Report

Mutation in Rab3 GTPase-Activating Protein (RAB3GAP) Noncatalytic Subunit in a Kindred with Martsolf Syndrome

Irene A. Aligianis,[1,2] Neil V. Morgan,[1] Marina Mione,[3,9] Colin A. Johnson,[1] Elisabeth Rosser,[5] Raoul C. Hennekam,[6] Gill Adams,[7] Richard C. Trembath,[8] Daniela T. Pilz,[10] Neil Stoodley,[11] Anthony T. Moore,[4] Steve Wilson,[3] and Eamonn R. Maher[1,2]

[1]Section of Medical and Molecular Genetics, University of Birmingham, and [2]West Midlands Regional Genetics Service, Birmingham Women's Hospital, Birmingham, United Kingdom; [3]Department of Anatomy and Developmental Biology and [4]Institute of Ophthalmology, University College London, [5]North East Thames Regional Genetics Service and [6]Clinical and Molecular Genetic Unit, Institute of Child Health, Great Ormond Street Hospital for Children, [7]Paediatric Service, Moorfields Eye Hospital, and [8]Division of Genetics and Molecular Medicine, King's College (Guy's Campus), London; [9]Instituto Fondazione Italiana per la Ricerca sul Cancro Oncologia Molecolare, Milan; [10]Institute of Medical Genetics, University Hospital of Wales, Cardiff; and [11]Department of Neuroradiology, Frenchay Hospital, Bristol, United Kingdom

We identified a homozygous missense mutation in the noncatalytic subunit (RAB3GAP2) of RAB3GAP that results in abnormal splicing in a family with congenital cataracts, hypogonadism, and mild mental retardation (Martsolf syndrome). Recently, mutations in the catalytic subunit of RAB3GAP (*RAB3GAP1*), a key regulator of calcium-mediated hormone and neurotransmitter exocytosis, were reported in Warburg micro syndrome, a severe neurodevelopmental condition with overlapping clinical features. RAB3GAP is a heterodimeric protein that consists of a catalytic subunit and a noncatalytic subunit encoded by *RAB3GAP1* and *RAB3GAP2*, respectively. We performed messenger RNA–expression studies of *RAB3GAP1* and *RAB3GAP2* orthologues in *Danio rerio* embryos and demonstrated that, whereas developmental expression of *rab3gap1* was generalized (similar to that reported elsewhere in mice), *rab3gap2* expression was restricted to the central nervous system. These findings are consistent with *RAB3GAP2* having a key role in neurodevelopment and may indicate that Warburg micro and Martsolf syndromes represent a spectrum of disorders. However, we did not detect *RAB3GAP2* mutations in patients with Warburg micro syndrome. These findings suggest that RAB3GAP dysregulation may result in a spectrum of phenotypes that range from Warburg micro syndrome to Martsolf syndrome.

Rab proteins (which belong to the Ras family of small G proteins) are prime regulators of vesicular membrane transport in both the exocytic and endocytic pathways. The active forms of Rab proteins have multiple functions in cargo selection and as scaffolds for the sequential assembly of effectors required for vesicle budding, cytoskeletal transport, and target membrane fusion (Takai et al. 2001; Zerial and McBride 2001). The four members of the Rab3 subfamily (Rab3A, Rab3B, Rab3C, and Rab3D) have been implicated in regulated exocytosis of neurotransmitters and hormones (Takai et al. 1996; Schluter et al. 2002; Li and Chin 2003; Sudhof 2004). The activity of Rab3 proteins is tightly regulated by RabGDI (GDP dissociation inhibitor), Rab3GEP, and RAB3GAP. The latter two determine the balance of active (GTP) to inactive (GDP) forms, and RAB3GAP specifically converts active Rab3-GTP to the inactive -GDP form (Fukui et al. 1997; Wada et al. 1997; Nagano et al. 1998). Rab3A is the most abundantly expressed Rab protein in the brain and is present in virtually all synapses. Through binding to its effector Rim, Rab3A has a critical role in the release of neurotransmitter vesicles (Li and Chin 2003; Sudhof 2004). Rab3A, Rab3B, and Rab3C are also expressed in endocrine tissues, and Rab3B is expressed at high levels in the anterior pituitary, where it has been implicated in gonadotrophin release (Tasaka et al. 1998; Schluter et al. 2002). Recently, we found germline-inactivating mutations in the catalytic subunit of Rab3GAP (*RAB3GAP1* [Ensembl accession number ENSG00000115839; GenBank accession number D31886]) in 12 of 18 kindreds with Warburg micro syndrome (MIM 600118) (Aligianis et al. 2005).

