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Severe Mycobacterial Infections in Two Chinese Kindreds with Interleukin-12 Receptor β 1 Deficiency

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IL-12 β 1 deficiency is characterized by selective susceptibility to weakly virulent organisms including *Mycobacterium bovis* BCG, non-tuberculous environmental mycobacteria and non-typhoidal salmonellosis. We report 3 cases of BCG disease and 1 case of disseminated tuberculosis in 2 pairs of Chinese siblings with IL-12R β 1 deficiency.

Family 1 (F1)

P1 is the second child of non-consanguineous couple. Her elder brother (P2), without prior BCG vaccination, died of disseminated tuberculosis at 6 years old. After routine BCG vaccination, P1 developed a tender, progressively enlarged left axillary mass at 1.5 months of age. Later the left cervical lymph nodes were also involved. Pus aspirated from the infected lymph nodes showed copious acid-fast bacilli. Response to standard anti-mycobacterial therapy was suboptimal with persistent ulceration and purulent discharge from the infected lymph nodes. At 23 months she died of refractory disseminated BCG and fulminant hepatic failure related to anti-mycobacterial drugs.

Family 2 (F2)

P3, was the second child of non-consanguineous parents. Her brother (P4) died of disseminated BCG at 1 year old and because of this, BCG vaccination was withheld in P3. At the age of 2 months, lymphocyte subsets and immunoglobulin pattern were normal and BCG was given to P3. Three months later, she presented with left axillary lymph node enlargement and discharge. She was treated with standard anti-mycobacterial drugs which brought her disease under control.

Diagnosis of *IL12RB1* mutation

P1 had a novel nonsense mutation 853C>T (Q285X) in exon 9. P3 had a known splice-site mutation 1791+2T>G. (Fig. 1) P2 and P4 died before genetic confirmation could be made. In both cases, the parents were heterozygous for the respective mutant allele and wild-type allele.

Discussion

To date at least 77 cases of IL12R β 1 deficiency were reported from various ethnic groups, among them 32 had BCG lymphadenopathy or disseminated BCG. In those without BCG disease, a known history of BCG vaccination was present in 14 patients [2, 5, 7-9]. If taking our index patients and their siblings into account, the percentage of BCG disease in BCG vaccinated, IL-12R β 1 deficient individuals is 71.4% (35 out of 49). The mortality attributable to disseminated BCG is 6/35 (17.1%).

P2 of Family 1, without history of BCG vaccination, died of disseminated tuberculosis. To date only 4 IL-12R β 1 deficient patients were identified to have culture-proven *M. tuberculosis* infections, including one from Morocco [3], one from Turkey [6] and a pair of siblings from Spain. [4] Majority of IL-12R β 1 deficient patients without history of tuberculosis originated from European countries where incidence of TB was low (3.9 – 13 / 100,000 population) compared with than that in Spain (25 / 100,000), Turkey (28 / 100,000) and Morocco (110 / 100,000). [10] Therefore, the apparently low incidence among IL-12R β 1 deficient individuals could be a matter of chance of exposure [1], and

IL12R β 1 deficiency may not be recognized in patients who have severe TB as the sole presentation. Given the endemicity of tuberculosis in China (incidence = 101 / 100,000) [10], it is possible that children with severe forms of tuberculosis may remain undiagnosed of defects in the IL-12-IFN- γ axis.

In view of a family history of disseminated BCG disease after vaccination (P4), basic immune workup had been done before BCG vaccination in P3 and was unrevealing. The diagnosis of IL-12RB1 deficiency was made only after she presented with BCG lymphadenopathy and investigations on the IL-12-IFN- γ axis was performed. As routine immunological workup is normal, patients with defects of the IL-12-IFN- γ axis can be identified only if such a diagnosis is contemplated. Clinicians should be alerted by family history of adverse BCG reaction and detailed investigation may be required before BCG vaccination can be safely given.

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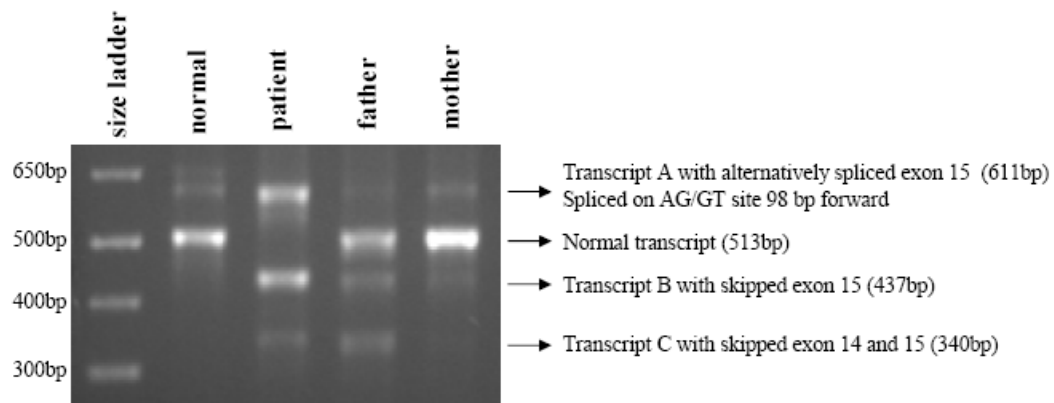


Figure 1. *IL12RB1* RT-PCR analysis in Patient 3 (P3). Agarose gel electrophoresis of RT-PCR products indicated that there is no primary mRNA transcript expressed in the patient's sample. Transcripts A is expressed in all samples. Transcripts B and C with skipped exon 15 and 14-15 respectively were expressed in patient's and parents' samples.