA CCGC TC                         | CACAG CTCG GACA CCGC TC                         |
| GCTAG CTAG CTCCT TCTC GA                        | GCTAG CTAG CTCCT TCTC GA                        |
| AGCTC GCGA CACA CACA GA                         | AGCTC GCGA CACA CACA GA                         |
| CAGCT CCGA CACA GCTC GC                         | CAGCT CCGA CACA GCTC GC                         |
| CTGAC ACGT GCTA GCTA GC                         | CTGAC ACGT GCTA GCTA GC                         |
| TCTCG ATAT AGCT CGCG AC                         | TCTCG ATAT AGCT CGCG AC                         |
| TCCCT GAAA CAGC TCCG AC                         | TCCCT GAAA CAGC TCCG AC                         |
| AGACC TGAC CTGA CACG TG                         | AGACC TGAC CTGA CACG TG                         |
| ACGTA GGGC TCTC GATA TA                         | ACGTA GGGC TCTC GATA TA                         |
| ATATA GCGC TCCC TGAA AC                         | ATATA GCGC TCCC TGAA AC                         |
| CACCG CTCG AGAC CTGA CC                         | CACCG CTCG AGAC CTGA CC                         |
| CCTCT CGAG ACGT AGGG CT                         | CCTCT CGAG ACGT AGGG CT                         |
| CACAC AGAT ATAT AGCC CT                         | CACAC AGAT ATAT AGCC CT                         |
| CAGCT CGTCA CACC GCTC GA                        | CAGCT CGTCA CACC GCTC GA                        |
| TAGCT AGCT CCTC TCGA GA                         | TAGCT AGCT CCTC TCGA GA                         |
| CTCGG GACA CACA TCGA TA                         | CTCGG GACA CACA TCGA TA                         |
| GCTCC GACA CAGC TCGC AC                         | GCTCC GACA CAGC TCGC AC                         |
| GACCG TGCT AGCT AGCT CC                         | GACCG TGCT AGCT AGCT CC                         |
| CGATA TAGC TCGC GACA CA                         | CGATA TAGC TCGC GACA CA                         |
| CTGAA ACAG CTCG GACA CA                         | CTGAA ACAG CTCG GACA CA                         |
| CCTGA CCTG AACG TGCT AG                         | CCTGA CCTG AACG TGCT AG                         |
| AGGGC TCTC GATA TAGC TC                         | AGGGC TCTC GATA TAGC TC                         |
| AGCGC TCCC TGAA ACAG CT                         | AGCGC TCCC TGAA ACAG CT                         |
| GCTCG AGAC                                      | GCTCG AGAC                                      |

ACGCTG CTAG CTAG CTCCT TCTT  
ATATA GCTC GCGA CACA CAC/  
GAAAC AGCT CGGA CACA CG/  
TGACC TGAC ACGT GCTA GC/  
GGGCT CTCG ATAT AGCT CG/  
GCGCT CCCT GAAA CAGC TCT/  
CTCGA GACC **AA** CTCGA CA/  
CGAGA CTGA GGGC TCTC GA/  
AGATA TATA GCGC TCCC TG/  
CGCAC ACCG CTCG AGAC CT/  
AGCTC CTCT CGAG ACGT AG/  
GACAC ACAC AGAT ATAT AG/  
GACAC AGCT CGCA CACC GC/  
GTGCT AGCT AGCT CCTC TC/  
ATAGC TCGC GACA CACA CA/  
AACAG CTCG CACA CAGC TC/  
ACCTG ACAC GTGC TAGC TA/  
GCTCT CGAT ATAG CTCG CG/  
GCTCC CTGCA AACA GCTC CG/  
CGAGA CTTG ACCT GACA CG/  
AGACG TAGG GCTC CTGA TA/  
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GCTAG CTAG CTCCT TCTC GA/  
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CAGCT CGCA CACA GCTC GC/  
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TCCCT GAAA CAGC TCCG AC/  
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CCTCT CGAG ACGT AGGG CT/  
CACAC AGAT ATAT AGCG CT/  
CAGCT CGCA CACC GCTC GA/  
TAGCT AGCT CCTC TCGA GA/  
CTCGC GACA CACA CAGA TA/  
GCTCC GACA CAGC TCGC AC/  
GACCG TGCT AGCT AGCT CC/  
CGATA TAGC TCGC GACA CA/  
CTGAA ACAG CTCG GACA CA/  
CCTGA CTTG AACG TGCT AG/  
AGGGC TCTC GATA TAGC TC/  
AGCGC TCCC TGAA ACAG CT/  
GCTCG AGAC

TGACC TGAC ACGT GCTA GCT/  
GGGCT CTCG ATAT AGCT CGC/  
GCGCT CCCT GAAA CAGC TCC/  
CTCGA GACC **AA** CTCGA CAC/  
CGAGA CTGA GGGC TCTC GA/  
AGATA TATA GCGC TCCC TAG/  
CGCAC ACCG CTCG AGAC CTG/  
AGCTC CTCT CGAG ACGT AGG/  
GACAC ACAC AGAT ATAT AGC/  
GACAC AGCT CGCA CACC GCT/  
GTGCT AGCT AGCT CCTC TCG/  
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AACAG CTCG CACA CAGC TCG/  
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GCTCC CTGA AACA GCTC CGA/  
CGAGA CTTG ACCT GACA CGT/  
AGACG TAGG GCTC CTGA TAT/  
ATATA TAGC GCTC CTG AAA/  
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CTCTCT **CG** AGAC GTAG GCG/  
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ACGTA GGGC TCTC GATA TAG/  
ATATA GCGC TCCC TGAA ACAG/  
CACCG CTCG AGAC CTGA CCT/  
CCTCT CGAG ACGT AGGG CTC/  
CACAC AGAT ATAT AGCG CTCT/  
CAGCT CGCA CACC GCTC GAG/  
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CTCGC GACA CACA CAGA TAT/  
GCTCC GACA CAGC TCGC ACAG/  
GACCG TGCT AGCT AGCT CCT/  
CGATA TAGC TCGC GACA CAG/  
CTGAA ACAG CTCG GACA CAG/  
CCTGA CTTG AACG TGCT AGCG

ACGTG CTAG CTAG CTCCTCTC GAGA CGTA GGGC TCTC T  
ATATA GCTC GC GA CACA CACA GATA TATA GCGC TCCC T  
GAAAC AGCT CGCA CACA  
TGACC TGAC ACGT GCTA  
GGGCT CTG CAT ATAGT  
CGCGT CCCT GAAA CAGC  
CTCGA GAGT TAC CTGA  
CGAGA CTGA GGGC TCTC  
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GTGCT AGCT AGCT CCTC  
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AACAG CTCG GACA CAGC  
ACCTG ACAC GTGC TAGC  
GCTCT CGAT ATAG CTCT  
GCTCC TCGA AACG GCTC  
CGAGA CTTG ACCT GACA  
AGACG TAGG GCTC TCGA  
ATATA TAGC GCTC CTCT  
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CTCC CG AGAC GTAG  
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CAGCT CGCA GACA GCTC  
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TCTCG ATAT AGCT CCGC  
TCCCT GAAA CAGC TCCG  
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ACGTA GGGC TCTC GATA  
ATATA GCGC TCCC TGAA  
CACC GCTC AGAC CTGA  
CCTCT CGAG ACGT AGGG  
CAGT GAT ATAT AGGC  
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CGATA TAGC TCGC GACA  
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CCTGA CTTG AACG TGCT  
AGGGC TCTC GATA TAGC  
AGCGC TCCC TGAA ACAG  
GCTCG AGAC

ACGCTG CTAG CTAG CTCCT TCTC GAGA CGTA GGGC TCTC T  
ATATA GCTC GCGA CACA CACA GATA TATA GCGC TCCC T  
GAAAC AGCT C **CA** CACA G  
TGACCT TGAC ACGT GCTA G  
GGGCT CTCG ATAT AGCT C  
CGCCT CCCT GAAA CAGC G  
CTCGA GACC **AA** CTGA C/  
CGAGA CTGA GGGC TCTC G/  
AGATA TATA GCGC TCCC T  
CGCAC ACCG CTCG AGAC C/  
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CGAGA CCGT ACCT GACA C/  
AGACG TAGG GCTC TCGA T/  
ATATA TAGC GCTC CTGA A/  
CACAC CGCT CGAG ACCT G/  
CTCCT C **CG** AGAC GTAG G/  
CACAC ACAG ATAT ATAG C/  
CAGAC CTCG CACA CCGC T/  
GCTAG CTAG CTCCT TCTC G/  
AGCTC GCGA CACA CACA G/  
CAGCT CCGA CACA GCTC G/  
CTGAC ACGT GCTA GCTA G/  
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TCCCT GAAA CAGC TCCG A/  
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ACGTA GGGC TCTC GATA T/  
ATATA GCGC TCCC TGAA A/  
CACC G CTCG AGAC CTGA C/  
CCTCT CGAG ACGT AGGG C/  
CACA **GG** ATAT ATAT AGCT C/  
CAGCT CGCA CACC GCTC G/  
TAGCT AGCT CCTC TCGA G/  
CTCGC GACA CACA CAGA T/  
GCTCC GACA CAGC TCGC A/  
GACCG TGCT AGCT AGCT C/  
CGATA TAGC TCGC GACA C/  
CTGAA ACAG CTCG GACA C/  
CCTGA CTTG AACG TGCT A/  
AGGGC TCTC GATA TAGC T/  
AGGCT TCCC TGAA ACAG C/  
GCTCG AGAC