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Address for correspondence and reprints: Dr. Eamonn R. Maher, Section of Medical and Molecular Genetics, University of Birmingham, Institute of Biomedical Research, Birmingham B15 2TT, United Kingdom. E-mail: E.R.Maher@bham.ac.uk

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This severe autosomal recessive disorder is characterized by ocular defects (microphthalmos, microcornea, congenital cataracts, and optic atrophy) and neurodevelopmental ones (microcephaly, cortical gyral abnormalities such as pachygyria and polymicrogyria, hypoplasia of the corpus callosum, severe mental retardation, and spastic cerebral palsy) and hypothalamic hypogenitalism (Warburg et al. 1993; Rodriguez et al. 1999; Megarbane et al. 1999; Nassogne et al. 2000; Ainsworth et al. 2001; Derbent et al. 2004; Graham et al. 2004). Linkage to *RAB3GAP1* was excluded in some families without mutations, confirming locus heterogeneity. RAB3GAP is a heterodimeric complex consisting of a 130-kDa catalytic subunit, encoded by *RAB3GAP1* on chromosome 2q21.3, and a 150-kDa noncatalytic subunit (Fukui et al. 1997; Nagano et al. 1998), the gene for which—*RAB3GAP2* (Ensembl accession number ENSG00000118873; GenBank accession number AF004828)—is located on chromosome 1q41. Previously, we did not detect mutations in *RAB3GAP2* in six families with Warburg micro syndrome without *RAB3GAP1* mutations (Aligianis et al. 2005). However, to further investigate the potential role of *RAB3GAP2,* we (1) analyzed neurodevelopmental expression of *RAB3GAP1* and *RAB3GAP2* in a model organism and (2) undertook further *RAB3GAP2* mutation analysis in Warburg micro syndrome and in the related Martsolf syndrome (MIM 212720), which shares clinical features but is a milder disorder.

Expression of RAB3GAP1 and RAB3GAP2 orthologues in zebrafish.—To further investigate the potential neurodevelopmental role of *RAB3GAP2,* we compared the expression patterns of *RAB3GAP1* and *RAB3GAP2* orthologues in developing and adult zebrafish. Two ESTs showing similarities to *RAB3GAP1* and *RAB3GAP2* were identified through BLAST searches (zebrafish *rab3gap1* [GenBank accession number AI629291] and *rab3gap2* [GenBank accession number CF348222]), and riboprobes were prepared for in situ hybridization studies.

The zebrafish plasmids were linearized with *Sal*I and were transcribed with SP6-RNA polymerase, and riboprobes were purified using quick spin columns (Roche) and were stored in 50% formamide at −70°C. In situ hybridization studies on cryostat sections were performed as described elsewhere (Costagli et al. 2002). Sections were then mounted in glycerol. Images were captured with a Polaroid digital camera connected to a Nikon Optiphot-2 microscope, by use of ×4, ×10, and ×20 Plan-apo lenses. Digital images were stored as 1,600 ×1,200 pixels at a resolution of 300 dpi and were manually arranged, to form composite pictures, with Adobe Photoshop 5.5. *Danio rerio* aged 2 and 4 wk from the University College London fish facility were used in all experiments. Fish were raised at 28°C with a cycle of 14 h light and 10 h darkness. Animals were handled in accordance with U.K. and European Union regulations for laboratory animals. Animals were terminally anesthetized with 0.3% tricaine methane sulphonate (MS222 [Sigma]) and were fixed overnight in 4% paraformaldehyde in 0.1 M phosphate buffer (PB), pH 7.4. They were then rinsed in PB and were equilibrated in 10% and 20% sucrose in PB at 4°C for 48 h. Tissue was embedded in OCT compound (Agar), was frozen on dry ice, and was cut serially at 20 μm in coronal and sagittal planes. Sections were collected on Superfrost slides (BDH) and were stored at −70°C in sealed boxes until ready to use.

