# Towards a decision-making support tool for the identification of chromosome structural abnormalities in conventional cytogenetics: Development of a prototype for the detection of del(5q) deletion based on artificial intelligence.


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# Protocol CHROMAI

## Automatic detection of chromosome abnormalities in hematological malignancies by artificial intelligence

**Laboratory of chromosome genetics of Brest University Hospital**

**ISEN- Engineer university: Expertise in image analysis and artificial intelligence**

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# Protocol CHROMAI

**Our long term aims** are to:

- Identify chromosomes with abnormalities (in particular structural ones),
- Automatically annotate the abnormality.

Using artificial intelligence, with training on karyogram images.

# Artificial intelligence

## DATASET (INPUT)

- Size of the dataset (the more, the better)
- Possibility to increase the size
  = data augmentation
- Annotated data

Ex: in this project : chromosome images

## TRAINING

Convolutional Neural Network : CNNs
- many exist
- must be tested for the performance

## VALIDATION

5-cross validation
Metrics: specificity, sensitivity, accuracy
*F1*-score, etc.

# Protocol CHROMAI

**State-of-the-art :** Deep learning on recurrent chromosome abnormalities

- One publication on trisomy
- Two publications on t(9;22) (found in CML) (Wang et al, 2010 ; Pravalphruekul et al,2020 ):
  comparison to a reference template or on t(9;22)
  90- 97% of *F1*-score (measure that reflects both specificity and sensitivity)
- Cox *et al.* (*Bioinformatics, 2021)*: on 13 different abnormalities
  94% of *F1*-score
  CNN: VGG and ResNet
  dataset: 13-146 images; test on 6 – 10 images

One of our challenges (secondary question): Is it possible to identify an abnormality without training on this specific one? We raise the issue of the training on all possible abnormalities: frequent recurrent, rare recurrent and non recurrent ones.

# The originality of our approach

## cytogenetics

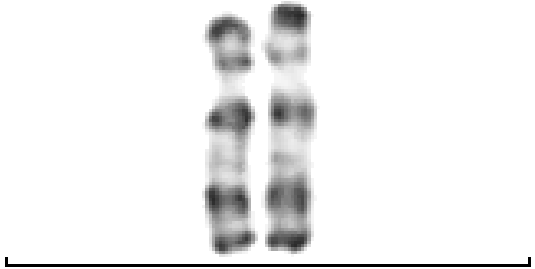
- Homologous chromosomes rarely display similar abnormalities
- To detect any change in the banding pattern between the two chromosomes of a pair.

## computer science

- Comparison of homologous chromosomes
- Use of a Siamese architecture that allows comparison

To train a network to identify identity/dissimilarity between homologous chromosomes

To train a network to identify identity/dissimilarity between homologous chromosomes