ACGCTG CTAG CTAG CTCCT T  
ATATA GCTC GCGA CACA G  
GAAAC AGCT C **CA** CACA G  
TGACCT TGAC ACGT GCTA G  
GGGCT CTCG ATAT AGCT C  
CGCCT CCCT GAAA CAGC G  
CTCGA GACC **AA** CTGA C/  
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GACAC AGCT CGCA CACC G/  
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ACCTG ACAG GTGC TAGC T/  
GCTCT CGAT ATAT CTCG C/  
GCTCC CTGA AACA GCTC C/  
CGAGA CCGT ACCT GACA C/  
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CTCCT C **CG** AGAC GTAG G/  
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GCTAG CTAG CTCCT TCTC G/  
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CAGCT CCGA CACA GCTC G/  
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TCTCG ATAT AGCT CCGC A/  
TCCCT GAAA CAGC TCCG A/  
AGACC TGAC CTGA CACG T/  
ACGTA GGGC TCTC GATA T/  
ATATA GCGC TCCC TGAA A/  
CACC G CTCG AGAC CTGA C/  
CCTCT CGAG ACGT AGGG C/  
CACA **GG** ATAT ATAT AGCT C/  
CAGCT CGCA CACC GCTC G/  
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GGGCT CTCGAT ATAT AGCT CGC  
CGCCT CCCT GAAA CAGC TCC  
CTCGA GACC A CTA GCA CAC  
CGAGA CTGA GGGC TCTC GAT  
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ACCTG ACAC GTGC TAGC TAG  
GCTCT CGAT ATAG CTCG CGA  
GCTCC CTGA AACAC GCTC CGA  
CGAGA C T G ACCT GACA CGT  
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ATATA TAGC GCTC TCTG AAA  
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CTCCT C CAGAC GTAG GGC  
CACAC ACAG ATAT ATAG CGC  
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GCTAG CTAG CTCC TCTC GAG  
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CAGCT CCGA CACA GCTC GCA  
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TCTCG ATAT AGCT CCGC ACA  
TCCCT GAAA CAGC TCGC ACA  
AGACC TGAC CTGA CACG TGC  
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ATATA GCGC TCCC TGAA ACA  
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CCTCT CGAG ACCT AGGG CTC  
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TAGCT AGCT C TCT TCGA GAC  
CTCGC GACA CACA CAGA TAT  
GCTCC GACA CAGC TGCG ACA  
GACCG TGCT AGCT AGCT CCT  
CGATA TAGC TCGC GACA CAC  
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CCTGA C T G AACG TGCT AGC  
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GCTCG AGAC

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CTCGA GACC **A** C CTGA CACG TGCT AGCT AGCT CCTC T  
CGAGA CTGA GGGC TCTC GATA TAGC TCGC GACA CACA  
AGATA TATA GCGC TCCC TGAA ACAG CTCC GACA CAGC  
CGCAC ACGC CTCG AGAC CTGA CTTG ACAC GTGC TAGC T  
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AACAG CTCC GACA CAGC TCGC ACAG CGCT CGAG ACCT G  
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ATATA TAGC GCTC CTTG AAAC GCTC CCGA CACA GCTC G  
CACAC CGCT C GAG ACCT GACC TGAC ACGT GCTA GCTA G  
CTCCT CTG **G** AGAC CTAG GGGCT CTGAT ATAT **A** T GCTC  
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GCTAG CTAG CTCCT CTCG GAGA GCTC GGGC TCTC GATA T  
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CAGCT CCGA CACA GCTC GCAC ACGC CTCG AGAC CTGA C  
CTGAC AGCT GCTA GCTA GCTC CTCT CGAG **A** TAGGCG  
TCTCG ATAT AGCT GCGC ACAC ACAG ATAT AGGCG C  
TCCCT GAAA CAGC TCCG ACAC AGCT CGCA CACC GCTC G  
AGACC TGAC CTGA CACG TGCT AGCT AGCT CCTC TCGA G  
ACGTA GGGC TCTC GATA TAGC TCGC GACA CACA CAGA T  
ATATA GCGC TCCC TGAA ACAG CTCC GACA CAGC TCGC A  
CACC G CTCG AGAC CTGA CTTG ACAG GTGC TAGC TAGC T  
CCTCT CGAG AGCT AGGG CTCT CGAT ATAG CTCT CGAC A  
CACA **G** AT ATAT AGCG CTCC CTGA AAAC GCTC CGAC A  
CAGCT CGCA CACC GCTC GAGA CTTG ACCT GACA CTTG C  
TAGCT AGCT CCTC TCGA GACG TAGG GCTC TCGA TATA G  
CTCGC GACA CACA CAGA TATA TAGC GCTC CTTG AAAC A  
GCTCC GACA CAGC TCGC ACAC CGCT CGAG ACCT GACC T  
GACCG TGCT AGCT AGCT CCTC TCGA GACG TAGG GCTC T  
CGATA TAGC TCGC GACA CACT CACA GATA TATAG GCTC C  
CTGAA ACAG CTCG CACA CAGC TCGC ACAC CGCT CGAG A  
CTTGA CTTG AAGC TGCT AGCT AGCT CCTC TCGA GACG T  
AGGGC CTTCT GATA TAGC TCGC GACA CACA GATA TAT

**En moyenne, un nouveau-né porte 50 à 100 nouvelles mutations.**

TAGCT AGCT CCTC TCGA GACG TAGG GCTC T  
GACAC ACAC AGAT ATAT AGCG CTCCT CTGA A  
AGCTC GCAC ACGC CTGAG AGCG CTGCA AGA  
GCTCC TCTC GAGA CGTA GGGC TCTC GATA T  
CACAGAT ATAT AGAG CCTC CCCT GAAA CAGC T  
CACAC CGCT CGAG CGCT GACC TCAG ACCT GGC  
CTCGA GACG TAGG GCTC TCGA TATA GCTC GC  
ATATA GCGC TCCC TGAA ACAG GCTC GACA CA  
TCGAG ACCT GACCT TCGA AGT GCTA GCTA GC  
GTAGG GCTC TCGA TATA GCTC GCGA CACA CA  
GCTCC CTGA AACG GCTC GCAG ACAG CTCG CA  
CTCGA CTTG ACAG GTGC TAGC TAGC TCTC CT  
CTCTC GATA TAGC TCGC GACA CACA CAGA TA  
TGAAA CAGC TCCG ACAC AGCT CGCA CACC GC  
CTGAC AGCT GCTA GCTA GCTC CTCT GCGA AC  
ATATA GCTC GCGA CACA CACA GATA TATA GC  
ACCGC TCGA GACC TGAC CTGA CAGC TGCT AG  
GAGAC GTAG GGCT CTCG ATAT AGCT CGCG AC  
ATAG GCTC TCTG AAAC AGCT CCGA CACA GC  
CGAGA CTTG ACCT CGA CGTG CTAG CTAG CT  
GACGT AGGG CTCT CGAT ATAG CTCG CGAC AC  
AGCGC TCCC TGAA ACAG CTCG GACA GAGC TG  
CCGCT CGAG ACCT GACC TGAC ACGT GCTA GC  
AGAGC TAGG GCTC TCGA TATA GCTC GCGA CA  
TAGCG CTCG TCGA AACG GCTC GCAG ACAG CT  
GAGAC CTGA CTTG ACAC GTGC TAGC TAGC TG  
AGGGC TCTC GATA TAGC TCGC GACA CACA  
CGTAG GGCT CTCG ATAT AGCT CGCG ACAC AC  
CGCTC CTTG AAAC AGCT CCGA CACA GCTC GC  
ACCTG ACCT GACA CGTG CTAG CTAG CTCG TC  
GCTCT CGAT ATAG CTCG CGAC ACAC ACAG AT  
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GCTCG AGAC CTGA CTTG ACAG GTGC TAGC TA  
GCTCG AGAC CTGA CTTG ACAG GTGC TAGC TA  
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ACGTA GGGC TCTC GATA TAGC TCGC GACA CA  
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ACACA CAGA TATA TAGC GCTC CTTG AAAC AG  
AGACC TGAC CTGA CAGC TGCT AGCT AGCT CG  
ACACC GCTC GAGA TAGC TAGC TCTC CTCG AG  
CGATA TAGC TCGC GACA CACA CAGA TATA TA  
TCTCG ATAT AGCT CGCG ACAC ACAC AGAT AT  
GAAAC AGCT CCGA CACA GCTC GCAC ACGG CT  
TAGCT CCTC TCGA GACG TAGG GCTC TCGA TA  
TAGCT CCTC TCGA GACG AGGT AGGG CTCT CG  
GTGCT AGCT AGCT CTCG TCGA CGAG ACCT AG  
AGCTC GCAC ACGC CTCG AGAC CTGA CTTG AG  
AGCTC GCAC ACGC CTCG AGAC CTGA CTTG AG

