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Genotype-phenotype correlations for the Lissencephaly spectrum of eight children

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INTRODUCTION

Lissencephaly is a neuronal migration disorder leading to paucity or absence of cerebral gyration, along with abnormal histological architecture of the cerebral cortex. *LIS1* and *DCX* were initially identified as the causative genes of this disorder. We report a clinical and molecular characterization of eight children with common clinical features.

METHODS

- **Cytogenetic tool:** R-band Karyotype, Fluorescent *In Situ* Hybridization (FISH), Array Comparative Genomic Hybridization (array CGH)
- **Molecular tool:** Next Generation Sequencing (target capture of 189 genes in correlation with cortical malformation)

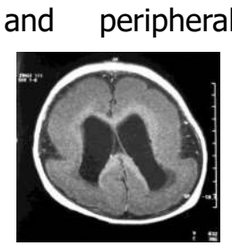
RESULTS

➢ Clinical and genetic characterization of patients with deletion or mutation of *LIS1* gene

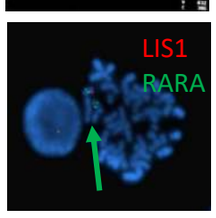
Patient 1

✓ Psychomotor delay, axial and peripheral hypotonia

✓ **IRM:** diffuse agyria



➢ **FISH** shows no hybridization to chromosome 17 using the *LIS1* specific probe on 17p13.3

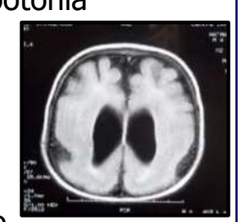


46,XX,ish del(17p13.3)(*LIS11)**

Patient 2

✓ Dysmorphic features, epilepsy, hypotonia

✓ **IRM:** posterior agyria, anterior pachygyria



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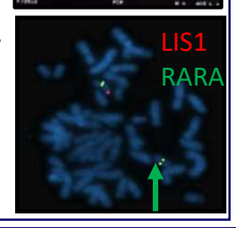
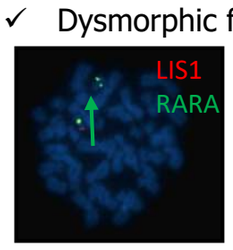


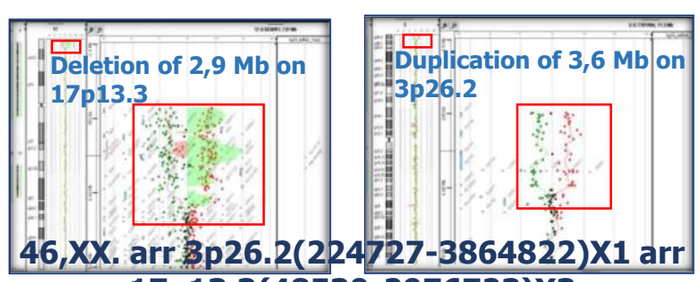
46,XY,ish del(17p13.3)(*LIS11)**

Patient 3

✓ Dysmorphic features, axial hypotonia



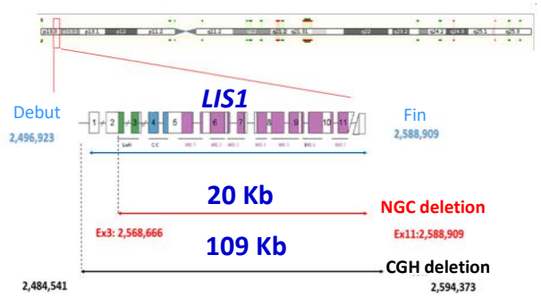
46,XX,der(17)t(3;17)(p26.2;p13.3)mat



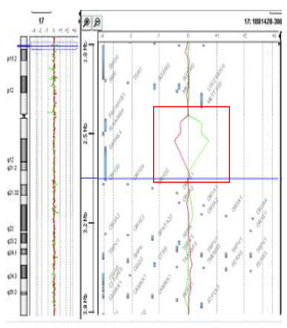
46,XX. arr 3p26.2(224727-3864822)X1 arr 17p13.3(48539-2976723)X3

