we speculated that the karyotypic abnormality could be implicated in the infant's disease.

Analyses of type I procollagen gene products synthesised by fibroblastic cells (#GM 09324, mother, and 09325, father; National Institute of General Medical Sciences Human Genetic Mutant Cell Repository, Coriell Institute for Medical Research, Camden, NJ, USA) cultured from biopsies of parental skin have now been completed. The techniques used are described elsewhere.2 The synthesis of procollagen I and II chains, the electrophoretic mobility of the chains, and the efficiency of secretion of the intact molecules were all normal. It seems unlikely that the karyotypic abnormality present in the mother and infant was responsible for the infant's disease.

De novo mutations in type I collagen genes are the most frequent cause of lethal osteogenesis imperfecta.2 While it is possible that the rearrangement involving 7p13q22 could predispose to mutations which alter COLIA2, we have no direct evidence that supports this hypothesis. The product of this couple's third pregnancy was normal by sonography at 18 weeks' gestational age and the infant was normal at birth.

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References


Genetic heterogeneity in Waardenburg's syndrome

Sir,

Since the original description, many associations1 and heterogeneity2 have been described in Waardenburg's syndrome (WS). Here we report a study of three sibs of consanguineous parents (uncle-niece) with features suggestive of WS associated with obstructive ileal lesions, inherited as autosomal recessive trait, which we believe may be a variant of WS.

A female neonate was noted at birth to have a white forelock, bilateral blue irides, white eyelashes, a malformed right pinna, and multiple hypopigmented patches of varying sizes on the face (fig 1), both upper arms, and forearms. The inner canthal distance was 22 mm, interpupillary distance 44 mm, and outer canthal distance 70 mm, all within normal limits. Over the next 12 hours, the baby

![Image 1](http://jmg.bmj.com/) White forelock, light coloured irides, and white eyelashes.

![Image 2](http://jmg.bmj.com/) Atretic ileal segments.
developed clinical features of lower intestinal obstruction and died of aspiration pneumonia before surgery could be performed. At necropsy, multiple ileal bands and a narrowed distal ileum were noted (fig. 2). Histopathological examination showed the presence of ganglion cells in the normal looking proximal ileum as well as in the distal narrowed segment.

One male and one female sib are alive and unaffected, two male sibs not known to be affected died, and two other sibs (both males) were seen earlier with exactly the same pigmentary disorders of the hair and skin who died in the neonatal period because of intestinal obstruction. One of the sibs had ileal atresia and died postoperatively and the other died at home. Histopathological examination was not done in either of these sibs. In none of our cases could deafness be ascertained because of age. Examination of both parents, three surviving grandparents, and several aunts and uncles did not show any features of WS.

Shah et al. from India described 12 newborns with pigmentary disorders of eye, hair, and skin with total intestinal aganglionosis, which they considered to be a variant of WS. The autosomal recessive inheritance noted in some of their cases has created interest in the heterogeneity of WS. Our present cases were clearly inherited as autosomal recessive traits and showed great similarity to the cases of Shah et al., except for the intestinal manifestations; the ileal lesions were only found in our cases. The association of Hirschsprung’s disease with classical WS is well known. Farndon and Bianchi described a Pakistani child of consanguineous parents with features of type I WS and total aganglionosis and considered this association to be a distinct clinical entity with autosomal recessive inheritance. An association between WS and atresic gastrointestinal lesions at the oesophageal and anal level was described earlier, but, to the best of our knowledge, no case of ileal atresia and band lesions has been described in association with either WS or its variants. Aganglionosis could be explained by a common pathological process of faulty neural crest migration. However, postduodenal atresia, like ileal atresia, is more often the consequence of a vascular accident resulting from torsion of a long mesenteric attachment that suspends the small intestine from the posterior abdominal wall. The complex development of the intramural neuro-regulatory system leaves ample room for considering various mechanisms that lead to the mal-development of the gut. Nutman et al. speculated that the gene in WS disrupts cell migration in the gastrointestinal tract, accounting for the various atretic lesions.

Waardenburg’s syndrome has been described in many populations throughout the world. However, the peculiar association of features suggestive of WS with total intestinal aganglionosis and ileal atresia and bands, manifesting in the neonatal period, with an autosomal recessive mode of inheritance, seems peculiar to the population of the Indian subcontinent.

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References

Current trends in the prevalence at birth of neural tube defects in Singapore

Sir,

A decline in the prevalence at birth of neural tube defects (NTD) has been reported in most western countries. The reasons for the decline are unknown as the aetiology of NTD is still not well understood. Increased public health awareness, more demand for genetic counselling, improved maternal environment, better prenatal care, and early detection and termination of pregnancy have been suggested to be responsible for the reduction of the prevalence at birth of NTD. On the other hand, some authors in the United Kingdom do not agree that prenatal screening and increase in the number of terminations of pregnancy are the main factors behind the recent decline. Furthermore, in the United States the decline started well before 1970 when screening was not widely available.

A retrospective study of NTD was conducted in our hospital to see if there was a change in the prevalence at birth of NTD in the last 12 years (1976 to 1987). In this period, as a general practice in this hospital, only mothers who had had an infant with