A CAC AGCT CGCA CACC GCTC GAGA CTTG ACCT GACA CGTG CTAG CTAG CTCC TCTC GAGA CGTA GGGC TCTC GATA TAGC TCGC GACA CACA  
 A GCTA GCTC CTCT CGAG AGCT AGGG CTCT CGAT ATAG CTCG CGAC ACAC ACAG ATAT ATAG CGCT CCCT GAAA CAGC TCCG ACAC AGCT CGCA  
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 T TCGC ACAC CGCT CGAG ACCT GACC TGAA CGTG CTAG CTAG CTCC TCTC GAGA CGTA GGGC TCTC GATA TAGC TCGC GACA CACA CAGA TATA  
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 C ACCG CTCG AGAC CTGA CTTG ACAC GTGC TAGC TAGC TCCT CTCG AGAC GTAG GGCT CTG ATAT AGCT CGCG ACAC ACAC AGAT ATAT AGGC  
 A GAGA CGTA GGGC TCTC GATA TAGC TCGC GACA CACA CAGA TATA TAGC GCTC CTTG AAAA CAGCT CCGA CACA GCTC GCAC CCGT CTCG AGAC  
 T ATAG CGCT CCCT GAAA CAGC TCCG ACAC AGCT CGCA CACC GCTC GAGA CTTG ACCT GACA CGTG CTAG CTAG CTCC TCTC GAGA CGTA GGGC  
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 C GTAG GGCT CTG ATAT AGCT CGCG ACAC ACAC AGAT ATAT AGGC CTCC CTGA AAAA GCTC CGAC ACAG CTCG CACA CCGC TCGA GACC TGAC  
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ACC GCTC GAGA CTCT ACCT GAGA CTGT CTAG CT  
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ACG TAGG GCTC TCGA TATA GCTC GCGA CACA CA  
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GGC TCTA TAGC TAGC TCGC GACA CACA CAGA TA  
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GCT CCTC TCGA GACG TAGG GCTC TCGA TATA GCG  
GCT CCCT GAAA CAGC TCGC ACAC AGCT CGCA CAG  
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TCGA CAGC TGCT AGCT AGCT CCTC TCGA CAGC AG  
CGA TATA GCTC GCGA CACA CACA GATA TATA GCG  
GCT CGCA CACC GCTC GAGA CTTG ACCT GACA CG  
GCT CGCA CACC GCTC GAGA CTTG ACCT GACA CG  
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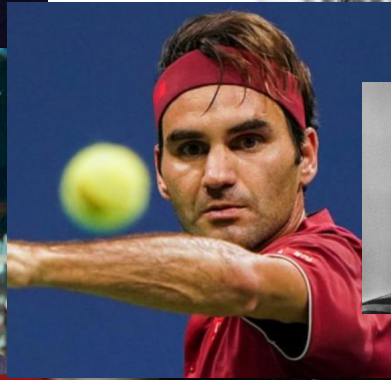
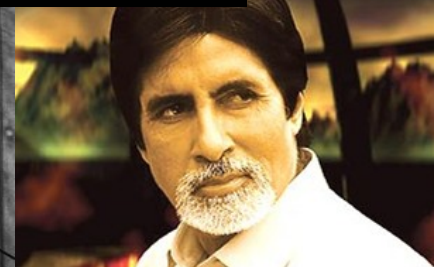
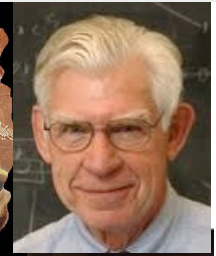
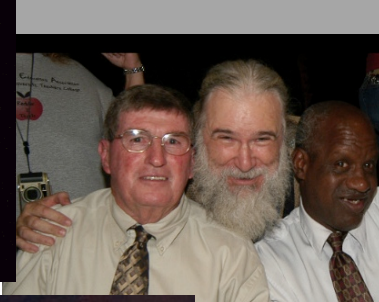
[illegible]

10/11/2018

Nous sommes tous différents les uns des autres.



# Diversité humaine



# Variations génétiques

Neutres

Prédisposantes

Pathogéniques

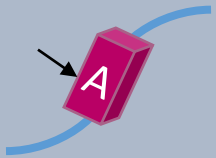
La variabilité génomique offre  
la possibilité d'évoluer et de s'adapter...

... mais certains changements peuvent  
être **délétères** et conduire à l'apparition  
de **maladies génétiques**.

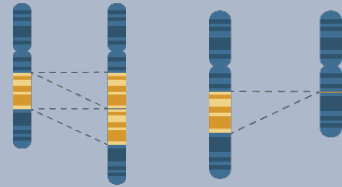


# Maladie mendélienne versus maladie multifactorielle

## Hérédité mendélienne



SNVs  
(monogénique)

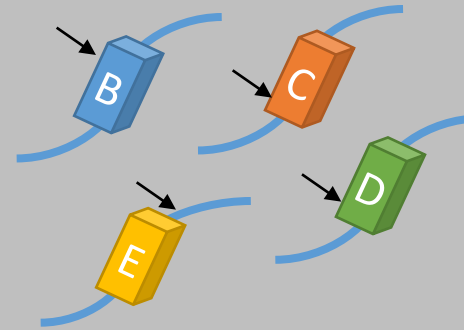


CNVs  
(chromosomique)

**1 variant d'impact fort**

Ex : mucoviscidose ou microdélétion 22q11

## Hérédité multifactorielle ou complexe



Environnement

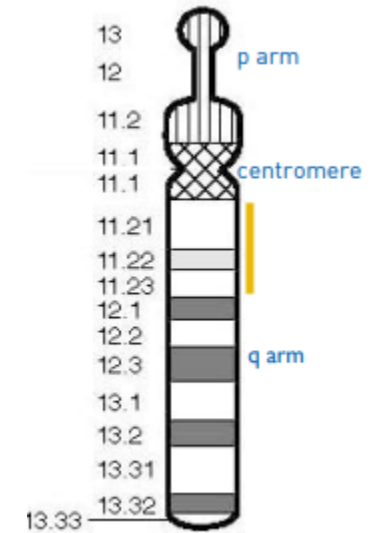
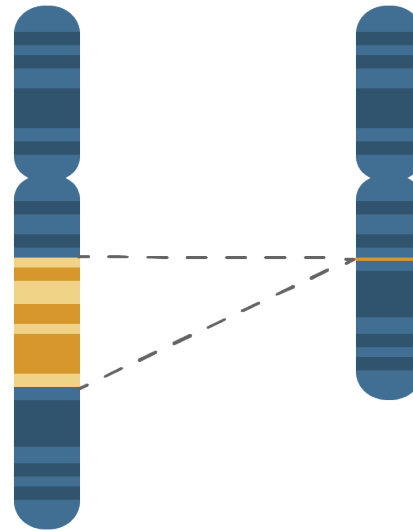
Polygénique  
**Multiples variants  
d'impact faible**

Ex : obésité

# Microdélétion 22q11

**CNV = Copy Number Variant**

**Deletion**





# Historique

1955

Dr Eva Sedlackova

Anomalies du palais et  
particularités

morphologiques

Syndrome vélo-facial

1965

Dr Angelo DiGeorge

Anomalie du thymus,  
hypocalcémie,  
malformation cardiaque

Syndrome de DiGeorge

1976

Drs Takao et Kinouchi

Malformation cardiaque,  
particularités  
morphologiques

Conotruncal anomaly face  
syndrome

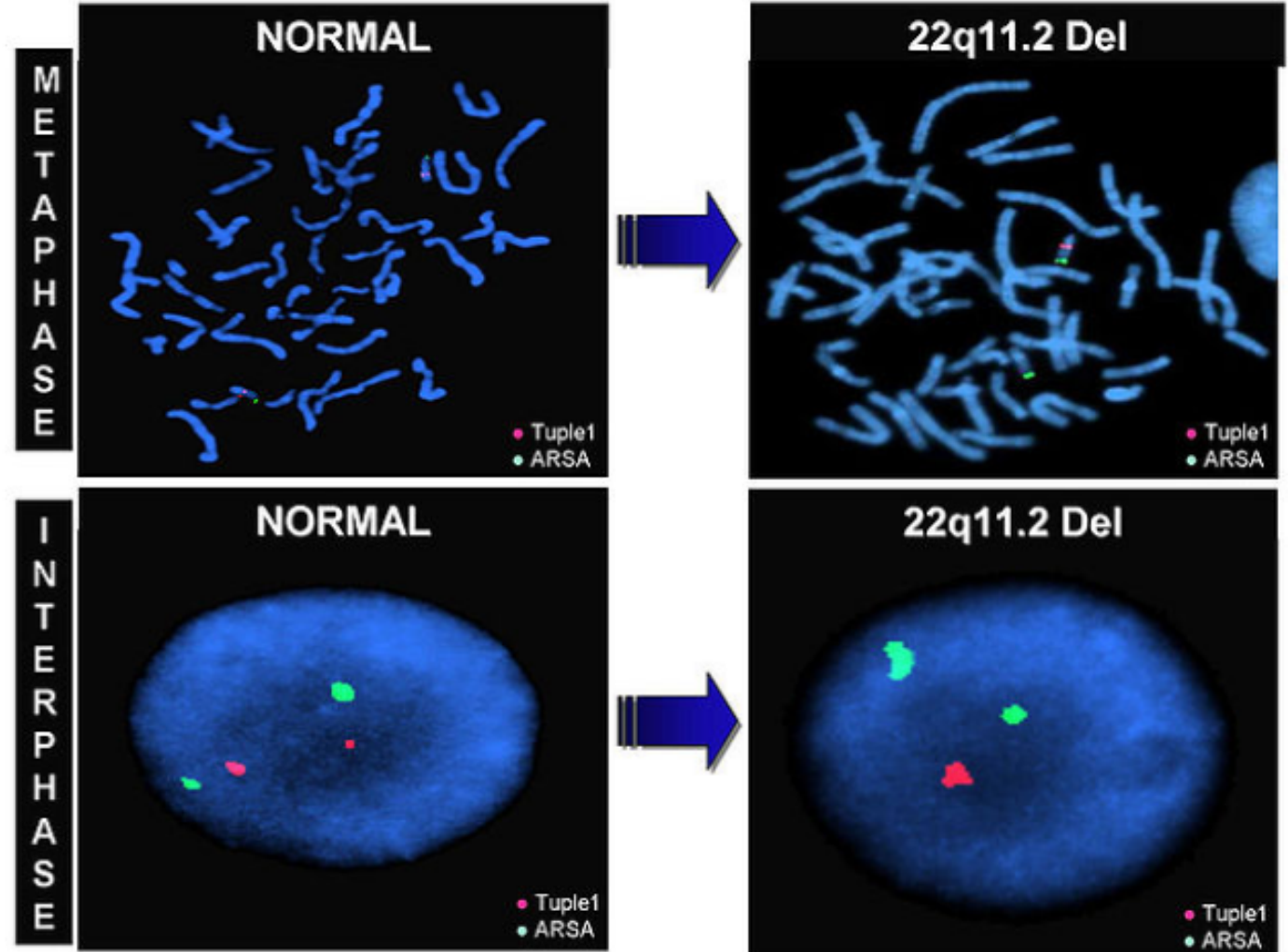
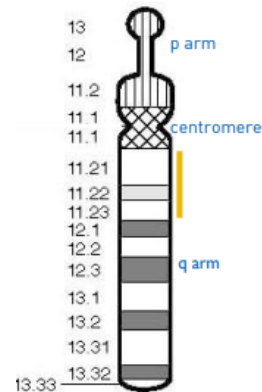
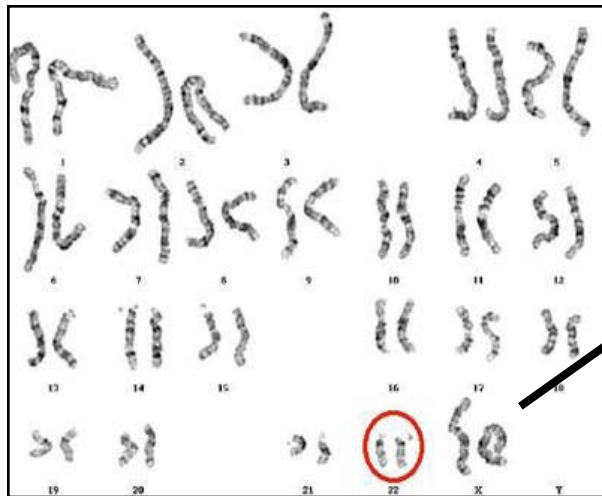
1978