We found that, whereas *rab3gap1* was ubiquitously expressed during development, expression of *rab3gap2* started during larval stages (3–4 d postfertilization), and transcripts could be clearly detected only in the CNS (data not shown). The analysis of its expression pattern and the comparison with *rab3gap1* expression was conducted in 3–4-wk-old zebrafish (figs. 1 and 2). Both subunits were expressed in the CNS in areas with high neuronal density, and were excluded from the regions enriched with fiber tracts and neuropil. In the forebrain of 3–4-wk-old zebrafish, the transcripts of both *rab3gap* subunits were largely coexpressed in the dorsal (predominantly in the region marked as "Dl" in fig. 1*A* and 1*B*) and ventral ("Vv" in fig. 1*A* and 1*B*) telencephalon, in the posterior region of the dorsal telencephalon ("Dp" in fig. 1*C* and 1*D*), and in the preoptic area (POA) (fig. 1*C* and 1*D*). In addition, *rab3gap1* was strongly expressed throughout the hypothalamic region (fig. 1*E*), whereas *rab3gap2* expression in the hypothalamus was restricted to the ventral zone ("Hv" in fig. 1*F*) and the pituitary ("Pit" in fig. 1*F*). In the eye, *rab3gap1* (fig. 2*A*) was strongly expressed throughout the internal nuclear layer (INL) and was weakly expressed in the photoreceptors, whereas the expression of *rab3gap2* (fig. 2*B*) was confined to the remnants of the ciliary margin (CM), the proliferative zone of the retina.

Identification of a RAB3GAP2 *neurodevelopmental phenotype.*—To investigate the role of *RAB3GAP2* in human neurodevelopmental disease, we investigated families with clinical features overlapping those seen in Warburg micro syndrome, and we identified a homozygous germline *RAB3GAP2* mutation in all three children of a family with a Martsolf syndrome–like phenotype.

Clinical report.—The proband (subject IV-1; see fig. 3) was the first child of consanguineous Pakistani parents. He was born at 38 wk by cesarean section, with a birth weight of 1.87 kg, and was noted to have congenital cataracts, microphthalmia, micropenis, and cryptorchidism at birth. Bilateral cataract extraction was performed at age 6 wk. At age 5 mo, he was hypotonic, and his motor development was delayed. He gained head control at age ~1 year and sat at age 2 years, at which time a brain CT scan was reported as normal. He toe

