Chromosomal inversions as a hidden disease-modifying factor

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The authors have declared that no conflict of interest exists.

Background and Aim

- Inversions are a type of chromosomal rearrangement involving two-point breakage of a given chromosome, followed by end-to-end rotation of the broken segment. Inversions can be pathogenic when the breakpoints disrupt a functionally important gene but otherwise exhibit to a minimal impact upon disease phenotypes.
- Given the recombination-suppressing nature of heterozygous inversions during meiosis, it can be hypothesized that they represent a possible phenotypic modifier of somatic recombination-associated diseases; however, human models verifying this hypothesis have not been reported.
- Somatic recombination has been linked to revertant mosaicism in genetic disorders. Ichthyosis with confetti type 1 (IWC-I), a rare autosomal dominant skin disorder caused by frameshift mutations in *KRT10*, is the most extreme example of “recombination-induced” revertant mosaicism.
- To address the phenotype-modifying effects of inversions in human diseases, we sought to analyze an IWC-I patient who harbors a heterozygous inversion.

Report of a case

Clinicopathological features

A 35-year-old Japanese man presented with severe ichthyosis since birth.

- Ichthyosiform erythroderma
- Low height/weight (151cm/38kg)
- Ectropion, eclabion, microtia
- Thoracic kyphosis, joint contractions

- Hyperkeratosis
- Parakeratosis
- Few keratohyalin granules
- Acanthosis

Mutation analysis

This splice-site mutation was already reported in patients with IWC-I, resulting in a single splice variant, r.1374_1381del (p.Ser458Argfs*120).

Identification of revertant spots

His ichthyotic skin was interrupted by ~60 whitish, greenish, or brownish patches without scales (arrowhead).

Diagnosis: IWC-I

Discussion

This case (35 yo) Previously reported case (35 yo)

p.Ser458Argfs*120 Hotz et al. Acta Derm Venereol, 2016.

“~60 revertant spots” “Thousands of revertant spots”

What makes the difference?

We hypothesized that inversions might underlie this intriguing phenomenon.

G-banded karyotyping and FISH

The patient and his father are heterozygous for inv(17)(p13q12). The inversion itself is non-pathogenic.

The breakpoint of the inversion is located in the RP11-141B22 locus.

Possible mechanism of fewer revertant spots in this case

Conclusions

- Heterozygous inversions are potential modifiers of human disease phenotypes.
- Somatic recombination is the major, and likely the exclusive mechanism of revertant mosaicism in IWC-I.