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References

Affara NA, Chalmers IJ, Ferguson-Smith MA (1993) Analysis of the SRY gene in 22 sex-reversed XY females identifies four new point mutations in the conserved DNA binding domain. Hum Mol Genet 2:785–789

Epstein CJ (1986) The consequences of chromosome imbalance: principles, mechanisms, and model. Cambridge University Press, New York

Goodfellow PN, Lovell-Badge R (1993) SRY and sex determination in mammals. Ann Rev Genet 27:71–92

Hall JG, Sybert VP, Williamson RA (1982) Turner's syndrome. West J Med 137:32–34

Hawkins JR (1994) Sex determination. Hum Mol Genet 3: 1463–1467

Hawkins JR, Taylor A, Berta P, Levilliers J, Van der Auwera B, Goodfellow PN (1992*a*) Mutational analysis of SRY: nonsense and missense mutations in XY sex reversal. Hum Genet 88:471–474

Hawkins JR, Taylor A, Goodfellow PN, Migeon CJ, Smith KD, Berkovitz GD (1992*b*) Evidence for increased prevalence of *SRY* mutations in XY females with complete rather than partial gonadal dysgenesis. Am J Hum Genet 51: 979–984

Iida T, Nakahori Y, Komaki R, Mori E, Hayashi N, Tsutsumi O, Taketani Y, et al (1994) A novel nonsense mutation in the HMG box of the SRY gene in a patient with XY sex reversal. Hum Mol Genet 3:1437–1438

Jager RJ, Harley VR, Pfeiffer RA, Goodfellow PN, Scherer G (1992) A familial mutation in the testis-determining gene SRY shared by both sexes. Hum Genet 90:350–355

Lovell-Badge R, Robertson E (1990) XY female mice resulting from a heritable mutation in the primary testis-determining gene, Tdy. Development 109:635–646

McElreavy K, Vilain E, Abbas N, Costa JM, Souleyreau N, Kucheria K, Boucekkine C, et al (1992*a*) XY sex reversal associated with a deletion 5′ to the SRY "HMG box" in the testis-determining region. Proc Natl Acad Sci USA 89: 11016–11020

McElreavey KD, Vilain E, Boucekkine C, Vidaud M, Jaubert F, Richaud F, Fellous M (1992*b*) XY sex reversal associated with a nonsense mutation in SRY. Genomics 13:838–840

Munsterberg AE, Kitajewski J, Bumcrot DA, McMahon AP, Lassar AB (1995) Combinatorial signaling by Sonic hedgehog and Wnt family members induces myogenicbHLH gene expression in the somite. Genes Dev 9:2911–2922

Page LA, Beauregard LJ, Bode HH, Beitins IZ (1990) Hypothalamic-pituitary-ovarian function in menstruating women with Turner syndrome (45,X). Pediatr Res 28:514–517

Palmer CG, Reichmann A (1979) Chromosomal and clinical findings in 110 females with Turner syndrome. Hum Genet 35:35–49

Pear WS, Nolan GP, Scott ML, Baltimore D (1993) Production of high-titer helper-free retroviruses by transient transfection. Proc Natl Acad Sci USA 90:8392–8396

Poulat F, Soullier S, Goze C, Heitz F, Calas B, Berta P (1994) Description and functional implications of a novel mutation in the sex-determining gene SRY. Hum Mutat 3:200–204

Schmitt-Ney M, Thiele H, Kaltwaßer P, Bardoni B, Cisternino M, Scherer G (1995) Two novel SRY missense mutations reducing DNA binding identified in XY females and their mosaic fathers. Am J Hum Genet 56:862–869

Tajima T, Nakae J, Shinohara N, Fujieda K (1994) A novel mutation localized in the 3′ non-HMG box region of the SRY gene in 46,XY gonadal dysgenesis. Hum Mol Genet 3: 1187–1189

Zeng YT, Ren ZR, Zhang ML, Huang Y, Zeng FY, Huang SZ (1993) A new de novo mutation (A113T) in HMG box of the SRY gene leads to XY gonadal dysgenesis. J Med Genet 30:655–657

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Founder Effect, Seen in the British Population, of the 172 Peripherin/*RDS* Mutation—and Further Refinement of Genetic Positioning of the Peripherin/*RDS* Gene

To the Editor:

Peripherin/retinal degeneration slow (RDS) is a membrane-associated glycoprotein found in the outer segments of retinal rod and cone photoreceptor cells. It is thought to play a role in membrane structural stabilization, in conjunction with retinal outer segment membrane protein 1 (ROM1).