Dr Schprintzen

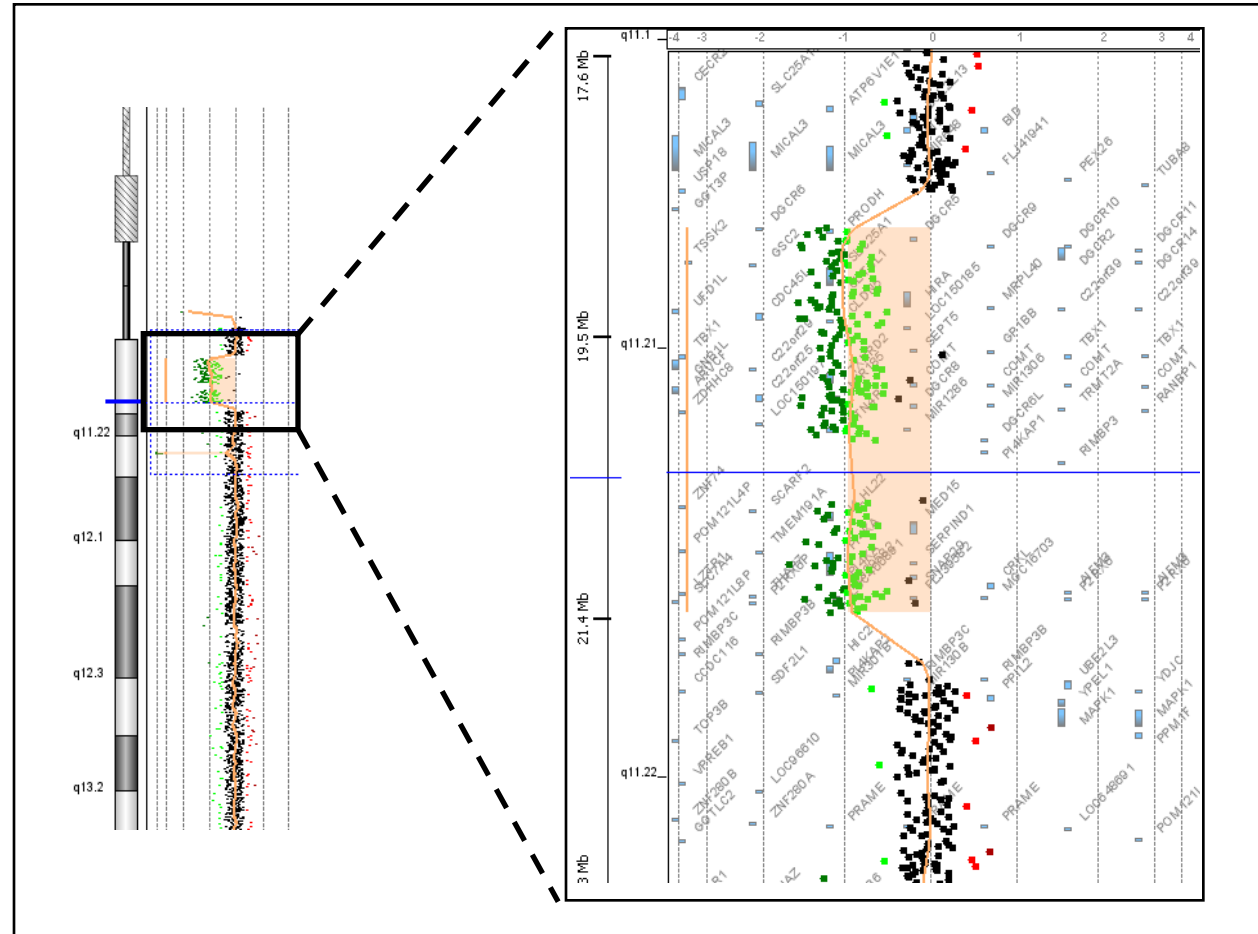
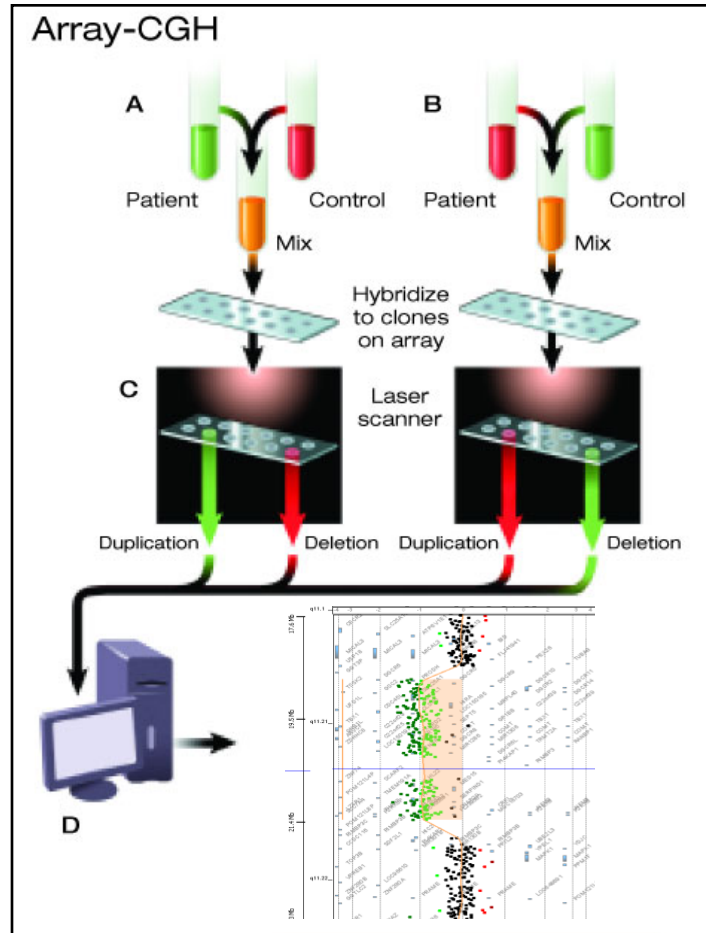
Anomalie cardiaque, fente  
palatine, particularités  
morphologiques

