Role of Phosphoinositide-Specific Phospholipase C η 2 in Isolated and Syndromic Mental Retardation

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Key Words

Mental retardation • 1p36 deletion syndrome • Phospholipase C η 2 • Signaling

Abstract

Deletions in the distal region of the short arm of chromosome 1 (1p36) are widely diffuse, both as somatic abnormalities in tumors and as constitutive in the congenital 1p36 deletion syndrome. The deletion size varies from 1.5 to 10 Mb, with common breakpoints located from 1p36.13 to 1p36.33. Patients bearing constitutional deletion of a smaller region, 1p36.3, present with a number of features, including mental retardation. The gene *PLCH2*, codifying for the phosphoinositide-specific phospholipase C (PI-PLC) η 2, maps on the 1p36.32 region. PI-PLC η 2, expressed in the brain after birth, is a key enzyme in cellular calcium mobilization. In the brain, calcium plays a role in axon growth and retraction, growth cone guidance, synapse formation, and responses to various neurotransmitters. For its role in the nervous system, PI-PLC η 2 might be a putative candidate gene for the neurodevelopmental delay observed in patients bearing 1p36.3 deletions.

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Introduction

Mental retardation (MR) affects 2–3% of the population, but its causes remain unexplained in 40% of the cases. Subtle telomeric rearrangements are responsible for about 1% of MR [1]. Deletions in the distal region of the short arm of chromosome 1 (1p36) are widely diffuse, both as somatic abnormalities in tumors [2] and as congenital syndrome. Constitutional deletion of 1p36 results in a recognizable syndromic pattern (1p36 deletion syndrome, OMIM #607872) considered due to the deletion of contiguous genes. The syndrome is characterized by a number of features, including MR of variable degree [3, 4]. The frequency of monosomy 1p36 is 1 in 5–10,000 births [4, 5]. Deletions occur equally in both females and males and no ethnicity differences have been registered [4, 5].

The first constitutional deletion of chromosome 1p36 was described in a child presenting with neuroblastoma (NB) [6]. Besides MR, features were reported, including a typical dysmorphism characterized by microcephaly, brachycephaly, prominent forehead, midface hypoplasia, pointed chin, deep-set eyes, flat nasal bridge, and low set or asymmetric ears with thickened helices; facial clefting was also described [7, 8]. Features also include vision and hearing problems, seizures and growth delay [9]. Occa-

sionally, hypothyroidism and heart defects were described [4]. Patients with redundant skin on the nape and neck [10], intestinal malrotation and annular pancreas [11], spinal stenosis [12], skin teleangiectasies and hyperpigmentation associated to polydactyly [13], and gastrointestinal problems [4] were also described.

Prenatal features of 1p36 deletion syndrome were described, including intrauterine growth retardation, and multiple congenital anomalies, especially of the brain, such as ventriculomegaly or hydrocephalus, cerebral atrophy, leukoencephalopathy, and abnormalities or agenesis of the corpus callosum [14]. Polymicrogyria, periventricular nodular heterotopia, and pachygyria were also described [15].

Deletions involving a smaller region, 1p36.3, were identified in 0.5–0.7% of isolated MR [16], suggesting that this might represent the critical region containing one or more genes contributing to the neurological manifestations.

Cytogenetics and Clinical Data

Deletion of the 1p36 region results from both interstitial and terminal deletions of variable size and different breakpoints, as characterized by overlapping BAC contigs spanning 10.5 Mb [17]. About 95% of the deletions arise *de novo*, 60% occurring on the maternally and 40% on the paternally derived chromosome [17]. Deletions vary from size 1.5 to 10 Mb, with common breakpoints located from 1p36.13 to 1p36.33 [18]. The great number of genes mapping in this region complicates the identification of candidate genes involved in specific features. Moreover, it was observed that the severity of the phenotype is only partially related to the extent of the deletion.

A premeiotic model for the generation of complex rearrangements in the 1p36 region, such as successive progression of breakage, fusion and bridging events, has been proposed [19]. As some of the identified breakpoints fall within repetitive DNA, these sequences might play a role in 1p36 deletions [4]. Therefore, segmental duplications, low copy repeats and short repetitive DNA sequence elements might mediate the generation and/or the stabilization of 1p36 terminal deletions [19]. Non-allelic recombination of homologous palindromic low copy repeats at 1p36 terminal might also result in complex rearrangements [20]. Copy number variation also seems to influence gene expression by disrupting coding sequences, perturbing long-range gene regulation or altering gene dosage [21].