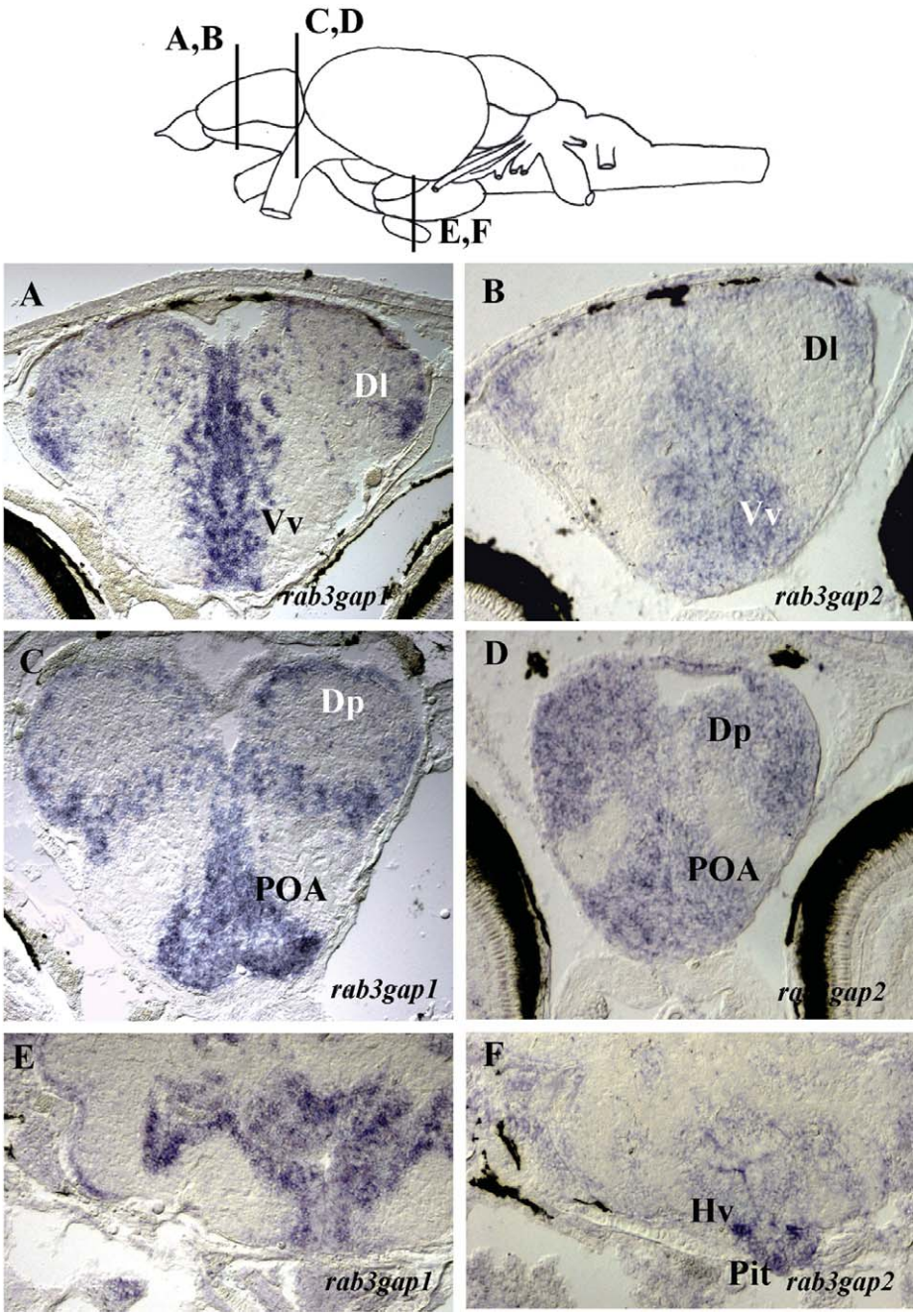

Figure 1 Brain expression patterns of *rab3gap1* and *rab3gap2* in zebrafish. In the forebrain of 3–4-wk-old zebrafish, the transcripts of both *rab3gap* subunits are largely coexpressed in the dorsal (predominantly in Dl [*A* and *B*]) and ventral (Vv [*A* and *B*]) telencephalon, in the posterior region of the dorsal telencephalon (Dp [*C* and *D*]), and in the POA (*C* and *D*). In addition, *rab3gap1* is strongly expressed throughout the hypothalamic region (*E*), whereas *rab3gap2* expression in the hypothalamus is restricted to the ventral zone (Hv [*F*]) and the pituitary (Pit [*F*]).

walked from age ~3.5 years, when spastic diplegia was noted. His first words were at age ~3 years. At age 11 years, he had mild learning difficulties, was microcephalic (occipitofrontal head circumference [OFC] 49 cm at age 8 years; <3rd percentile) and walked with a walker. He was bilingual and attended special school. Eye examination showed small pupils, aphakia, hypermetropia, and controlled secondary glaucoma. Visual acuity was poor (2/650 right eye [RVA] and 3/60 left eye [LVA]). There were no distinctive facial dysmorphisms.

Subject IV-3, the proband's sister, was born by normal delivery at 39 wk after an uncomplicated pregnancy.