Mutations in the *RDS* gene give rise to retinal degenerations with a wide phenotypic spectrum. The majority of mutations result in macular dystrophies (reviewed in Keen and Inglehearn 1996). Specific mutations in the *RDS* gene may lead to a wide inter- and intrafamilial variability of phenotype, as seen in one family with retinitis pigmentosa, pattern dystrophy, and fundus flavimaculatus, in three different members with a deletion at codon 153/154. (Weleber et al. 1993)

Mutation analysis by heteroduplex and direct sequencing of PCR-amplified coding exons of the *RDS* gene was performed in 300 British patients with dominantly inherited macular dystrophies; 7.3% of this group had peripherin/*RDS* mutations, segregating with disease. One particular mutation accounted for 11 of

Table 1

Peripherin/RDS Mutations Carried by 10 Families That Do Not Have a 172 Mutation

Mutation Number	Mutation	Phenotype
1	220Arg→Trp	Pattern dystrophy
2	213Cys→Arg	Pattern dystrophy
3	234ins (1 bp)	Pattern dystrophy
4	258Tyr→stop	Pattern dystrophy[a]
5	210Pro→Arg	Pattern dystrophy
6	224ins (37 bp)	Adult vitelliform
7	140ins (1 bp)	Pattern dystrophy[b]
8	219Pro→Arg	Macular dystrophy
9	221Arg→Gln	Pattern dystrophy
10	87del (8 bp)	Pattern dystrophy

[a] Previously reported by Wells et al. (1993).
[b] Previously reported by Keen et al. (1994).

the 22 mutations found in the macular-dystrophy group. This change, identified as a C→T change at codon 172, results in an Arg→Trp change (hereafter designated "172Arg→Trp"). This amino acid is located in the second intradiskal loop of the protein. This loop is thought to be the most important for the functioning of the protein, stabilizing the photoreceptor discs through homophilic or heterophilic interactions across the intradiskal space, and associating covalently with ROM1.

The 172Arg→Trp mutation was found in 11 families (1 of these families has previously been reported by Wells et al. 1993). One additional family was found to have an 172Arg→Gln mutation segregating with disease (this family also has previously been reported by Wells et al. [1993]). The mutations carried by the other 10 families are given in table 1.

Mutations at codon 172 have previously been reported by Wroblewski et al. (1994) and Reig et al. (1995); Wroblewski et al. described three families, two with 172Arg→Trp mutations and one with a 172Arg→Gln mutation, all giving rise to macular dystrophy, and Reig et al. described one Spanish family with a 172Arg→Trp mutation causing central areolar choroidal dystrophy. Two of these latter three families are included in the present study. Phenotypic studies of patients with mutations at codon 172 have been performed by Nakazawa et al. (1995), Wada et al. (1995), and Piguet et al. (1996). All of these groups studied single families and noted that the patients showed a characteristic autosomal dominant macular phenotype. This would suggest that, in addition to the 172Arg→Trp mutation being due to a founder effect in the British population, mutations at codon 172 are not uncommon in causing macular dystrophy.

We investigated whether this preponderance of the mutation at codon 172 was the result of a founder effect or was due to a mutational hotspot in the gene. Haplotype analysis of these 12 families by means of six microsatellite repeat markers, distributed over a 20cM interval around the *RDS* locus, showed remarkable conservation of alleles between the families. Affected individuals share at least five of the alleles. The family with a 172Arg→Gln mutation was included as a control in the analysis (table 2). The frequencies of the alleles that constitute the disease haplotype in the British population are given in table 3. Both their low frequency and the absence of this haplotype, in its entirety, in any of our 50 controls (taken from the same population as that containing the macular-dystrophy families) would therefore support the conclusion that this mutation is due to a founder effect. All 11 families are therefore ancestrally related, with an initial mutation event occurring many generations ago.