Syndrome vélo-cardio-  
facial

# 1992 : Identification de la délétion

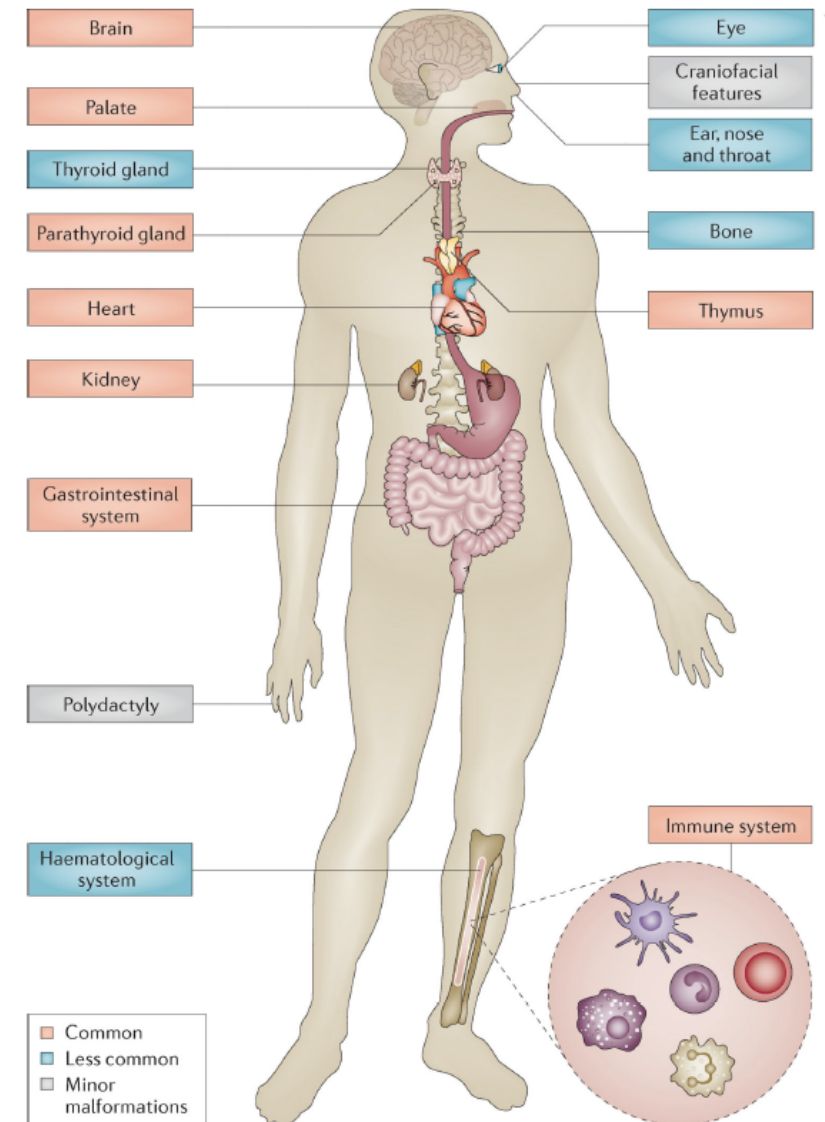


# Technologies de détection : array-CGH



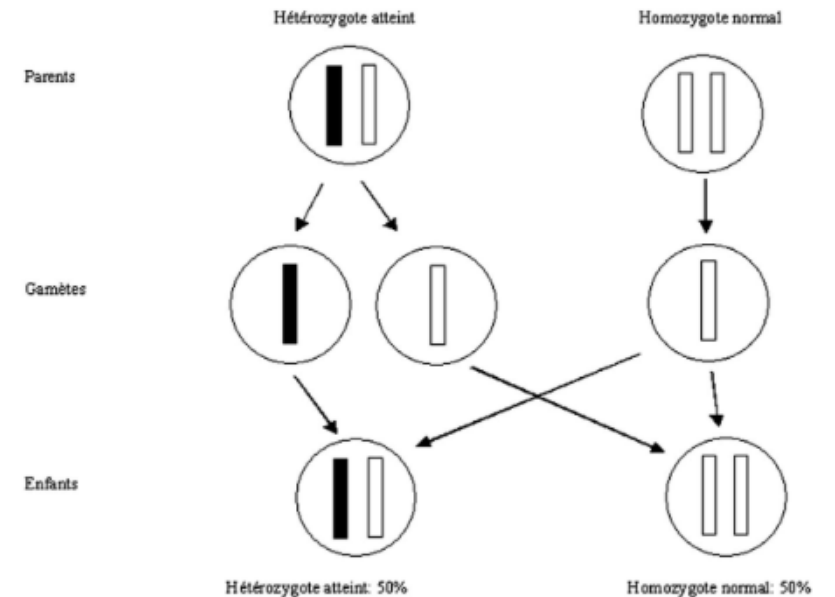
# Microdélétion 22q11 : symptômes

- Malformation cardiaque
- Anomalies du palais (fente palatine, insuffisance vélo-palatine,...)
- Trouble du développement variable
- Particularités faciales
- Trouble immunitaire variable
- Hypocalcémie
- Troubles psychiatriques
- Autres malformations : vertébrales, uro-génitales, gastro-intestinales,....



# Fréquence

- Environ 1/3'500-4'000 naissances vivantes ; 1/1'000 fœtus
- Mode de survenue
  - Dans 93% des cas, *de novo*
  - Dans 7% des cas, héritée d'un parent
- Hérité autosomique dominante



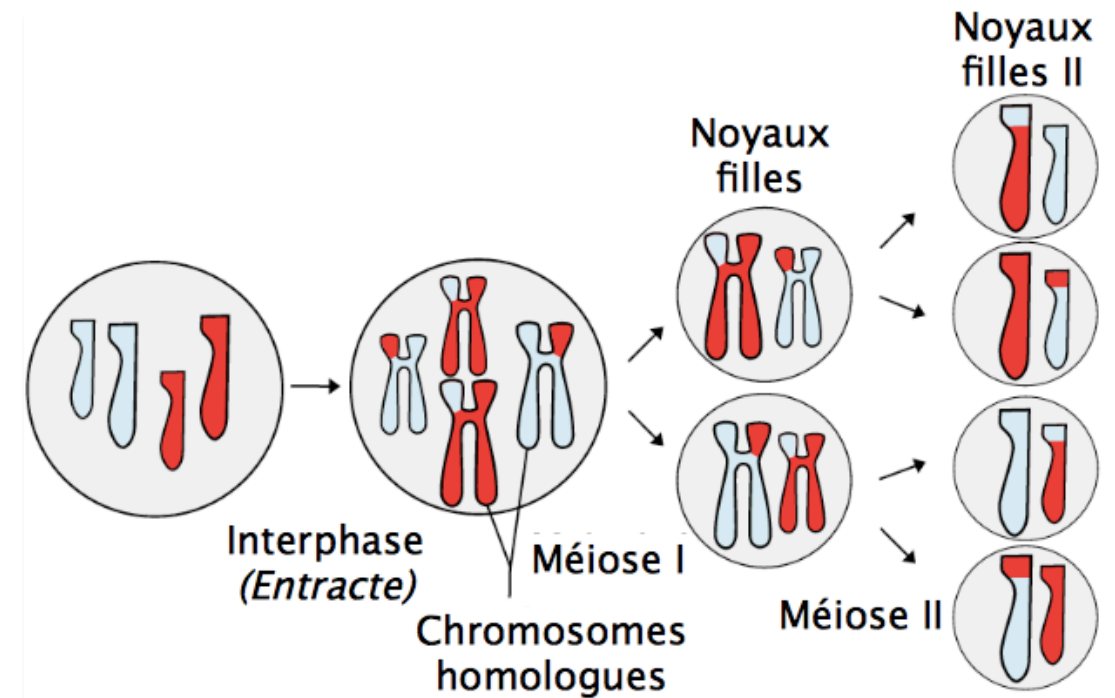




***Hérédité***

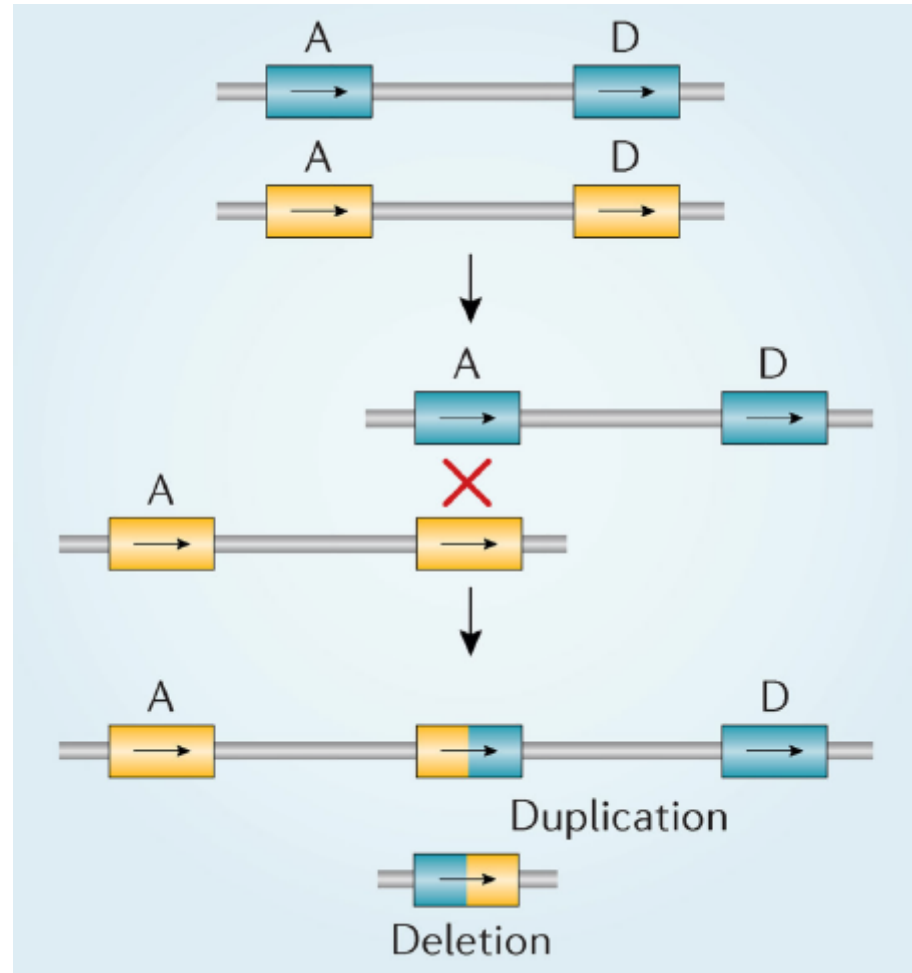


# Fabrication des ovocytes et spermatozoïdes



# Pourquoi et comment la délétion survient-elle ?

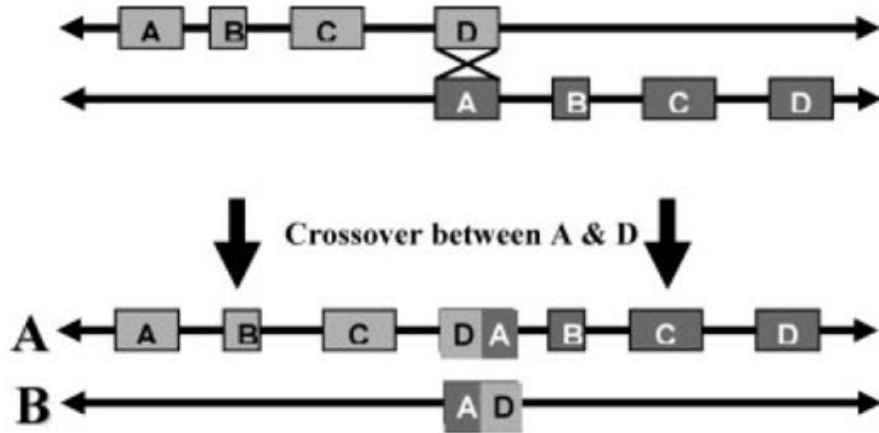
LCR : Low Copy Repeat  
Portions de génome  
présentes plus d'une  
fois dans le génome et  
qui se ressemblent à  
plus de 90%