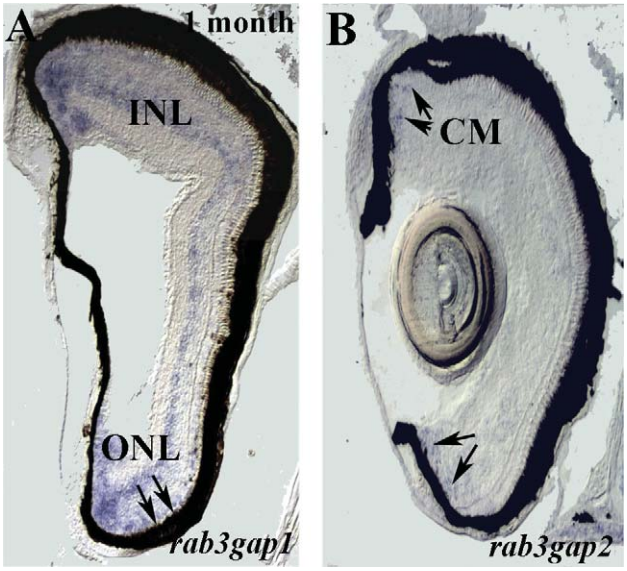

Figure 2 Eye expression patterns of *rab3gap1* and *rab3gap2* in zebrafish. In the eye, *rab3gap1* (*A*) is strongly expressed throughout the INL and in the CM and is only weakly expressed in the photoreceptors (*arrows*; outer nuclear layer [ONL]), whereas the expression of *rab3gap2* (*B*) is confined to the remnants of the CM, the proliferative zone of the retina.

Her birth weight was 3.060 kg, and her OFC was 34 cm (<10th percentile); she had dense bilateral cataracts and microphthalmia. After cataract surgery at age 4 mo, she developed secondary glaucoma, which required a vitrectomy and peripheral iridectomy. Prior to the glaucoma, her fundal examination was normal. Postsurgery visual acuity was reduced (RVA 6/38; LVA 6/120). Hypotonia was noted in infancy, and she later developed spastic diplegia. She had global developmental delay and sat at age 14 mo, stood with support at age 17 mo, walked with support at age 3 years, and developed speech at age 2 years. At age 5 years, she had moderate learning difficulties and required special schooling, but she was bilingual in English and Punjabi. Growth was normal (height and weight at the 50th percentile), but she had borderline microcephaly, with an OFC just >3rd percentile. She had a low anterior hairline and was hirsute, but she did not have any distinctive facial dysmorphisms.

Subject IV-2 was born, at term, with congenitally corrected transposition of the great vessels. His birth weight was 2.4 kg (50th percentile), and OFC was 33 cm (<10th percentile). He had micropenis and bilateral cryptorchidism, congenital cataracts, and microphthalmia. Left cataract removal was performed at age 2 mo. Immediately postoperatively, he suffered a cardiac arrest of unknown etiology, and, following resuscitation and artificial ventilation, he was found to have severe hypoxic ischemic encephalopathy with convulsions. His ischemic encephalopathy has been associated with profound global developmental delay and spastic quadriplegia. CT and magnetic resonance imaging (MRI) scans showed cerebral atrophy in a pattern consistent with hypoxic damage, and electroencephalogram showed poor background activity, with minimal variability and very little central activity. He was facially hirsute but did not have any dysmorphic facial features.

