CLINICAL QUIZ (p265) ANSWER

What neonatal intestinal problem is our patient suffering from?

Hirschsprung's disease confirmed by rectal biopsy. Hirschsprung's disease (HSCR) is now considered to be a kind of neurocristopathy that characterised by complete absence of neuronal ganglion cells from any portion of the intestinal tract which may include distal rectum and a variable length of contiguous proximal intestine.[1] The most common type of HSCR is short-segment disease (80%) where aganglionosis is only found at the rectosigmoid colon. The prevalence of HSCR varies amongst ethnic groups. The incidence rates in Asian is around 2.8 in 10,000 newborns.[2]

The genetics of HSCR is complex. Chromosomal abnormalities are present in 12% of cases, and Down syndrome is the most common cause.[3] Clinically it is useful to classify patient with HSCR into isolated or syndromic forms. Syndromic forms are usually associated with neurodevelopmental problem, facial dysmorphism or other organ malformation and may be associated with syndromes like Down syndrome, Neurofibromatosis 1, Smith-Lemli-Opitz syndrome, as well as Mowat Wilson syndrome. Therefore early referral of syndromal form to clinical geneticist for assessment is recommended.

How is the diagnosis established in this patient?

Mowat Wilson syndrome or Hirschsprung Disease-Mental Retardation syndrome (MWS; OMIM# 235730). Our patient has typical facial features compatible with MWS, including widely spaced eyes, board separated eyebrows, low hanging columella, triangular chin, freshly uplifting ear lobes, long face with open-mouthed and happy expression. MWS was first described in 1998 by Mowat et al.[4] It is a rare multiple congenital malformation syndrome with prevalence of around 1 in 70,000 newborns.[5] It is characterised by distinctive facial features, moderate to severe grade intellectual disability and majority of patients, like our patient, have more than one major organ anomaly involving HSCR, heart, central nervous system or genitourinary system.[6]

What genetic test should be ordered for this patient?

***ZEB2* gene sequencing analysis**. *ZEB2* (OMIM# 605802) located in chromosome 2q22.3 is the only gene that associated with MWS. It encodes the zinc finger E-box binding homeobox 2 (ZEB2) protein. In couple with SMAD proteins[7] of TGF-β signaling pathway, ZEB2 is important for the normal function of neural crest. During embryogenesis, the migration of neural crest cells is essential for normal development of central nervous system, smooth muscle of gastrointestinal tract and cardiac muscle. This is why the dysfunction of *ZEB2* gene would lead to widespread phenotypes in MWS such as HSCR, congenital heart disease and neurodevelopmental delay.

In our patient, there is a *de novo* frameshift mutation that changes the 565th codon to termination codon. This is shown in Figure 2. Although this mutation has not been reported in literature before, the protein-truncating nature of

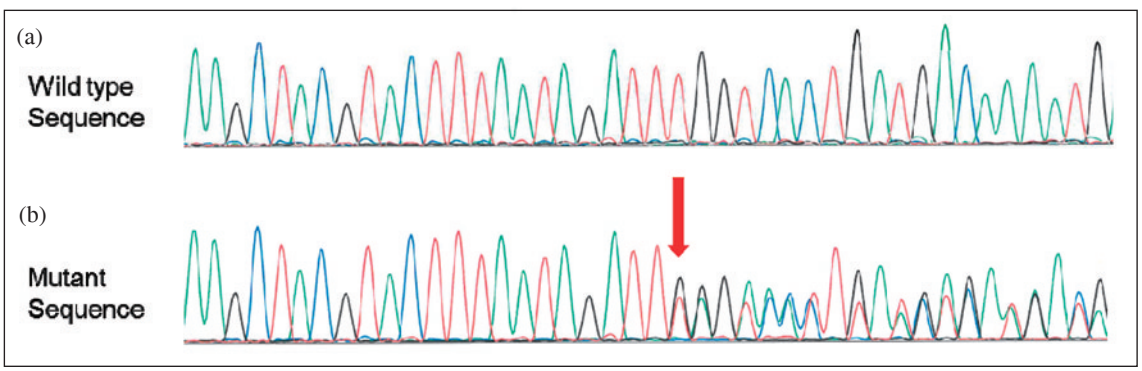

Figure 2 (a) Electropherogram of wild type (normal control) in exon 9 of *ZEB2* gene. (b) Electropherogram of our patient. There is a heterozygous deletion of 5 base pairs and insertion of 10 base pairs starting from the 1694th nucleotide (indicated by arrow) resulting in a frameshift change and premature protein termination. Reference sequence: *ZEB2* [NM_014795.3]

this mutation makes it very likely to be pathogenic, thus confirmed the diagnosis of MWS in our patient molecularly.

Sequencing analysis of *ZEB2* should be considered as first line genetic investigation of MWS since it detects mutations in approximately 80% of affected individuals.[8] If sequencing analysis fails to detect mutation, deletion/duplication analysis or fluorescent in situ hybridization for large gene deletions could be considered.

How to manage this patient and what is the recurrence risk for family members?

As MWS is a multiple congenital malformation syndrome, multidisciplinary approach with input from different specialties are essential, particularly focus on developmental training and seizure control. This should include: (1) early surgical intervention to treat HSCR and congenital heart anomalies if present, although some congenital heart disease can be treated with medication.[9] (2) Referral to a neurologist if symptoms of seizures are present. (3) Ophthalmological assessment and monitoring. (4) Rehabilitation specialist should be involved to provide support regarding the physical disability, i.e. how the disabilities affect everyday life, choice of aids and home adaptation. Education and speech therapy should begin in early life since there is a high risk of developmental delay in cognitive, language, motor and speech. (5) Although most cases arise *de novo* within the family the recurrence risk for subsequent siblings usually quoted as 1-2%, as the somatic or germline mosaicism in parents cannot be excluded. Proper genetic counselling should be provided.

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