Four classes of rearrangements were suggested for terminal deletions of 1p36: simple terminal truncations, interstitial deletions, derivative chromosomes and more complex rearrangements involving other chromosome pairs [22]. The observed phenotypes might be the result of gene disruption, but it was suggested that deletion of dosage-sensitive genes and inversion, perhaps resulting in a position effect of adjacent chromatin, might also contribute [23–25].

However, the above mechanisms do not fully describe complex rearrangements. Authors agree that more complex models or simultaneous occurrence of multiple events cannot be excluded. The precise localization of the breakpoints in subjects with apparently pure deletion might help to speculate about the role of single genes on the clinical features, but the variability of the deletion sizes do not completely explain the phenotypic variability among patients. Some authors suggested that the phenotype associated to monosomy 1p36 might be due to a position effect rather than a contiguous gene syndrome. In fact, 2 patients exhibiting similar clinical findings but non-overlapping deletions were described [26].

MR, developmental delay and/or learning disabilities are present in nearly 100% of 1p36 deletion syndrome-affected patients [4]. No correlation between the severity of the neurological impairment and the deletion size has been identified. Attempts to correlate patients' clinical features and outcome, deleted band size and candidate genes are still ongoing. A more precise refinement of the deletion breakpoint by using molecular cytogenetic techniques allowed the identification of smaller deleted regions.

An array comparative genomic hybridization on subjects affected with Smith-Magenis-like phenotype allowed the identification of a 44-year-old woman bearing the deletion of 1p36.32-33. The patient presented with short stature, obesity, prognathism, dental anomalies, brachydactyly, scoliosis, eye anomalies, chronic ear and respiratory infections, sleep and behavioral problems. The patient also presented with learning difficulties [27].

A group of patients ranging in age from 3 to 47 years, bearing 1p36.3 monosomy, presented with microcephaly, prominent forehead, deep set eyes, flat nasal bridge, mid-face hypoplasia, relative prognathism, brain anomalies, optic atrophy, ear anomalies, hearing loss and skeletal deformities [12]. These patients also had MR [12].

A female patient bearing a *de novo* deletion of 1p36.32-33 partially presenting with Prader-Willy syndrome features showed mild MR and behavioral problems [28].

Fig. 1. Chromosome 1 (human pair) showing the position of PLCH2, in the 1p36.32 region, and the flanking markers D1S243 and D1S468.

A female infant bearing a de novo unbalanced 1;18 translocation causing 1p36-pter monosomy presented with facial dysmorphism, virilization of the external genitalia and psychomotor retardation [29].

A 14-year-old male patient bearing a complex rearrangement of 1p36.3, including interstitial deletion of about 1 Mb at the 1p36.32 region, presented with congenital bilateral cataract, blepharophimosis, ptosis, cho-

anal atresia, deafness, short neck, skeletal anomalies, transient hypogammaglobulinemia, growth delay and MR with seizures and speech absence [30].

A female patient bearing 1p36.3 deletion presented with dysmorphism, NB and MR [31].

Although data remain controversial, MR seems to be constantly present in patients bearing 1p36.3 rearrangements. As a matter of fact, deletions of 1p36.3 are associ-

ated to neurodevelopmental impairment of variable degree, suggesting that this region might contain one or more genes associated with neurological features.

Notwithstanding the great number of cases, the complexity of the karyotypes, the variable size of pure deletions and the presence of numerous genes in the region of interest do not help to clarify the relationship with the clinical features. No candidate genes have been identified, although attempts have been made in order to obtain a genotype-phenotype correlation.

The proto-oncogene V-Ski Avian Sarcoma Viral Oncogene Homolog (SKI; OMIM *164780) is considered a likely candidate for the cleft lip/palate found in 17% of monosomy 1p36.3 patients [32].

A gene regulating the closure of craniofacial sutures (matrix metalloprotease 23 A, MMP23A; OMIM *603320; matrix metalloprotease 23 B; OMIM *603321) was mapped on chromosome 1p36.3 [33].

The potassium channel, voltage-gated, shaker-related subfamily, beta member 2 gene (KCNAB2; OMIM *601142) was deleted in the majority of seizures presenting patients with 1p36.3 deletion [34].