Table 2

Ancestral Disease Haplotype Shared by 11 Families That Have the 172Arg→Trp Mutation in Peripherin/*RDS,* Compared with Ancestral Disease Haplotype of a Family That Has the 172Arg→Gln Mutation

	Haplotype in Families with 172Arg→Trp Mutation											Haplotype in Family with 172Arg→Gln Mutation
Marker	Family 1	Family 2	Family 3	Family 4	Family 5	Family 6	Family 7	Family 8	Family 9	Family 10	Family 11	
D6S258	3	3	3	3	3	6	6	6	6	2	2	4
D6S276	2	6	6	7	7	7	7	7	7	7	5	5
D6S291	1	1	1	1	1	1	1	1	1	1	1	2
D6S271	5	5	5	5	5	5	5	5	5	5	5	1
D6S282	3	3	3	3	3	3	3	3	3	3	3	3
D6S459	2	2	2	2	2	2	2	2	2	2	2	2
D6S294	5	5	5	5	4	4	5	5	5	5	5	3

Table 3

Allele Frequencies of Disease Haplotype in 50 Ethnically Matched Controls from the British Caucasian Population

Marker	Allele of Disease Haplotype	Frequency in Control Population
D6S258	6	.21
D6S276	7	.22
D6S291	1	.2
D6S271	5	.18
D6S282	3	.12
D6S459	2	.11
D6S294	5	.11

In addition, recombination events telomeric and centromeric to the *RDS* gene were observed in two separate individuals, both with the 172Arg→Trp mutation; therefore, these two individuals do not share the complete disease haplotype with the other individuals in these 11 families. This has enabled us to genetically localize the *RDS* gene to a 1.2-cM region between D6S1582 and D6S271 (table 4 and fig. 1).

We can therefore conclude that the most commonly occurring peripherin/*RDS* mutation in the British population is the 172Arg→Trp mutation, and this is consistent with the hypothesis of a founder effect. Prior to identification of the 172Arg→Trp mutation, these 11 families had been referred separately with different diagnoses, including cone dystrophy, macular dystrophy, and central areolar choroidal dystrophy. After review of the clinical data, it was clear that these families shared a common phenotype (S. M. Downes, unpublished data). All had significant loss of central vision, with a distinctive retinal appearance. This characteristic phenotype seen in these 11 families should alert the clinician

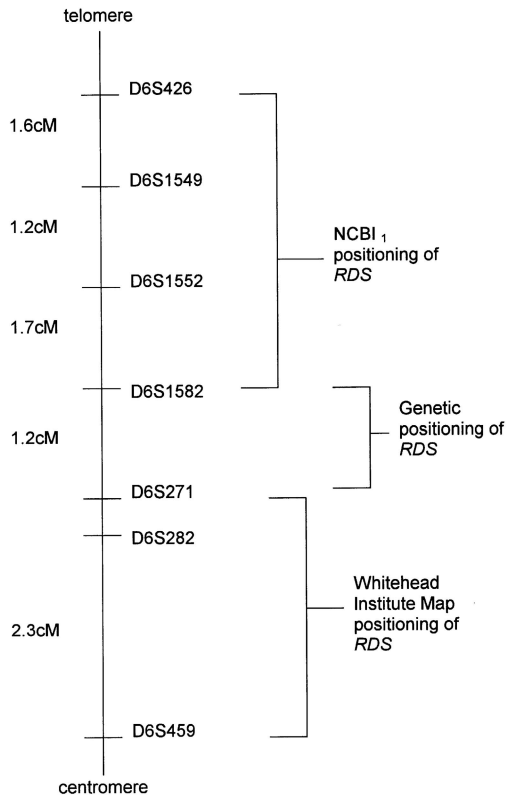

Figure 1 Genetic positioning of *RDS* on chromosome 6p, based on the recombinations seen in the families in the present study. (Information from the National Center for Biotechnology, National Institutes of Health)

Table 4

Recombination Events Enabling Genetic Positioning of *RDS*

Marker	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
D6S258	6	6	6	6	6	3	3
D6S276	7	7	7	7	7	7	6
D6S291	1	1	1	1	1	1	2
D6S1552	3	3	3	3	3	3	1
D6S1582	3	3	3	3	3	3	4
RDS							
D6S271	4	5	5	5	5	5	5
D6S282	2	3	3	3	3	3	3
D6S459	2	2	2	2	2	2	2
D6S294	4	4	4	5	5	5	5

NOTE.—Patients 1 and 2 are child and parent, respectively; patient 2 shows a recombination event centromeric to the *RDS* gene, whereas patient 7 shows a telomeric crossover. By means of the disease haplotype of the extended ancestral families, the *RDS* gene has been positioned between D6S1582 and D6S271, a distance of 1.2 cM (CEPH data).

to the possibility of a peripherin/RDS mutation at codon 172.

