

aCGH may be useful in Case of Dominant Disorders Known to be Caused by Gene Mutations: Two Case Reports

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Abstract

We describe two cases where clinical diagnoses were carried out (Rett syndrome-like and Nicolaides-Baraitser syndrome) with no identified mutation respectively in the *CDKL5* and the *SMARCA2* genes. Conversely a chromosomal microdeletion with contiguous deletion of a part of these two genes was found by arrayCGH in each corresponding case. The aim of this report is then to highlight the possible implication of chromosomal microdeletions with contiguous gene deletions in dominant pathologies where no mutation is found in the causative gene.

Keywords aCGH; Dominant Mutation; Chromosomal Microdeletion

Case Reports

In case of suspicion of rare dominant syndromes and when the mutated gene has already been identified, most of the clinicians ask for molecular biology to find the causal mutation. We had two cases where clinical diagnoses were carried out (Rett syndrome-like and Nicolaides-Baraitser syndrome) with no identified mutation respectively in the *CDKL5* and the *SMARCA2* genes. Conversely a chromosomal microdeletion with contiguous deletion of a part of these two genes was found by aCGH (array Comparative Genomics Hybridation) in each corresponding case.

Mutations in cyclin-dependent kinase-like 5 gene (*CDKL5*) also known as serine-threonine kinase 9 gene (*STK9*) located in Xp22, have been described to cause an early infantile epileptic encephalopathy 2 (EIEE2; OMIM#300672). This rare encephalopathy consists of a severe early onset seizure disorder with a phenotype overlapping with that of Rett syndrome and X-linked infantile spasms. The implication of *CDKL5* gene in this pathology was first found in two patients carrier of an apparently de novo balanced X;autosome translocation disrupting the *CDKL5* gene [1]. Many cases and many reviews have been reported since then [2,3] and the *CDKL5*-linked encephalopathy is now well known by neuropediatricians. We report a case where molecular analysis of the *CDKL5* gene was performed in a 2-year-old female presenting clinical feature suggestive of *CDKL5* mutations, consisting of early drug-resistant spasms and partial seizures with generalized hypotonia. No mutation was found. Then aCGH using Nimblegen Whole Genome tiling CGX 135K (hg18) showed a de novo 99 kb deletion in Xp22.13 confirmed by quantitative PCR. This

chromosomal microdeletion comprises the proximal part of the *CDKL5* gene, and explains the clinical findings.

Nicolaides-Baraitser syndrome (NCBRS) was first described in 1993 by pediatric neurologist Paola Nicolaides and clinical geneticist Michael Baraitser [4]. It is a distinct and recognizable entity (OMIM#601358) probably underdiagnosed until now. Main clinical features are severe mental retardation with absent or limited speech, seizures, short stature, sparse hair, typical facial characteristics, brachydactyly, prominent finger joints and broad distal phalanges [5]. The causative mutation was recently identified in the *SMARCA2* gene located in 9p24 and encoding the core catalytic unit of the SWI/SNF ATP-dependent chromatin remodeling complex involved in the regulation of gene transcription [6]. The *SMARCA2* gene was analyzed in one of our patient, a 3-year-old male presenting with delayed development, hypotrophy, sparse hair, dysmorphic features associating down slant palpebral fissures, prominent eyelashes and upturned nasal tip suggestive of NCBRS. No abnormality was found in the gene sequence, and it was suggested to study the other genes implicated in the SWI/SNF complex. In the meantime, aCGH using Nimblegen Whole Genome CGX 135K (hg18) led to diagnose a *de novo* 85 Kb interstitial deletion in 9p24.3 confirmed by quantitative PCR. This chromosomal microdeletion encompasses a part of the *SMARCA2* gene, giving rise to the pathology.

In both described cases, the clinical findings led to the diagnosis that failed to be confirmed by molecular analysis of the causative genes, with no found mutation. Surprisingly instead of mutation in the causative genes, a chromosomal microdeletion was diagnosed with contiguous gene deletion. Interestingly some similar findings have been published recently in two cases of Rubinstein-Taybi syndrome (RSTS, OMIM#180849) caused by mutations of CREB-binding protein (*CREBBP*) gene located in 16p13.3: in the first one, a *de novo* 120 Kb microdeletion on the short arm of chromosome 16 was identified by

aCGH in a 3-year-old Malaysian Chinese girl with features suggestive of RSTS [7]; in the second case, a de novo reciprocal translocation: t(1;16)(p36.2;p13.3) with genomic deletions in both 1p36.2 and 16p13.3 was diagnosed in a 3-month-old boy presenting typical phenotype of RSTS [8].

Conclusions

Regarding these cases, the part of chromosomal microdeletions with contiguous gene deletions might be underestimated in dominant pathologies where no mutation is found in the causative gene. But it seems also important for clinicians and molecular biologists to keep in mind that the microdeletions are just ones example of non-single mutation changes in suspected genes that can lead to inherited diseases. For example it has been recently found for the acetylcholinesterase (AChE) gene that epigenetic changes in the promoter regions may occur [9] and that microRNAs (miR-608) may target a specific AChE allele [10]. Taken together these findings illustrate that absence of mutation in the causative gene of a rare dominant disease does not mean that this gene is not implicated in the pathology.

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