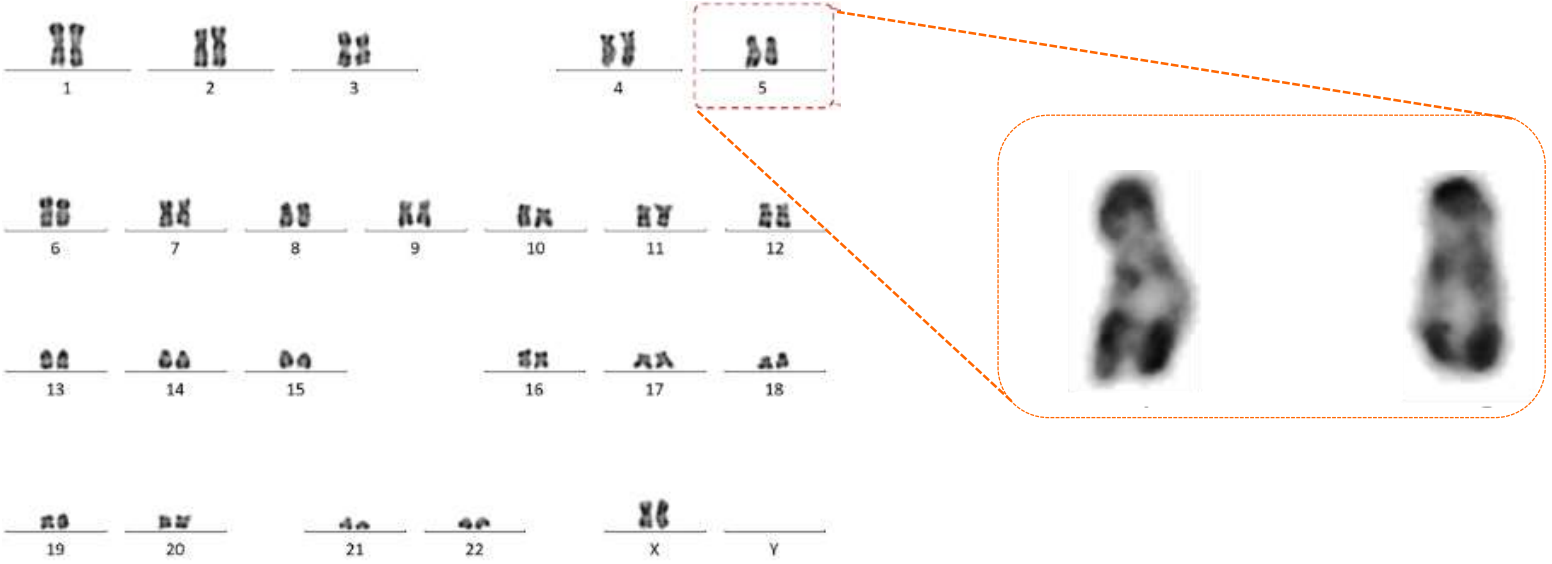
5

Normal pair

5

Deletion Del(5q)

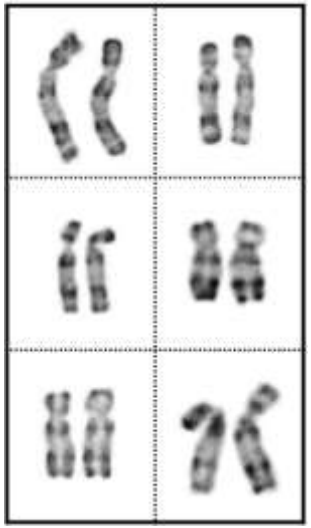
# Proof of concept on del(5q)




