Apparently balanced structural chromosome rearrangements (ABSCRs) and abnormal phenotype

I. Facts

II. Molecular basis of the phenomenon

I. Facts

- Live birth prevalence of ABSCRs is estimated around 0.8%-1%. 15-20 % of which occur de novo, and 80-85 % are inherited.

- Most individuals with ABSCRs have a normal phenotype. However, the risk for abnormalities exists. It is relatively low in inherited cases, but high in de novo cases (Table 1).

| TABLE 1: Patients with an apparently balanced chromosome rearrangement |
|-----------------------------|------------------|
| **Familial cases** | **Risk of an abnormal phenotype** |
| ascertained through | MR/MCA** | 10-15% |
| | sterility | 3% |
| **De novo cases** | 50% |

*Risk: proband excluded in familial cases

**MR: mental retardation, MCA: major congenital abnormalities

- De novo rearrangements represent a challenge in prenatal diagnosis given that the risk of malformations and learning disabilities is about 5-10%.

- In patients with an abnormal phenotype, ABSCRs host “cryptic” chromosomal rearrangements (more often deletions, rarely duplications), uncovered by molecular cytogenetics techniques, mainly the array CGH (Table 2).

| TABLE 2: Patients with an abnormal phenotype |
|-----------------------------|------------------|
| **Familial cases** | 25% |
| **De novo cases** | 33%* |

*In de novo cases with complex ABSCRs (with more than 3 breakpoints), imbalance was found in 90 %

- Conversely, patients with a normal phenotype and ABSCRs were found to carry no imbalance.

- The majority of de novo imbalances have a paternal chromosome origin.
- ABSCR breakpoints were compared in patients with normal and abnormal phenotype:
  No significant differences were found in GC contents, nor in the number of CpG islands, the number of
  genes, exons and genes disrupted, the number of segmental duplications and copy number variants in
  the 200 Kb window around and within the breakpoints.
  Only the number of breakpoints in G-bands versus R-bands was statistically significant (p < 0.01): patients with one or both breakpoints within R-bands had more often an abnormal phenotype.
  The proportion of gene disruption (at the breakpoints) was similar in patients with normal and
  abnormal phenotypes. However, genes implicated in biological processes of the nervous system,
  genes for transcription/regulation of transcription or signal transduction/signalling, and genes
  associated with known Mendelian diseases were more frequently disrupted in patients with an
  abnormal phenotype.

II. Molecular basis of the phenomenon

- A molecular analysis of 18 breakpoints in patients with an abnormal phenotype revealed 11
  microdeletions (deletions of 1 to 16 bp), 6 insertions (2-17 bp), 2 duplications (3 and 13 bp) and 3
  multiples sequences changes.
- The oligonucleotide composition of the breakpoints was studied. Alternating purine-pyrimidine
  sequences, polypurine or polypyrimidine tracts were found to be significantly overrepresented in
  the vicinity of deletions and translocation breakpoints junctions.
- Such sequences are prone to form non B-DNA configurations (triplex, tetraplex, cruciform, slipped or
  Z-DNA). They are detected for example near the breakpoints of the recurrent t(11;22).
- These structures are likely to slow down or arrest the replication fork processing. Serial steps of intra
  and/or inter chromosomal replication slippage can explain complex genome rearrangements.
- The initial breakage event involved in many constitutional and somatic translocations is thought to be
  the result of stalled DNA replications.
- A single DNA strand lesion -rather than a double stand break- as the initiating damage that causes
  replication fork stalling, may be the mechanism involved in this process.

Fig 1: Secundary structure at the breakpoint 8q24.13 in a t(8;22) translocation (from Gotter AL et coll., Genome Res 2007,17(4),470), Cold Spring Harbor Laboratory Press.
Fig 2: Numerous loci replicate at a given time, possibly favoring non-B DNA structure formation.

Contributor(s)
Written 03-2009 Jean Marie Rival
Medical genetic service - CHU Nantes, France

Citation
This paper should be referenced as such:
Rival JM. Apparently balanced structural chromosome rearrangements (ABSCRs) and abnormal phenotype. Atlas Genet Cytogenet Oncol Haematol, March 2009.
URL: http://AtlasGeneticsOncology.org/Educ/BalancedRearAbnorID30071ES.html
© Atlas of Genetics and Cytogenetics in Oncology and Haematology