The human γ -aminobutyric acid A receptor δ -subunit gene (GABRD; OMIM *137163), located at 1p36.3, was suggested to be implicated in abnormal neurodevelopment [35]. By contrast, the finding of a patient bearing a complex rearrangement including 1p36.32 deletion in which GABRD locus was not involved suggested that the neurological features might be correlated to the anomalous expression of other genes [36]. The patient, a 9-year-old female, presented with dysmorphic features including a small mouth with heaped-up palate, small chin and small overfolded ears, straight eyebrows, fifth finger clinodactyly and short toes. A slightly similar dysmorphism was described in the mother and in 2 sisters, whose cytogenetic analyses did not highlight anomalies. The patient had learning disability, ear problems and hypermetropia. Prenatal scan had detected nuchal edema and ventriculomegaly. Developmental retardation such as delayed ability to sit, speech delay, and late walking at 22 months was also reported. Molecular cytogenetic analyses in the proband detected 1p36.32 deletion between 1.4 and 2 Mb long not involving the GABRD locus [36]. The authors suggested the existence of association among learning difficulties, developmental delay and 1p36.32 deletion. Further analyses detected deletion of the phosphoinositide (PI)-specific phospholipase C (PI-PLC) η 2 codifying gene (PLCH2; OMIM *612836), which maps on 1p36.32 [36].

Discussion

PI-PLC η 2 belongs to the PI-PLC family, enzymes triggering the activation of protein kinase C and the release of calcium ions [37]. PI-PLCs play a central role in PI metabolism by regulating their spatiotemporal balance [37]. As a response to different stimuli, the binding of a signaling molecule to a G-protein-linked receptor in the plasma membrane (Gq) activates PI-PLC. In less than a second, PI-PLC cleaves the polar head group of phosphatidylinositol biphosphate (PIP₂) into diacylglycerol (DAG) and inositol trisphosphate (IP₃), both crucial molecules in signal transduction. DAG is an activator of several types of effector proteins. IP₃ induces calcium release from the endoplasmic reticulum. The initial calcium increase induced by IP₃ propagates as a wave through the cytoplasm often followed by a series of spikes. Being a pleiotropic messenger, calcium is a crucial mediator in many cell and tissue activities, including modifications of gene expression triggered through changes of its concentration. In instance, various studies showed that increase in cytoplasmic calcium is required for progression through the cell cycle, for actin polymerization and subsequent cell migration [37].

PI-PLC isoforms are codified by different genes. Each isoform has more than one alternative splicing variant, probably having slightly different activity [37].

Thirteen mammalian PI-PLC isoforms have been identified, divided into six sub-families on the basis of amino acid sequence, domain structure and mechanism of recruitment in response to activation [37]. Isoforms within the sub-families share the greatest sequence similarity and common domain organization, also sharing a general regulatory mechanism specific to the family [37].

The most recently identified sub-family is PI-PLC η , existing in two isoforms, η 1 and η 2. Expression of PI-PLC η 2 is restricted to the central nervous system, occurs after birth and continues throughout the adult life. PI-PLC η 2 is expressed in primary cultured neurons but not in astrocytes [38]. PI-PLC η 2 is a key player in calcium mobilization and signaling in neurons [39]. In the brain, calcium is involved in complex events such as axon growth and retraction, growth cone guidance, synapse formation, and response to neurotransmitters [40].

In vivo, PI-PLC η 2 is abundantly expressed in hippocampal pyramidal cells and olfactory bulb [40], organs which contribute to memory circuits. PI-PLC η 2 is also expressed in the cerebral cortex, a region involved in memory, thinking and understanding language processes [40]. These data suggest that PI-PLC η 2 might be in-

volved in these functions. PI-PLC $\eta 2$ was also found abundant in mouse habenula and retina, which both contribute to regulate the circadian rhythm [41].

The gene PLCH2, which codifies for PI-PLC $\eta 2$ enzyme, maps on the 1p36.32 region. Remarkably, involvement of no other candidate gene located in the same region was confirmed to be associated to the MR/brain abnormalities described in the 1p36 deletion syndrome. In fact, molecular cytogenetic analysis performed in 1 patient presenting with MR and learning disability detected the presence of GABRD loci. These data suggested to exclude the involvement of GABRD in the neurological manifestations [36]. Moreover, the 1p36.32 region was found deleted in a small percentage of isolated MR [16], in a number of patients presenting with mild MR and/or behavioral problems and/or learning disability [12, 24–28] and in a patient presenting with MR and altered regulation of the circadian rhythm such as sleeping disorders [26]. These observations suggest that PLCH2 might be a putative candidate gene for the brain/mental alterations due to its role in the central nervous system. In fact, 1p36.32 deletion causes the absence of PI-PLC $\eta 2$ enzyme following the deletion of PLCH2 gene.

As PI-PLC $\eta 2$ is involved in the formation and maintenance of neuronal networks and memory circuits, its absence might imply impairment of these functions and subsequent abnormal neuronal and intellectual development.

Further studies are required to verify this hypothesis, experimentally analyzing the function of PI-PLC $\eta 2$ and verifying the presence of PLCH2 anomalies such as deletions/mutations in patients presenting with MR, both syndromic and isolated.

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Disclosure Statement

The author has no conflicts of interest to declare.

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