Delineation of the Clinical Phenotype Associated With
OPHN1 Mutations Based on the Clinical and
Neuropsychological Evaluation of Three Families

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Recent reports have demonstrated that mutations in the OPHN1 gene were responsible for a syndromic rather than non-specific mental retardation. Abnormalities of the posterior fossa with cerebellar hypoplasia have been demonstrated in all male patients reported to date. We report here a new family with X-linked mental retardation due to mutation in OPHN1 and present unpublished data about two families previously reported, concerning the facial and psychological phenotype of affected males and carrier females. Our study confirms that cerebellar hypoplasia is a hallmark of this syndrome. In addition, affected males display facial similarities that can help the diagnosis. Most carrier females have mild mental retardation and subtle facial changes.

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INTRODUCTION

The OPHN1 gene was identified through the cloning of a balanced X-12 translocation in a girl presenting with mental retardation [Billuart et al., 1998]. The same group reported a mutation in OPHN1 in a family with non-specific X-linked mental retardation (XLMR) (MRX60). Recently, we and another group demonstrated that OPHN1 gene mutations were in fact associated with cerebellar hypoplasia [Bergmann et al., 2003; Philip et al., 2003]. Subsequently, des Portes et al. [2004] reevaluated the phenotype of family MRX 60 and the girl presenting with the balanced X-12 translocation. They found that all affected patients had the same cerebellar abnormalities, confirming that OPHN1 mutations were responsible of syndromic, rather than non-specific XLMR. Besides anomalies of the posterior fossa, all male patients display early hypotonia, walking and speech delay, and sometimes seizures and strabismus.

We report here a new family with X-linked mental retardation due to mutation in OPHN1. In addition, we present unpublished data about two families previously reported [Philip et al., 2003], concerning the facial phenotype of affected males and carrier females.

CLINICAL DATA

The pedigrees of the three families are presented in Figure 1. Two families (A and B) were briefly reported in a previous paper [Philip et al., 2003]. Figure 2 shows unpublished facial
photographs of four affected males (2a, 2b, 2d, 2e, 2f) and one unaffected male (2c) of family A. Figure 3 presents the facial appearance of two carrier females from family A (3a, 3b). The only affected male of family B is shown on Figure 4.

Family C: Patient C-II 4 was first seen at age 10. He was referred to our center of medical genetics for diagnostic evaluation when his elder sister (C-II 2) asked for genetic counseling. He was born at term after an uneventful pregnancy. Birth weight (3,500 g) and length (50 cm) were in the normal range. Occipitofrontal circumference (OFC) was not recorded. Psychomotor development was delayed. Language was acquired at age 5. He developed strabismus requiring surgical correction at 8 years. Physical examination at age 10 showed facial dysmorphism with a long face, deep-set eyes, marked infraorbital creases, short philtrum, and large ears (Fig. 5a). HC was 55 cm (+1 SD). At 22 years he had severe mental retardation and abnormal behavior. Reading was not acquired.

Patient C-III 3 was born at term after an uneventful pregnancy. Birth weight was 3,100 g (50th centile for age), length 48 cm, and OFC 36.5 cm (90th centile). Generalized hypotonia and psychomotor delay were noted during the first month with a bad ocular contact and a strabismus. At 7 months, he was referred to our neuropediatrics unit for diagnostic advice. The facial appearance was dysmorphic, with prominent forehead, infraorbital creases, strabismus, upturned philtrum, and large ears (Fig. 5b). OFC was 44 cm (50th centile). Psychomotor delay was evident with no speech development. At 16 months,
he could sit alone with difficulties. He had generalized tonic-clonic seizures, requiring anticonvulsant therapy. No intention tremor nor ataxia were observed.

The two obligate carrier females showed subtle facial changes, which were reminiscent of those seen in females from family A (Fig. 3c,d).

Behavioral Assessment

A complete psychological assessment was performed for three male patients (A-II4, A-II5, and B-II4) and two female carriers (A-II2 and C-II2). The battery included the age-appropriate Wechsler Intelligence scales, WISC III [Wechsler, 1996] or WAIS III [Wechsler, 2000]. We used also the Kaufman ABC (K-ABC) [Kaufman and Kaufman, 1993], although the age of the patients was out of the norms, to allow a better description of their strengths and weaknesses.

Mental retardation was observed for all three male patients, with full scale IQs (FSIQ) ranging from 46 to 54. In each case, the Performance IQ (PIQ) was better than the Verbal IQ (VIQ). BI4 showed the highest IQ and the largest inter subtest variation (FSIQ = 54, VIQ = 46, PIQ = 68). The flat profiles of the other patients may be due to floor effect. This was confirmed with the analysis of the K-ABC scores. The patients had better results in Gestalt Closure (3/3), Spatial Memory (2/3), and Triangles (1/3) than in the other subtests, indicating a relative advantage in the visuo-spatial tests.