Molecular genetic analysis.—A 10-cM genomewide linkage scan was performed on DNA from all three affected individuals in this family, by use of the Research Genetics version 10 mapping panel, as described elsewhere (Aligianis et al. 2002, 2005). All exons and intron-exon boundaries were amplified by PCR and then were sequenced, by direct sequencing, using the ABI3730 capillary sequencer. The sequencing primers for *RAB3GAP1* and PCR conditions are included in table 1. Linkage to *RAB3GAP1* was excluded, but all three affected individuals were homozygous for a 16-cM region between markers *GATA124F08* and *D1S549* that contained the *RAB3GAP2* locus (fig. 3). Additional microsatellite markers flanking the noncatalytic subunit of *RAB3GAP2* (*D1S2880, D1S2641,* and *D1S2689*) were typed and confirmed homozygous-by-descent. We then proceeded to sequence the 36 exons and intron-exon boundaries of *RAB3GAP2* and detected a homozygous 3154G→T (Gly1051Cys) missense substitution in all three affected individuals (fig. 4*A*). Both parents were heterozygous for this substitution, and it was not found in the 270 ethnically matched control chromosomes. Since the substitution is adjacent to the exon 28 splice-donor site, RNA was obtained from lymphocytes from two of the affected children and their parents. Lymphocyte RNA revealed that this mutation resulted in two transcripts (fig. 4*B*). Sequencing of the cDNA synthesized from these transcripts showed that the splice-site mutation resulted in exon 28 skipping and a frameshift (fig. 4*C*). Sequencing analysis of DNA from another family with Martsolf syndrome, reported elsewhere (Hennekam et al. 1988), did not detect a mutation in *RAB3GAP2* or *RAB3GAP1,* and linkage analysis excluded linkage to both genes. Also, we did not detect a *RAB3GAP2* mutation in an additional two families with Warburg micro syndrome without *RAB3GAP1* mutations.

Germline mutations in *RAB3GAP2* have not been reported elsewhere. Although it has been shown that the noncatalytic subunit does not influence RAB3GAP

The figure is available in its entirety in the online edition of *The American Journal of Human Genetics.*

Figure 3 Pedigree of family and fine mapping for markers flanking the *RAB3GAP2* gene (which is located between 216712122 and 216834147 bp) on chromosome 1. The parents are in generation III, and the affected siblings are in generation IV: IV-1, IV-2, and IV-3.

Table 1

PCR Primers and Conditions Used for *RAB3GAP2* Sequencing

The table is available in its entirety in the online edition of *The American Journal of Human Genetics*.

catalytic activity, our findings suggest a critical role for *Rab3GAP2* in human development. The expression of *rab3gap2* during zebrafish embryogenesis is consistent with the neurodevelopmental phenotype of *RAB3GAP2* mutation in humans. Elsewhere, we found that, in mouse embryos, *Rab3gap1* showed a low level of general expression throughout the embryo from E10 to E12. In addition to this continued generalized expression, there was also prominent expression in a number of organ systems, including the CNS and peripheral nervous system, at E14.5 (Aligianis et al. 2005). Consistent with this, we found that *rab3gap1* is ubiquitously expressed during zebrafish development. However, an unexpected and intriguing finding was the observed differences between *rab3gap1* and *rab3gap2* expression patterns in developing zebrafish. Thus, *rab3gap2* expression was restricted to the CNS, which suggests that this dictates the localization of Rab3gap activity during embryogenesis and hence explains the developmental phenotype of Warburg micro syndrome despite ubiquitous *rab3gap1* expression. We note that hypothalamic hypogonadism is a feature of Warburg micro syndrome and that, in zebrafish, *rab3gap1* is strongly expressed throughout the hypothalamic region. In contrast, *rab3gap2* expression in the hypothalamus is restricted to the ventral zone and the pituitary. In the eye, *rab3gap1* was strongly expressed throughout the INL and in the photoreceptors, whereas *rab3gap2* expression was confined to the remnants of the CM. We note that, in fish, the retina continues to grow with the eye throughout the life of the animal, and new retinal cells are added at the CM from neural glial stem cells. Further comparative studies of *RAB3GAP1* and *RAB3GAP2* expression in mice and humans may provide further insights into the relationship between these expression patterns and the Warburg micro syndrome and Martsolf syndrome phenotypes.