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References

Keen TJ, Inglehearn CF (1996) Mutations and polymorphisms in the human peripherin/RDS gene and their involvement in inherited retinal degeneration. Hum Mutat 8:297–303

Keen TJ, Inglehearn CF, Kim R, Bird AC, Bhattacharya S (1994) Retinal pattern dystrophy associated with a 4bp insertion at codon 140 in the RDS-peripherin gene. Hum Mol Genet 3:367–368

Nakazawa M, Wada Y, Tamai M (1995) Macular dystrophy associated with monogenic Arg172Trp mutation of the peripherin RDS gene in a Japanese family. Retina J Retinal Vitreous Dis 15:518–523

Piguet B, Heon E, Munier FL, Grounauer PA, Niemeyer G, Butler N, Schorderet DF, et al (1996) Full characterisation of the maculopathy associated with a Arg-172-Trp mutation in the RDS/peripherin gene. Ophthalmic Genet 17:175–186

Reig C, Serra A, Gean E, Vidal M, Arumi J, Delacalzada MD, Antich J, et al (1995) A point mutation in the RDS-peripherin gene in a Spanish family with central areolar dystrophy. Ophthalmic Genet 16(2):39–44

Wada Y, Nakazaawa M, Kikawa E, Chida Y, Shiono T, Tamai M (1995) Phenotypes of patients with autosomal dominant retinal degeneration associated with Tyr184Ser and Arg172Trp mutations of the peripherin/RDS gene. Invest Opthalmol Vis Sci 36:890

Weleber RG, Carr RE, Murphey WH, Sheffield VC, Stone EM (1993) Phenotypic variation including retinitis pigmentosa, pattern dystrophy, and fundus flavimaculatus in a single family with a deletion of codon 153 or 154 of the peripherin/*RDS* gene. Arch Ophthalmol 111:1531–1542

Wells J, Wroblewski J, Keen J, Inglehearn C, Jubb C, Eckstein A, Jay M, et al (1993) Mutations in the human retinal degeneration slow (RDS) gene can cause either retinitis pigmentosa or macular dystrophy. Nat Genet 3:213–218

Wroblewski JJ, Wells JA, Eckstein A, Fitzke F, Cubb C, Keen TJ, Inglehearn C, et al (1994) Macular dystrophy associated with mutations at codon 172 in the human retinal degeneration slow gene. Ophthalmology 101:12–22

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Cystic Fibrosis Transmembrane-Conductance Regulator Mutations among African Americans

To the Editor:

Cystic fibrosis (CF) is less common in African Americans than in Caucasians of northern European descent, with an estimated incidence of 1/15,300 (Hamosh et al., in press), although the severity of the disease is comparable across racial lines. Macek et al. (1997) recently reported in the *Journal* the identification of several CF transmembrane conductance regulator (CFTR) mutations of noteworthy prevalence in blacks. This information will help clinical laboratories to improve the sensitivity of CF mutation testing for African American patients.

We have identified a CFTR mutation in exon 7 in two unrelated individuals of African American descent who were not included in the study by Macek et al. The mutation, ΔF311, results in the loss of a phenylalanine residue in the fifth transmembrane domain of the CFTR protein. One of our patients is a 4-year-old African American female who presented, at age 7 mo, with hypochloremic metabolic alkalosis and dehydration. She was subsequently found to have sweat chloride values on two occasions of 75 and 83 mEq/liter. Her lung disease is mild, with only slight peribronchial thickening on chest x-ray, and she had *Staphylococcus aureus* in her sputum at age 3 years. She is considered pancreatic sufficient, on the basis of qualitative fecal fat analysis. Without pancreatic-enzyme supplementation, she has maintained a normal growth pattern, with height and weight at the 50th percentile. Mutation testing determined her genotype to be ΔF508/ΔF311. The ΔF311 allele was first detected by the appearance of a distinct heteroduplex pattern when PCR product encompassing exon 7 was electrophoresed on 10% polyacrylamide. The mutation was identified as ΔF311 by dideoxy sequencing. No additional ΔF311 alleles have been found after a screening of a further 271 patient samples (~8.5% African American) at the University of North Carolina in Chapel Hill.

The second patient was referred for genetic testing because of abnormal fetal ultrasound findings. The patient was a 25-year-old (G2 P0 SAB1) African American. An ultrasound performed at 17 wk gestation identified a fetus with a Dandy-Walker malformation and an echogenic bowel. Follow-up ultrasound at 18.2 wk gestation confirmed the CNS abnormalities and a grade II echogenic bowel. The patient was counseled with regard to the numerous causes of Dandy-Walker malformations, as well as with regard to the causes of echogenic bowel, including CF. The fetal karyotype was normal, but maternal and fetal CF testing identified a heteroduplex pattern identical to the ΔF311 heterozygote pos-