**Are those homologous chromosomes identical or not ?**

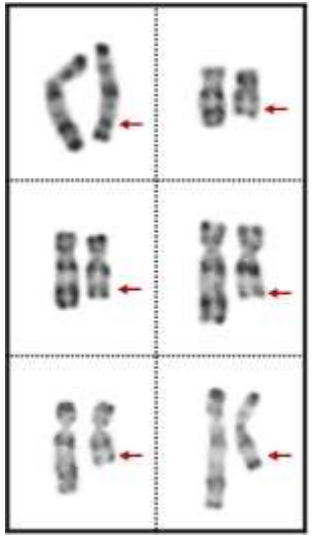
# Dataset

Normal pairs: **722** images



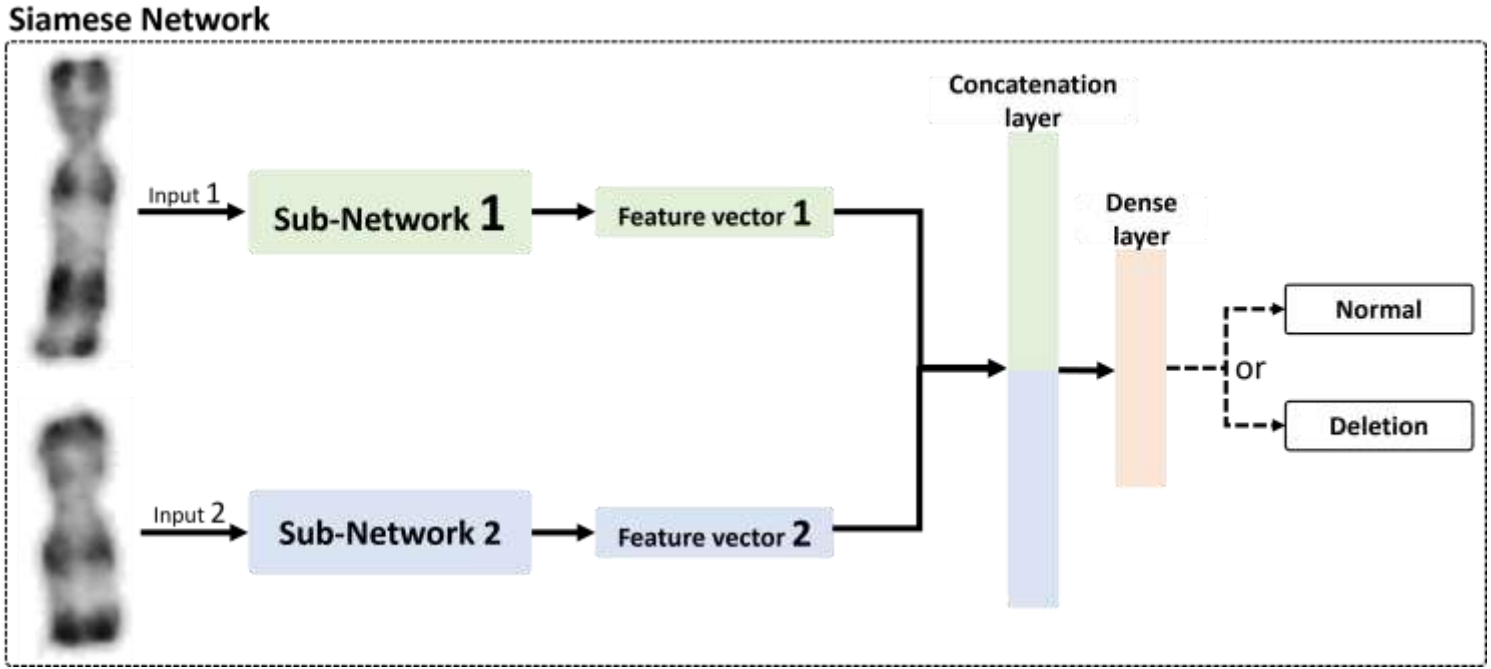
normal

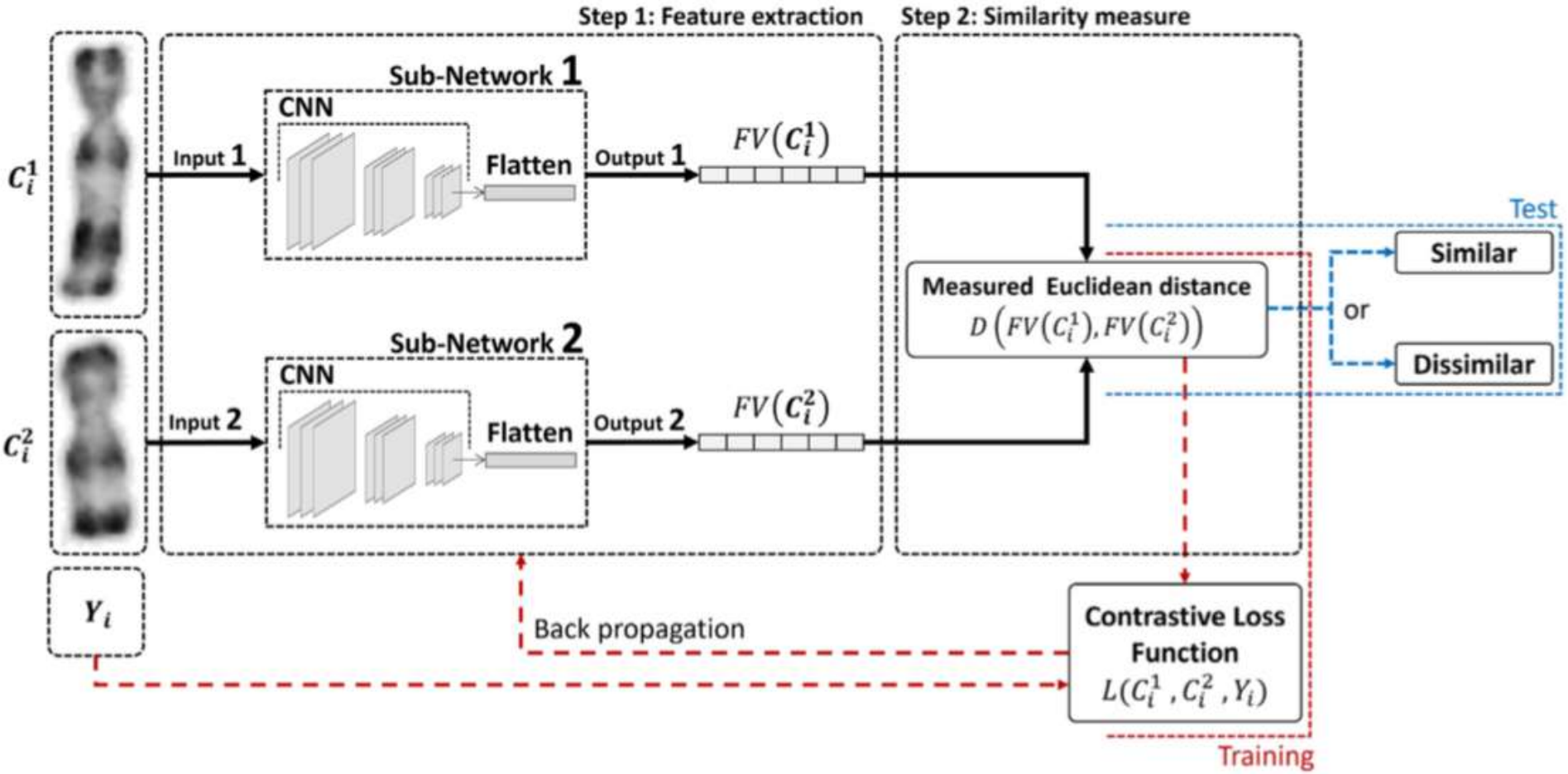
Pairs with a deletion del(5q) : **208** images