Recombinaison allélique non homologue

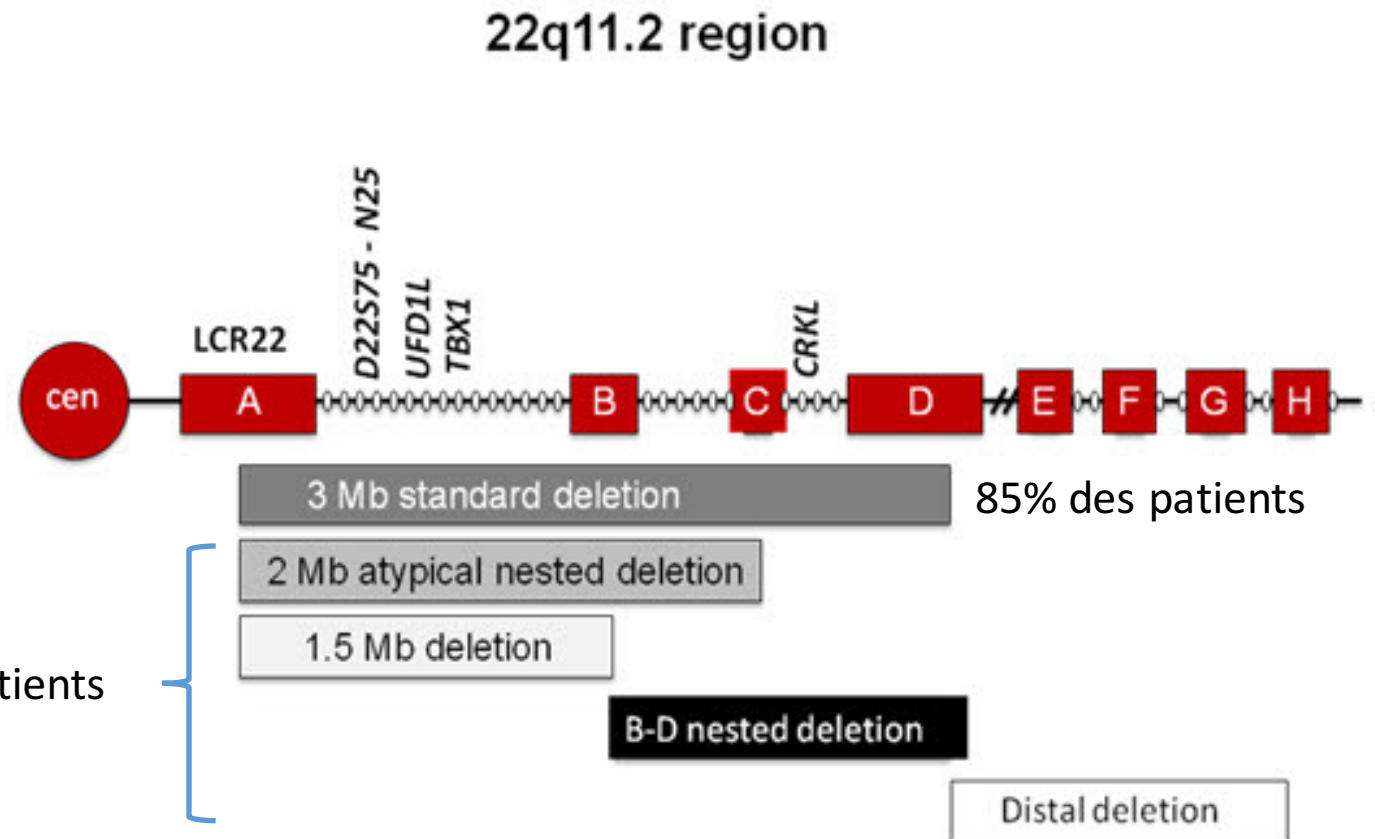
# Taille de la délétion ?

Entre 1.5 et 3 millions de nucléotides



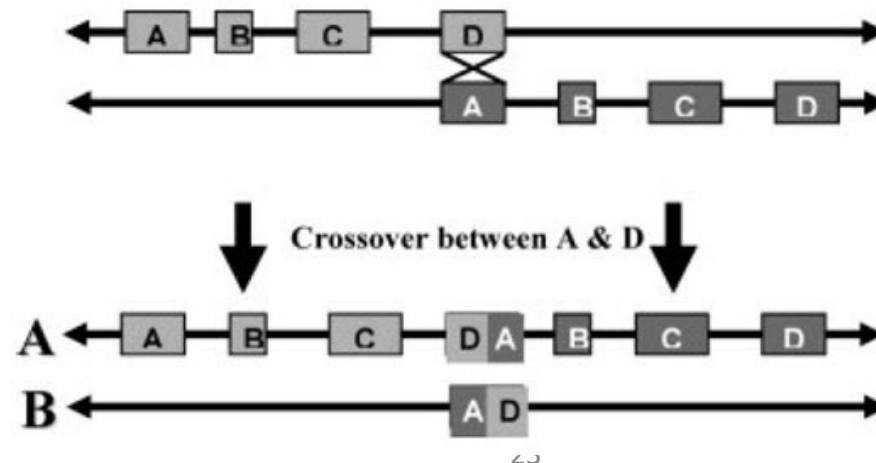
Chromosome 22  
Environ 12% de LCR  
Identiques à 99.7%

15% des patients



# Pourquoi la microdélétion 22q11 est-elle si fréquente ?

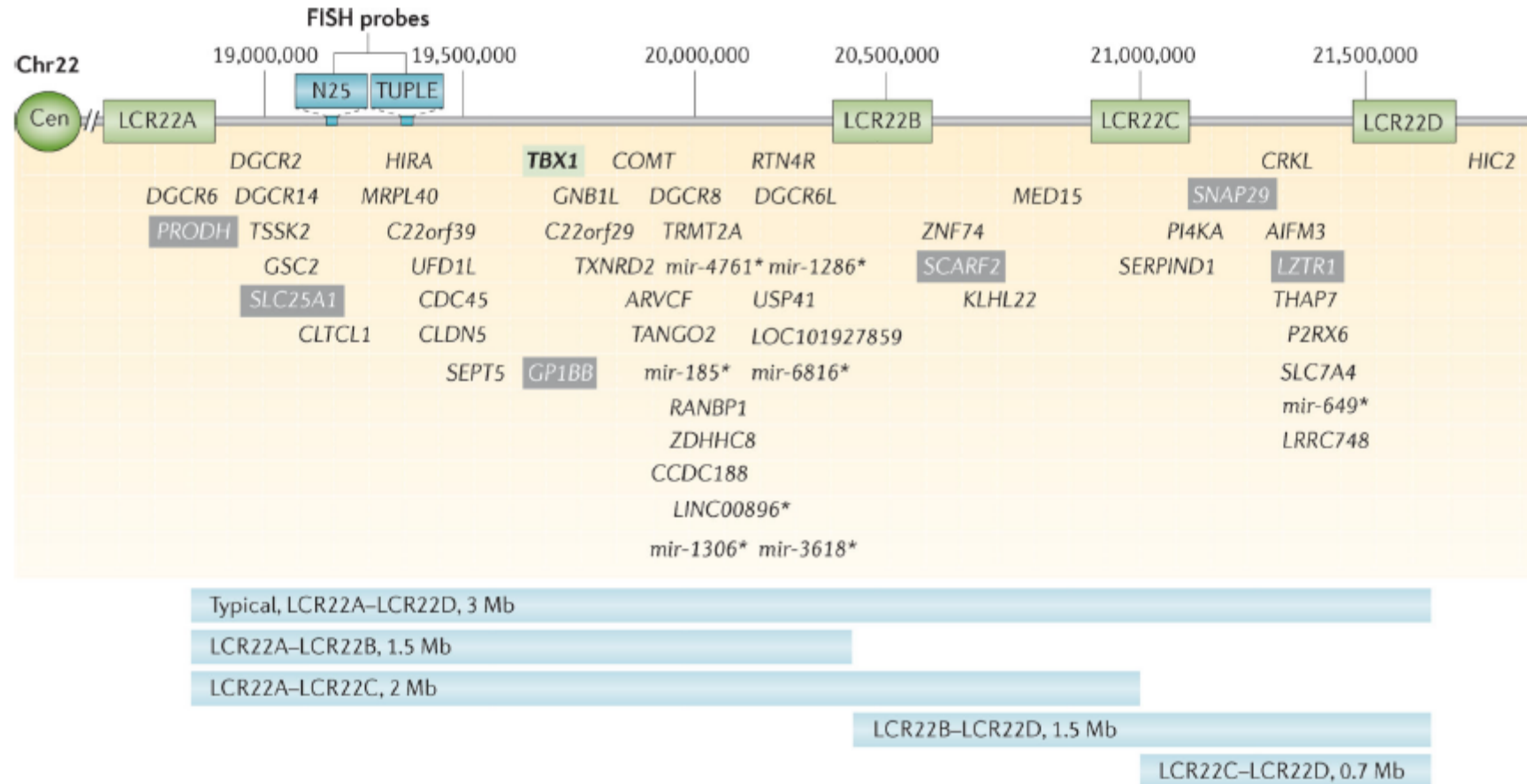
- A cause des LCRs
- On connaît encore mal la séquence des LCRs.
- Importance d'identifier cette séquence
  - Variabilité d'expression ?
  - Cela aurait-il un effet sur le risque d'avoir un enfant atteint ?





# Que contient la région 22q11 ?

## 22q11.2 deletion syndrome



Entre 30 et 46 gènes  
codant pour des  
protéines selon la taille  
de la délétion



# Questions ?

Comprendre pour pouvoir agir : prévenir et traiter

- Quel gène est responsable de quel symptôme ?
- Comment expliquer la variabilité d'expression ?  
Éléments prédictifs ?