Patient 4

✓ **IRM:** Agyria



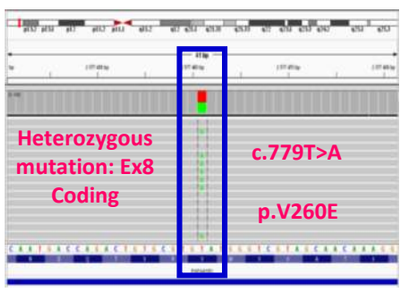
➢ **Capture target** shows a deletion in the *PAFAH1B1* gene between exon 3 up to exon 11



➢ **Array CGH analysis** confirmed this deletion and estimated the loss of at least 109 Kb on 17p13.3

Patient 5

✓ **IRM:** Lissencephaly



➢ **Capture target** shows a novel heterozgous missence mutation in the exon 8 of the *PAFAH1B1* gene

➢ **Sanger** sequencing shows De novo mutation in the *PAFAH1B1* gene

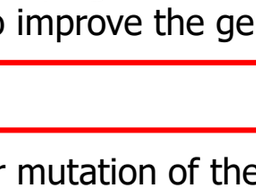
➢ Clinical and genetic characterization of patients with deletion or mutation of *DCX* gene

Patient 1

➢ **IRM:** Lissencephaly

➢ **Capture target** shows a deletion of all exon in the *DCX* gene

➢ Deletion confirmed by **FISH**



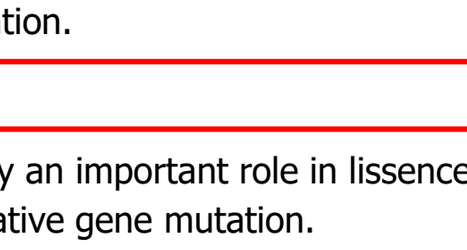
46,XY,ish del(Xq23)(*DCX*--)

Patient 2

➢ **IRM:** Lissencephaly

➢ **Capture target** shows a hemizygous missence mutation in the exon 2 of the *DCX* gene

➢ **Sanger** sequencing shows mutation inherited from a mother



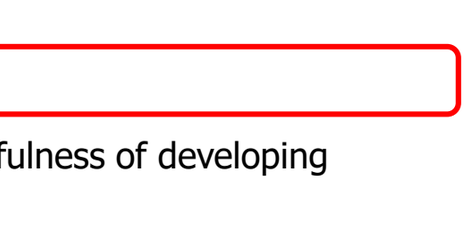
p. F146L c.436T>C Ex2

Patient 3

➢ **IRM:** Lissencephaly

➢ **Capture target** shows a hemizygous missence mutation in the exon 3 of the DCX gene

➢ **Sanger** sequencing shows De novo hemizygote mutation in the *DCX* gene



p.G304R c.910G>C

DISCUSSION

Lissencephaly is the most common neuronal migration disorder. The heterogeneity of the associated genes to lissencephaly has historically made it difficult to determine the specific etiology. Nevertheless, deletion or mutation of *LIS1* and *DCX* are the major candidate genes. *DCX* gene maps to chromosome Xq22.3-q23 and encodes a protein involved in microtubules stabilization. Deletions or mutations in *DCX* gene are associated with classical lissencephaly in males, whereas subcortical band heterotopia is observed about 10 times more frequently in females. Besides, males with *DCX* mutations have a gradient with anterior more severe than posterior. While, the *PAFAH1B1* gene maps to chromosome 17p13.3 and encodes platelet-activating factor acetylhydrolase isoform 1B α subunit and it is involved in a signal transduction pathway that is crucial for cerebral development. About 60% of patients with lissencephaly carry chromosome abnormalities or mutations in the *LIS1* gene. In fact, *LIS1* deletions extending from single-exon deletions to deletions of the entire coding region caused a more sever phenotype than missense mutation. Besides, *LIS1* mutation produces a gradient with posterior more severe than anterior. To date, mutation in the exon 8 of *PAFAH1B1* gene, and mutations in the exon 2 and 3 of *DCX* gene were identified for the first time and it is reported as deleterious and responsible mutation for the phenotypes of patients. The same applies for the others deletions which were reported as responsible deletion for the phenotypes of patients.

The combination of molecular cytogenetic methods and next generation sequencing contributes to further definition of the molecular characteristics associated with lissencephaly to improve the genotype-phenotype correlation.

CONCLUSION

Our data shows that deletion or mutation of the *LIS1* and *DCX* genes play an important role in lissencephaly, and spotlight the usefulness of developing approaches and methods for detection of a large number of known causative gene mutation.