deletion

# Pipeline


Siamese Network
Input 1
Sub-Network 1
Feature vector 1
Input 2
Sub-Network 2
Feature vector 2
Concatenation layer
Dense layer
Normal
or
Deletion


Step 1: Feature extraction
Step 2: Similarity measure
$C_i^1$
$C_i^2$
$Y_i$
Sub-Network 1
CNN
Input 1
Flatten
Output 1
$FV(C_i^1)$
Sub-Network 2
CNN
Input 2
Flatten
Output 2
$FV(C_i^2)$
Measured Euclidean distance
$D\left(FV(C_i^1), FV(C_i^2)\right)$
Test
Similar
or
Dissimilar
Back propagation
Contrastive Loss Function
$L(C_i^1, C_i^2, Y_i)$
Training

# Methods

- Dataset:

- separated into 5 sub-datasets of equivalent size for 5-cross validation
- without data augmentation
- with data augmentation : undersampling / oversampling

- Test 7 CNNs with :
    - Variation of parameter *m* (margin)

# Results for del(5q)

**Sensitivity:** how well the model can predict a **deletion** in the pair of homologous chromosomes

**Specificity:** how well the model can predict a pair of **normal** homologous chromosomes

n=5 experiments

| CNN | *m* | ACCURACY (%) | SENSITIVITY (%) | SPECIFICITY (%) | $F_1$-SCORE (%) | *p*-VALUE ($F_1$-SCORE) |
|---|---|---|---|---|---|---|
| DENSENET169 | 1 | $97,77(\pm0,39)$ | $96,04(\pm3,50)$ | $98,28(\pm0,82)$ | $95,00(\pm0,63)$ | $2.310^{-2}$ |
| XCEPTION | 10 | $95,20(\pm5,07)$ | $87,02(\pm13,64)$ | $98,98(\pm0,99)$ | $90,91(\pm7,92)$ | $2.810^{-2}$ |
| VGG19 | 1 | $97,99(\pm0,49)$ | $96,45(\pm2,84)$ | $98,42(\pm0,33)$ | $95,45(\pm1,17)$ | $1.510^{-1}$ *(ns)* |
| MOBILENET | 1 | $98,44(\pm0,46)$ | $98,97(\pm1,41)$ | $98,30(\pm0,81)$ | $96,40(\pm1,11)$ | $1.910^{-1}$ *(ns)* |
| RESNET101 | 1 | $98,32(\pm0,79)$ | $97,92(\pm2,17)$ | $98,43(\pm0,61)$ | $96,19(\pm1,81)$ | $4.310^{-1}$ *(ns)* |
| INCEPTIONRESNETV2 | 1 | $98,77(\pm0,73)$ | $99,47(\pm1,18)$ | $98,59(\pm0,86)$ | $97,14(\pm1,77)$ | $6.010^{-1}$ *(ns)* |
| INCEPTIONV3 | 1 | $98,88(\pm0,56)$ | $99,51(\pm1,09)$ | $98,72(\pm0,93)$ | $97,48(\pm1,23)$ | $7.410^{-1}$ *(ns)* |
| INCEPTIONRESNETV2 | 10 | $98,66(\pm0,63)$ | $97,58(\pm2,42)$ | $99,00(\pm0,64)$ | $97,01(\pm1,32)$ | – |

Results obtained with different CNN and *m* margin in 5-cross validation tests for detection of del(5q) after oversampling data augmentation