# Outils à disposition

## **Etudes génétiques**

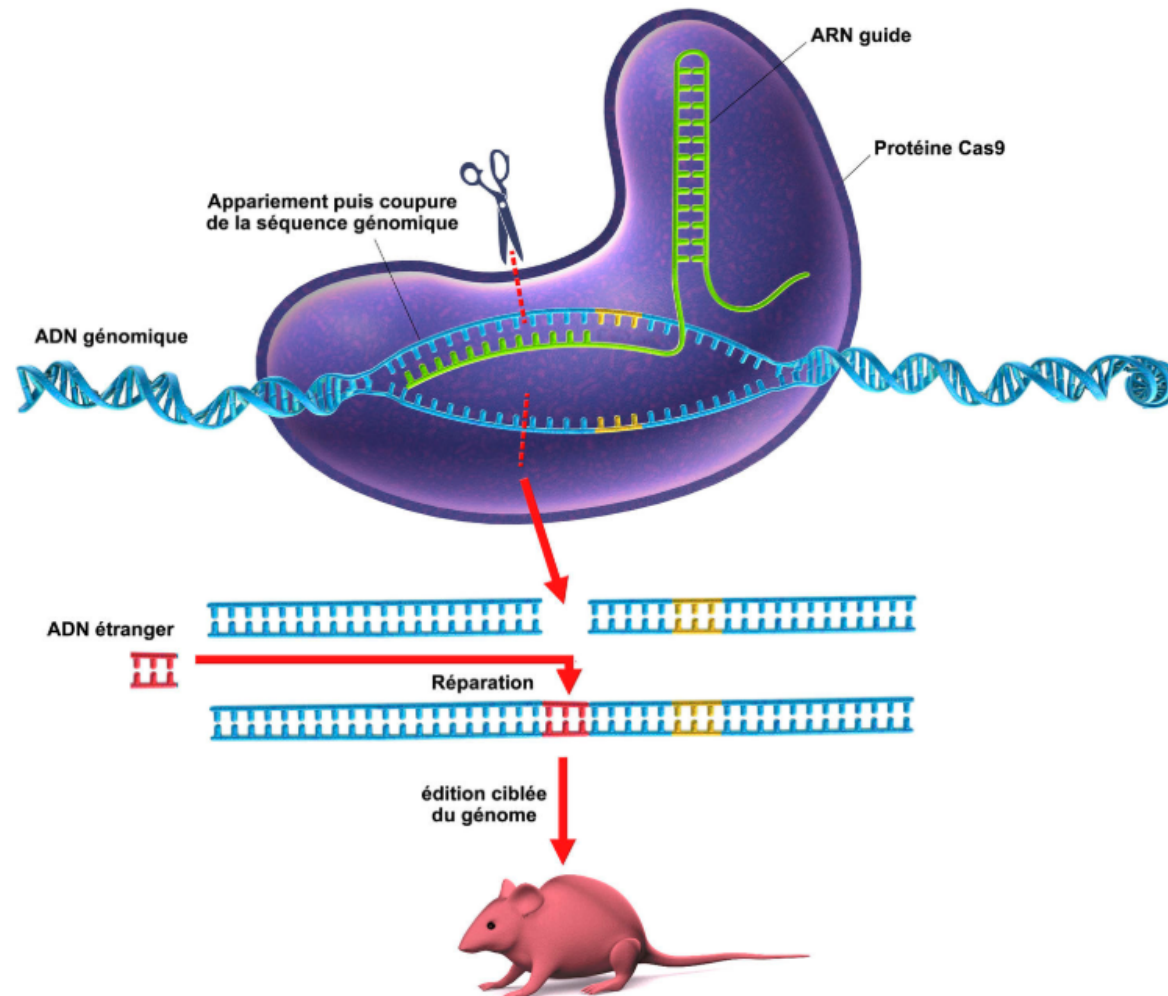
Modèles animaux  
Nouveaux outils  
d'editing du génome  
Séquençage à haut-  
débit

....

## **Etudes cliniques**

Cohorte de patients  
Sous-groupes en  
fonction du tableau  
clinique

# Modèles animaux : principes



Sont utiles parce que la plupart des gènes sont conservés et identiques entre l'humain et les modèles animaux.

# Quels modèles pour la microdélétion 22q11 ?

- Modèle murin
  - Mammifère avec anatomie développementale similaire à l'humain
  - Facile à gérer au laboratoire
- Autres modèles animaux : mouche, poisson-zèbre, ver
  - Moins chers que le modèle murin
  - Plus rapides

Jerome LA, Papaioannou VE. DiGeorge syndrome phenotype in mice mutant for the T-box gene *Tbx1*. Nat. Genet. 2001; 27:286–291. [PubMed: 11242110] By using mouse model approaches *Tbx1* was found to be required for craniofacial, thymus and parathyroid gland as well as cardiac development. This is a seminal paper in the field.

Guna A, Butcher NJ, Bassett AS. Comparative mapping of the 22q11.2 deletion region and the potential of simple model organisms. J. Neurodev. Disord. 2015; 7:18. [PubMed: 26137170]



# Quel gène est responsable de quel symptôme ?

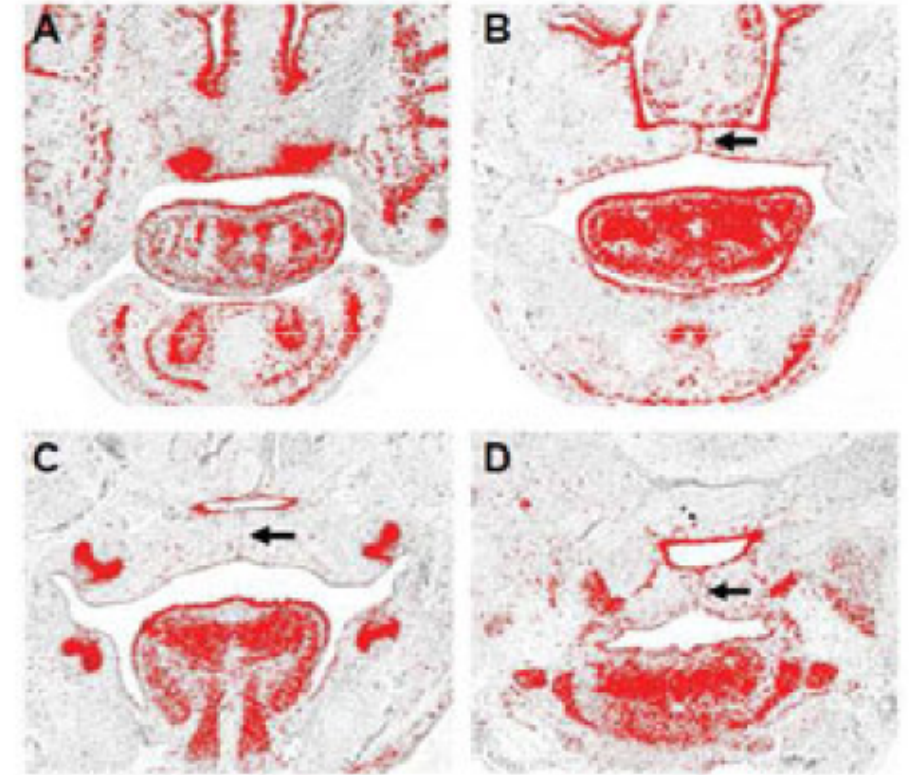
- Modèles animaux utiles pour l'étude anatomique, mais moins performants pour l'étude cognitive fine.
  - Malformation cardiaque : TBX1, UFD1L, CRKL
  - Fente : TBX1
  - Anomalies thymiques et parathyroïdes : TBX1

. Jerome LA, Papaioannou VE. DiGeorge syndrome phenotype in mice mutant for the T-box gene *Tbx1*. Nat. Genet. 2001; 27:286–291. [PubMed: 11242110] By using mouse model approaches *Tbx1* was found to be required for craniofacial, thymus and parathyroid gland as well as cardiac development. This is a seminal paper in the field.

30 Guna A, Butcher NJ, Bassett AS. Comparative mapping of the 22q11.2 deletion region and the potential of simple model organisms. J. Neurodev. Disord. 2015; 7:18. [PubMed: 26137170]

# TBX1

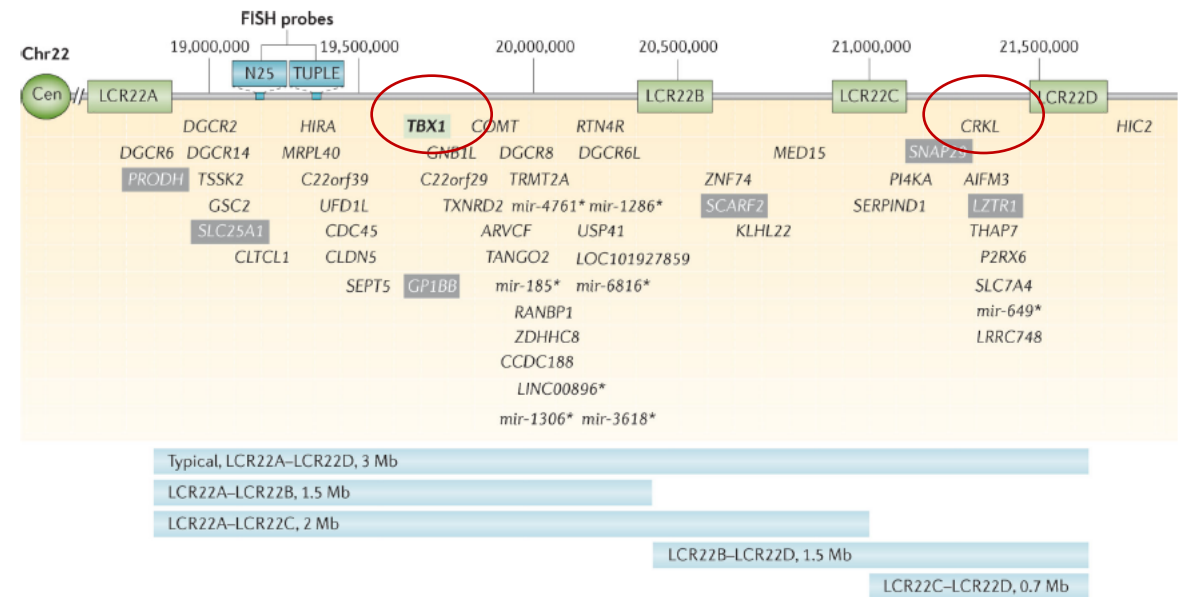
- Est exprimé dans les régions embryonnaires responsables de former la région crâniofaciale, le thymus, les parathyroïdes et l'arc aortique
- Ce gène est très sensible à un effet de dosage
- L'inactivation du gène chez la souris reproduit certains symptômes de microdélétion 22q11



**Fig. 3.** *Tbx1* expression in the craniofacial region of the developing mouse embryo at E14.5 (A-D). *Tbx1* is expressed in the incisor and molar tooth germs (A,C), epithelium of the nasal cavity (A,B), epithelium of the fused palatal shelves (B-D) including the midpalatal seam (arrowed) and the pharyngeal endoderm and mesoderm (D).