The precise mechanisms whereby *RAB3GAP1* and *RAB3GAP2* mutations cause human disease is unclear. In Warburg micro syndrome, *RAB3GAP1* mutations are associated with microgenitalia that may result from hypothalamic hypogonadotropinism and disordered neurotransmitter vesicle release. Ocular and neurodevelopmental defects and functional deficits might result either from abnormal neurotransmitter vesicular transport and exocytosis and/or from abnormal neurotrophic vesicle release during human development. In total, we analyzed 26 families with Warburg micro syndrome and two families with Martsolf syndrome for mutations in *RAB3GAP1* and *RAB3GAP2*. In 18 of 26 families with Warburg micro syndrome, we identified *RAB3GAP1* mutations but no *RAB3GAP2* mutations, which confirms that Warburg micro syndrome is a heterogeneous condition. However, a homozygous *RAB3GAP2* missense mutation that resulted in aberrant splicing was identified in one family with Martsolf syndrome (three siblings), but no *RAB3GAP1* or *RAB3GAP2* mutations were found in our other Martsolf kindred (Aligianis et al. 2005). The *RAB3GAP2*-mutation phenotype was milder than that seen with *RAB3GAP1* mutations in Warburg micro syndrome. Martsolf syndrome was reported in 1978 (Martsolf et al. 1978) in two brothers of Polish-Jewish origin with severe mental retardation, cataracts, short stature, primary hypogonadism, and minor digital and cephalic abnormalities. Since then, there have been several case reports of children with congenital cataracts, mental retardation, and hypogonadism to which the eponym Martsolf syndrome has been attached. These have confirmed autosomal recessive inheritance and further delineated the condition's clinical features (table 2) (Sanchez et al. 1985; Hennekam et al. 1988; Strisciuglio et al. 1988; Harbord et al. 1989). The minor features that have been described as being part of the condition can include brachycephaly, lax finger joints, talipes valgus, a pouting mouth, maxillary retrusion, and slight hirsutism. Although facial dysmorphisms have been described, these are subtle, and Harbord et al. (1989) described a family with Martsolf syndrome that did not have any distinctive dysmorphic features (members were microcephalic, with small jaws and slight hirsutism). Martsolf syndrome has many features in common with Warburg micro syndrome, but the ocular and neurodevelopmental defects are less severe in Martsolf syndrome. At present, it is unclear whether the milder phenotype observed in our family with an *RAB3GAP2* mutation (compared with that observed for *RAB3GAP1* mutations causing Warburg micro syndrome) is because either (1) the p130 subunit is more critical than the p150 subunit for Rab3GAP function or (2) the "leaky" nature of the splicing defect caused by the *RAB3GAP2* mutation allowed some normal protein to be produced and so ameliorated the clinical phenotype.

Our findings have (1) demonstrated ocular and CNS expression specificity for *RABGAP2,* (2) demonstrated genetic heterogeneity in Martsolf syndrome phenotypes, (3) linked Warburg micro syndrome and Martsolf syn-

The figure is available in its entirety in the online edition of *The American Journal of Human Genetics*.

Figure 4 The 3154G→T mutation in *RAB3GAP2*. The legend is available in its entirety in the online edition of *The American Journal of Human Genetics*.

Table 2

A Comparison of the Clinical Features of Micro Syndrome, the Reported Martsolf Cases, and the Family Described in the Present Report

The table is available in its entirety in the online edition of *The American Journal of Human Genetics*.

drome phenotypes such that novel genes for one disorder may be considered as candidate genes for the other, and (4) expanded the phenotypic spectrum of Rab3GAP dysfunction. Further mutation analysis of *RAB3GAP1* and *RAB3GAP2* in neurodevelopmental disorders associated with Warburg micro/Martsolf syndrome–like ocular and gonadal defects will provide insights into the phenotypic consequences of Rab3GAP dysfunction in human disease.

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Web Resources

Accession numbers and URLs for data presented herein are as follows:

Ensembl, http://www.ensembl.org/ (for human *RAB3GAP1* [accession number ENSG00000115839]) and *RAB3GAP2* [accession number ENSG00000118873)

Genbank, http://www.ncbi.nlm.nih.gov/Genbank/ (for human *RAB3GAP1* [accession number D31886], human *RAB3GAP2* noncatalytic subunit [accession number AF004828], *rab3gap1* [accession number AI629291], and *rab3gap2* [accession number CF348222])

Online Mendelian Inheritance in Man (OMIM), http://ncbi.nlm.nih.gov/Omim/ (for Warburg micro syndrome and Martsolf syndrome)

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