Molecular genetic approach to the diagnosis of a clinically equivocal retinopathy

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Background and Objectives: A pregnant female requested prenatal diagnosis for a congenital and complex eye disease segregating in her family. The three-generation pedigree of Romanian ethnic origin was suggestive of an X-linked inheritance, due to exclusively affected males and no father-to-son transmission. Affected individuals had bilateral optic nerve atrophy, microphthalmia, nystagmus, leukocoria, cataract, retinal detachment, eye tumors reported as retinoblastomas, moderate mental and motor retardation, and seizures. All efforts to obtain the detailed medical records of affected individuals were fruitless.

Methods: The disease locus was mapped utilizing 78 microsatellite markers that span the X-chromosome at ~2 Mb intervals, followed by candidate genes analysis and mutations detection by Sanger sequencing.

Results: Affected individuals share an ~10 Mb region between DXS1056 and GATA160B08 at Xp11.23-11.4. Candidate genes in this linkage interval included BCOR and NDP. Mutation screening identified a c.267C>A p.F89L mutation in the NDP gene in all affected individuals, previously described in a single unrelated Dutch family and speculated as causing Norrie disease.

Conclusions: In retrospect, clinical symptomatology fits the Norrie disease phenotype. The reported retinoblastomas were most likely pseudogliomas characteristic of Norrie disease. Detection of the c.C267A p.F89L mutation in a second unrelated family confirms the pathogenic nature of the mutation for Norrie disease.

Utilization of gene mapping through linkage analyses and candidate gene screening previously utilized exclusively for research applications, were applied at a diagnostic setting and were essential in deciphering the offending molecular defect and diagnosing a disease which due to lack of medical records and poor and misleading clinical history would have no chance of being diagnosed correctly. Clinical diagnosis and mutation identification were essential prerequisites for providing proper genetic counseling and prenatal diagnosis in this family.