# TBX1

- Patients avec mutation dans *TBX1*
  - Tableau de microdélétion 22q11
  - Malformation cardiaque
- Mais n'explique pas tous les symptômes
- Et certains patients avec délétions atypiques qui n'empportent pas *TBX1* ont quand même des malformations cardiaques : effet en aval sur *CRKL* ?
- Les souris mutantes dans *CRKL* ont le même tableau clinique que celles mutantes dans *TBX1*



# UFD1L

## A Molecular Pathway a Genetic Basis for Cardiac and Craniofacial Defects

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Microdeletions of chromosome 22q11 are the most common genetic defects associated with cardiac and craniofacial anomalies in humans. A screen for mouse genes dependent on *dreher*, a transcription factor implicated in neural crest development, identified *Ufd1l*, which maps to human 22q11 and encodes a protein involved in degradation of ubiquitinated proteins. Mouse *Ufd1l* was specifically expressed in most tissues affected in patients with 22q11 deletion syndrome. The human *UFD1L* gene was deleted in all 182 patients studied with 22q11 deletion, and a smaller deletion of approximately 20 kilobases that removed exons 1 to 3 of *UFD1L* was found in one individual with features typical of 22q11 deletion syndrome. These data suggest that *UFD1L* haploinsufficiency contributes to the congenital heart and craniofacial defects seen in 22q11 deletion.

Concomitant heart defects (CHDs) are the most frequent feature of DiGeorge's Syndrome (DGS). Extensive murine, re-

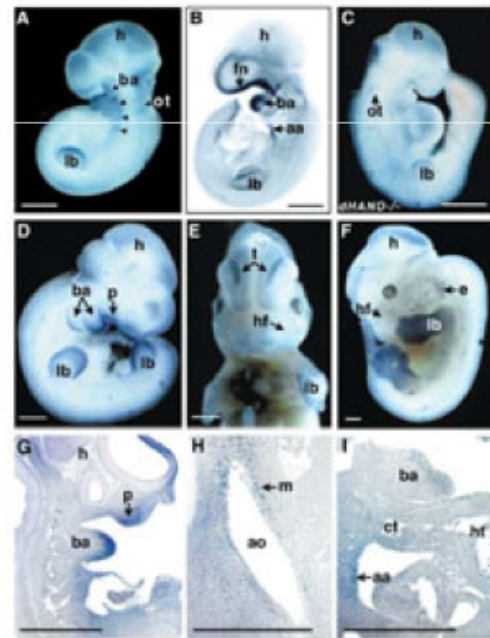
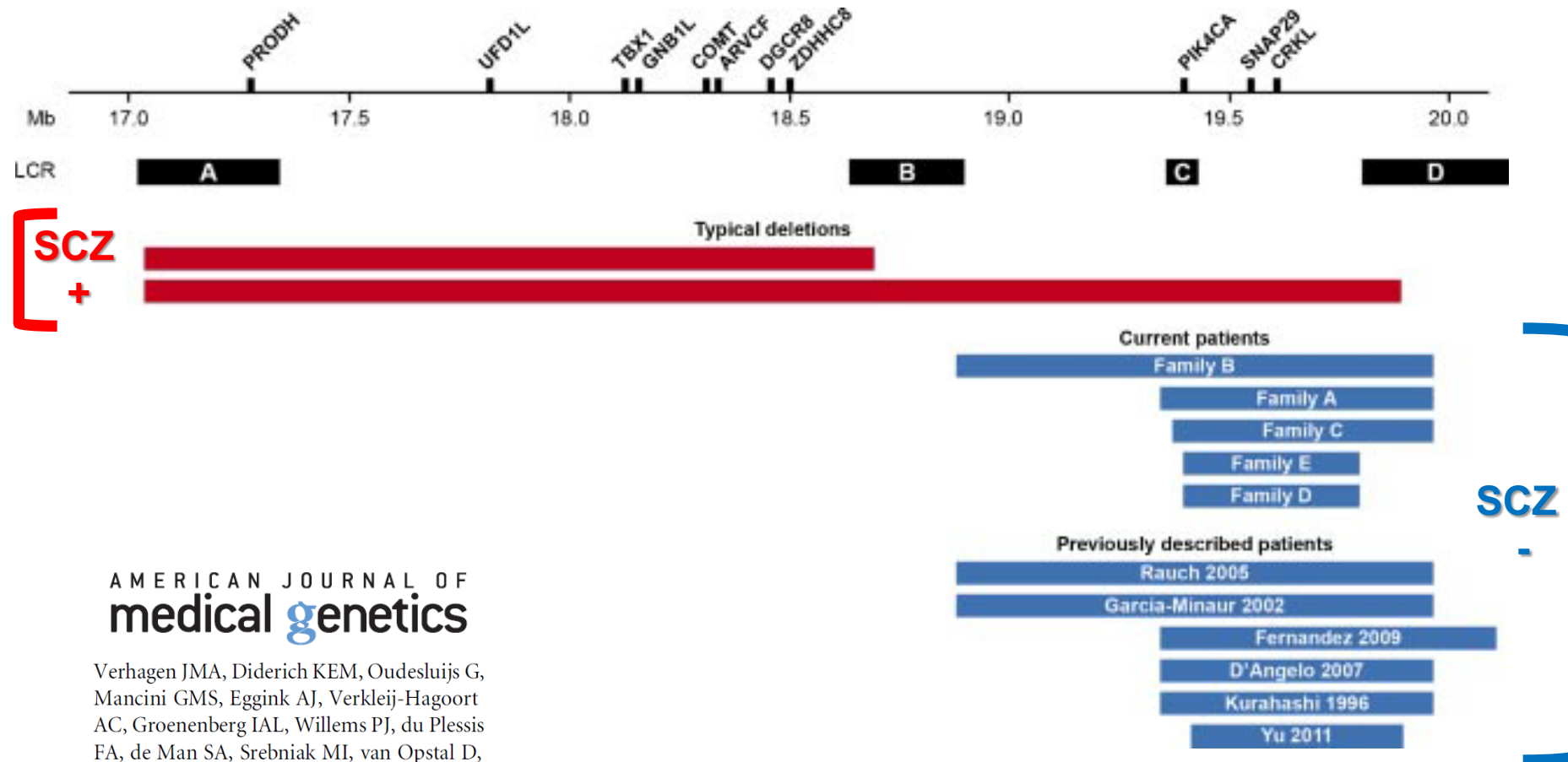


Fig. 2. Expression of *Ufd1l* in mouse embryos, detected by in situ hybridization. (A) Expression of *Ufd1l* in the branchial arches (ba), limb bud (lb), and otocyst (ot) was evident at E9.5 in a lateral view. Arrowheads mark first through fourth branchial arches. (B) Clearing of the embryo revealed expression of *Ufd1l* in the fourth aortic arch artery (aa), the branchial arch, and fronto-nasal (fn) region. (C) *Ufd1l* was also expressed in the branchial arch and aortic arch of *Ufd1l* mutant embryos. (D) *Ufd1l* was also expressed in the branchial arch and aortic arch of *Ufd1l* mutant embryos. (E) *Ufd1l* was also expressed in the branchial arch and aortic arch of *Ufd1l* mutant embryos. (F) *Ufd1l* was also expressed in the branchial arch and aortic arch of *Ufd1l* mutant embryos. (G) *Ufd1l* was also expressed in the branchial arch and aortic arch of *Ufd1l* mutant embryos. (H) *Ufd1l* was also expressed in the branchial arch and aortic arch of *Ufd1l* mutant embryos. (I) *Ufd1l* was also expressed in the branchial arch and aortic arch of *Ufd1l* mutant embryos.

# Quels sont les gènes impliqués dans le trouble développemental ou les symptômes psychiatriques ?

- Etudes en fonction du tissu d'expression de chaque gène
  - Complicé car la plupart des gènes de la microdélétion sont exprimés dans le cerveau
- Etudes selon la fonction des gènes
  - COMT
  - PRODH
  - GNB1L
  - PIK4CA

- Etudes en fonction de comparaison entre les patients



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Verhagen JMA, Diderich KEM, Oudesluijs G, Mancini GMS, Eggink AJ, Verkleij-Hagoort AC, Groenenberg IAL, Willems PJ, du Plessis FA, de Man SA, Srebniak MI, van Opstal D, Hulsman LOM, van Zutven LJCM, Wessels MW. 2012. Phenotypic variability of atypical 22q11.2 deletions not including *TBX1*.

Am J Med Genet Part A 158A:2412–2420.



# Comment s'explique la variabilité d'expression ?

LCR

Variants ponctuels sur  
l'autre chromosome 22

Epigénétique

Environnement



Variants ponctuels  
dans le reste du  
génom

CNV dans le reste du  
génom

Origine parentale  
Age parental

# Etude de cohortes de patients

- Sous-groupes en fonction du tableau clinique
  - Phénotypage extrêmement fin
  - Etudes radiologiques
  - Séquençage à haut-débit ou array-CGH très puissants

Mol Psychiatry. 2018 Jun 13. doi: 10.1038/s41380-018-0078-5. [Epub ahead of print]

**Large-scale mapping of cortical alterations in 22q11.2 deletion syndrome: Convergence with idiopathic psychosis and effects of deletion size.**

Psychol Med. 2018 Oct;48(14):2375-2383. doi: 10.1017/S0033291717003920. Epub 2018 Jan 17.

**Cortical morphology development in patients with 22q11.2 deletion syndrome at ultra-high risk of psychosis.**

Padula MC<sup>1</sup>, Schaer M<sup>1</sup>, Armando M<sup>1</sup>, Sandini C<sup>1</sup>, Zöller D<sup>1</sup>, Scariati E<sup>1</sup>, Schneider M<sup>1</sup>, Eliez S<sup>1</sup>.

The Danish 22q11 research initiative



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# Conclusions

- Condition très étudiée
  - Génétique
  - Clinique
- Modèles animaux
- Cohorte de patients
- Modèle pour l'étude de la schizophrénie (sans microdélétion 22q11)

# MERCI !!!!!

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## 22q11.2 deletion syndrome

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