# Comparison with top-performing models

Adaptation of the table from Cox et al, Bioinformatics 2021

**Table 5.** Comparison of our top-performing model's results on the test set to state-of-the-art methods

| Research study | Dataset size | Number of classes | | Normal chromosomes only | | Normal and abnormal chromosomes | |
|---|---|---|---|---|---|---|---|
| | | Normal | Abnormal | *F*1 | Acc | *F*1 | Acc |
| Sharma et al., 2018 | 5474 images | 24 | 0 | — | 90.42% | — | — |
| Swati et al., 2018 | 5474 images | 24 | 0 | — | 92.36% | — | — |
| Qin *et al.* (2019) | 87 831 images | 24 | 0 | 98.7%[a] | 98.9%[a] | — | — |
| Xie *et al.* (2019) | 5000 images | 24 | 0 | 95.6% | 95.7% | — | — |
| Yan *et al.* (2019) | 800 images | 2 | 2 | — | — | — | 97.5%[b] |
| Pravalphruekul *et al.* (2020) | 2600 images | 24 | 2 | — | — | — | 79% |
| Cox | 4548 images | 24 | 15 | 96.4% | 96.6% | 94.0% | 93.4% |
| ours | | 4 | 2 | | | 97,48 % [a] | 98,88% [a] |

*Note*: Our model is the first to classify all normal chromosomes and multiple structural abnormalities with efficiency comparable to models trained on only normal chromosomes. Compared to models trained to classify structurally abnormal chromosomes, our model performs remarkably better despite being tasked with more potential classes from which to classify.

[a]Results are from a 5-fold cross validation set.

[b]Results from a validation set (opposed to a test set).

# Performance on additional abnormalities inv(3)
# Without training on chr3 and inv(3)
# Training on chr5 and del(5q)

| | | Without data augmentation | Oversampling data augmentation | undersampling data augmentation |
|---|---|---|---|---|
| | INVERSION INV(3) / NORMAL 3 | W/ODA XCEPTION ($m = 5$) | ODA INCEPTIONRESNETV2 ($m = 10$) | UDA INCEPTIONRESNETV2 ($m = 1$) |
| | | WITH TRAINING ONLY ON DEL(5Q) DELETION DATASET | | |
| | ACCURACY (%) | 80.00($\pm$3.18) | 76.59($\pm$4.05) | 68.25($\pm$13.66) |
| (Inv) | SENSITIVITY (%) | 46.32($\pm$25.37) | 30.10($\pm$6.63) | 25.20($\pm$6.05) |
| (normal) | SPECIFICITY (%) | 82.97($\pm$1.12) | 82.19($\pm$0.33) | 82.01($\pm$1.88) |
| | $F_1$-SCORE (%) | 22.9($\pm$8.59) | 19.41($\pm$2.61) | 24.47($\pm$5.21) |
| | MCC(1 is the best) | 0.17($\pm$0.13) | 0.09($\pm$0.04) | 0.06($\pm$0.08) |

**Not very encouraging !!!**

# Performance on additional abnormalities inv(3) with specific training on chromosome 3 and inv(3)

| | Without data augmentation | Oversampling data augmentation | undersampling data augmentation |
|---|---|---|---|
| INVERSION INV(3) / NORMAL 3 | W/ODA | ODA | UDA |
| | XCEPTION ($m = 5$) | INCEPTIONRESNETV2 ($m = 10$) | INCEPTIONRESNETV2 ($m = 1$) |
| | WITH TRAINING ON INV(3) INVERSION DATASET | | |
| ACCURACY (%) | 98.65($\pm$2.03) | 96.41($\pm$3.02) | 81.25($\pm$20.52) |
| SENSITIVITY (%) | 100.00($\pm$0.00) | 94.03($\pm$8.61) | 63.28($\pm$30.43) |
| SPECIFICITY (%) | 98.46($\pm$2.26) | 98.00($\pm$3.19) | 100.00($\pm$0.00) |
| $F_1$-SCORE (%) | 94.82($\pm$8.67) | 88.91($\pm$12.97) | 74.05($\pm$23.38) |
| MCC (1 is the best) | 0.95($\pm$0.09) | 0.88($\pm$0.12) | 0.69($\pm$0.28) |

(Inv)
(normal)

**We achieve 94,82% of *F1*-score.**
**It is very encouraging for generalization of our pipeline on different abnormalities.**

# Conclusion

**Goal:** Detecting structural abnormalities in pairs of **homologous** chromosomes :

- Successful detection of deletion del(5q) from chromosome 5
  - with Xception: 97.5% *F1*-score
  - with InceptionResNetV2: 97.01% *F1*-score
- Highly performing Siamese architecture
- Importance of optimizing the margin *m*

- Is also successful on other abnormalities : here showed on inv(3)

The proposed Siamese model is a potential solution to generalize the identification of all types and categories of structural chromosome abnormalities.

# Conclusion

Our code is publicly available at:
https://github.com/MEABECHAR/ ChromosomeSiameseAD

**Future works:**

- Generation of abnormalities from normal karyotype by image treatment for train less frequent abnormalities and increase the potential of our pipeline.
- Validate as a decision-support tool and clarify its limits.

## Laboratory of chromosome genetics of Brest University Hospital

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