The two female carriers tested in our study, AI2 and CI2 had mild mental retardation, with FSIQ of 64 and 57, respectively. In both cases, the VIQ score was lower than the PIQ score (VIQ: 59 and 55; PIQ: 74 and 63, respectively), although the difference was not significant in AI2.

Neuroradiological Data

In the two families (A and B) already reported [Philip et al., 2003], brain imaging did show vermis hypoplasia and cystic dilatation of the cisterna magna with posterior dysplasia of the tentorium in all subjects. Supratentorially, mild to severe ventricular dilatation was seen, with a particular appearance of the frontal horns as a square shape of the ventricular wall.

In family C, brain anomalies consisted of underdeveloped frontal lobes in both cases, loss of brain volume with enlarged lateral ventricles, prominent subarachnoid spaces and a particular square shape of the frontal horns in C-III3. Cerebellar hypoplasia with a disorganized vermis was present in both cases with a retrocerebellar cyst in C-II4, and a large cisterna magna in C-III 3 (Fig. 6).

Molecular Analyses

For the selected patients, we sequenced each exon of the OPHNI gene. When a mutation was apparent on the sequence, we confirmed its presence by enzymatic restriction using either a naturally occurring restriction site or a modified oligonucleotide introducing a restriction site on the mutant allele only (data not shown). This test also allowed us to study the segregation of the mutation in the studied family (Fig. 1). The mutations in family A and B were already reported [Philip et al., 2003]. The mutation in family C is a deletion of two nucleotides at position 642 (numbering starting from the translation initiation codon). The presence of this mutation introduces a frame-shift after codon for threonine 214 which is subsequently followed by 34 alternative codons and a stop. The resulting protein, if it exists, would be predicted to have a length of 248 amino-acids instead of 802 for wild-type OPHNI.

DISCUSSION

Until recently, OPHNI gene was considered as the best example of a gene causing non-specific-mental retardation [Billuart et al., 1998]. The description of two sibs carrying a deletion of X chromosome encompassing the OPHNI and androgen receptor loci and presenting with mental retardation, seizures and cerebellar hypoplasia in addition to complete androgen insensitivity [Tentler et al., 1999], prompted our group and another to reconsider this gene in some families of syndromic X-linked mental retardation, including cerebellar hypoplasia. This study brings further evidence that OPHNI mutations are responsible for a distinct and recognizable phenotype. Neuroradiological findings constitutes the most specific symptom of OPHNI-related phenotype. The posterior fossa is involved in all cases. Cerebellar hypoplasia predominates at the level of the lower vermis. The involvement of cerebellar hemispheres is variable from enlarged cisterna magna to retrocerebellar cyst (and can lead to the appearance of a huge retrocerebellar cystic mass). Disorganization of the anterior vermis has also been reported [des Portes et al., 2004]. Supratentorially, there is a global reduction of the cerebral volume predominating in the frontal lobes which appear in some cases as underdeveloped lobes, and large lateral ventricles with a particular appearance of the frontal horns.

Following recent neurobehavioral and neuroimaging studies, the cerebellum emerges not only as a structure underlying the integration of motor responses, but also as a structure involved in specific cognitive tasks [Ciesielski et al., 1997]. Schmahmann and Sherman [1998] defined a clinical entity, the “cerebellar cognitive affective syndrome” (CCAS) characterized by: impairment of executive functions such as planning, set-shifting, verbal fluency, abstract reasoning and working memory; difficulties with spatial cognition including visual-spatial organization and memory; personality change with blunting of affect or disinhibited and inappropriate behavior; and language deficits. This CCAS manifests when the lateral hemispheres of the posterior cerebellum or the

Fig. 6. Brain MRI of patient C-III3, performed at 3 months of age. Axial (A) and coronal (B) T2 WI, sagittal inversion-recovery image (C). Note the enlarged cisterna magna (C), associated with cerebellar hypoplasia (A, B), and ventricular dilatation with square shape of the frontal horns (A). Also note the prominent subarachnoid spaces in the frontal regions and over the left hemisphere related to loss of volume with underdevelopment of the frontal lobes.
Our data, together with other reports from the literature [Bergmann et al., 2003; des Portes et al., 2004] confirm that OPHN1 mutations are associated with a specific phenotype. In case of familial XLMR, we suggest to restrict the screening of mutations in this large gene to families presenting with cerebellar hypoplasia. Moreover, the characteristic facial appearance and the presence of manifestations in transmitting females can suggest the diagnosis in apparently non-syndromic XLMR when no brain imaging is available. On the other hand, as the only patient affected in family B is the result of a de novo mutation, sporadic cases should be screened for OPHN1.

However, given the significant percentage of vermis hypoplasia in populations of mentally retarded patients [Soto-Ares et al., 2003], additional diagnostic criteria such as neuropsychological studies and facial changes are useful to select the patients for genetic screening in order to achieve the diagnosis of the OPHN1 gene mutations.

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REFERENCES


