The American Journal of Human Genetics

Supplemental Data

Nonrecurrent 17p11.2p12 Rearrangement Events that Result in Two Concomitant Genomic Disorders: The *PMP22-RAI1* Contiguous Gene Duplication Syndrome

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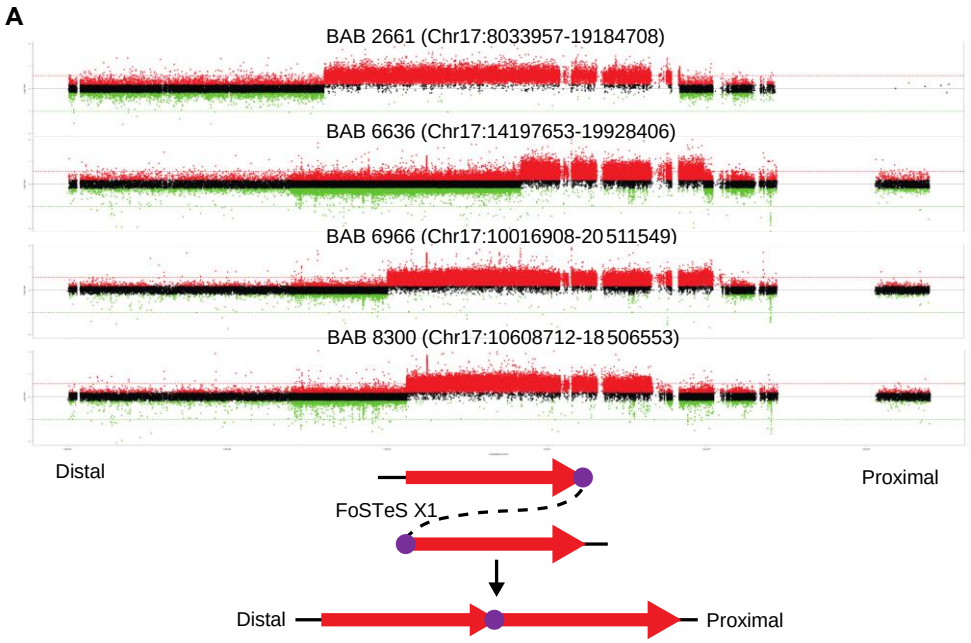
Supplemental Figures and Legends

Supplemental Figure 1



Mapped in Supplemental Reference 1:

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Dist GCCAAGTGCCCGGGATGAAGACCAAATACATATTTCACAATAGCAAACCCTTC
2661 GCCAAGTGCCCGGGATGAAGACCAATGTGTTAATTAGCTTGATTTAATCATT
Prox AAAAAATAAATAGATGAGGTGATGGATGTGTTAATTAGCTTGATTTAATCATT
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This study:

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Dist TTTTGGAAGTAGACTTCACTTTGTGCATAGCAATTGGCCATGACCCAGAATGA
6636 TTTTGGAAGTAGACTTCACTTTGTGCACAACAAAAAGTACAGCATCCATGAAT
Prox CAGACAGATATTCTCAAGCAGGTAAGACAACAAAAAGTACAGCATCCATGAAT

Dist TATTAGCTTCCAGGTTTTCCTTCATCAGGGAAGGTGACTACATCCACTTTCCT
6966 TATTAGCTTCCAGGTTTTCCTTCATCAGAAAACCACAGAGATCGCATTTTTCC
Prox GAAGTATAGAGGGGATACCTGTGTTCAGAAAACCACAGAGATCGCATTTTTCC

DIST TCATTTCATAGCACATAATTGTCTCCTGTTTTTTGTTTTCGTTTCTGTTTTTG
8300 TCATTTCATAGCACATAATTGTCTCCTAATTTCCGGTTCATTTTACTTGATGC
PROX TATGCTTATCATTTTGTACCATTCCCTAAATTCCGGTTCATTTTACTTGATGC
                          ▲
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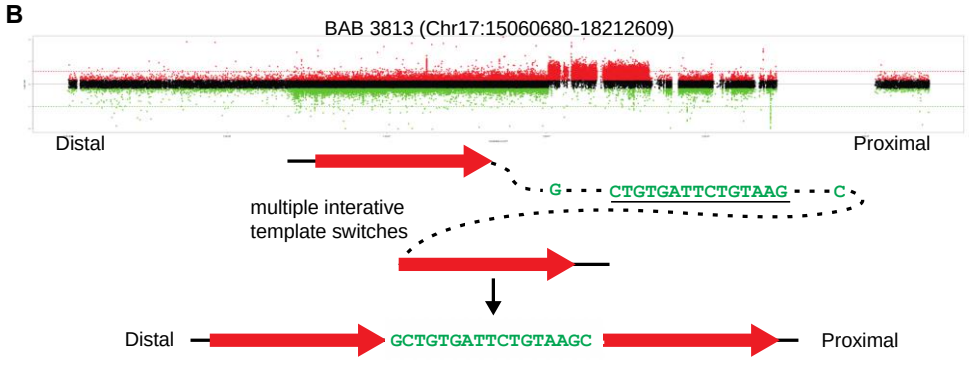


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Dist AAATGCTTTGGCCACTCTGGAAAATGTTGGTGTTTCCTCAAAAAGTTACAGAGTTATCA
3813 AAATGCTTTGGCCACTCTGGAGCTGTGATTCTGTAAGCCTGTAAGACCCACCTGGATCA
Prox TGGAGAAAATCCTCTGCTTTTAAAGGGCTCCTGTGATTCTGTAAGACCCACCTGGATCA
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Figure S1 – Subjects with simple duplications. A. The duplications and breakpoint junction sequences in BABs 2661 [1], 6966, 6636 and 8300. **B.** The duplication and breakpoint junction sequences in BAB 3813. Array CGH $\log_2$ ratio plot of each of the duplications is shown. The model of the iterative process generating the breakpoint junctions is shown underneath the array CGH plot(s) in **Figure S1A** and **S1B**. Genomic coordinates of the breakpoints are listed on top of each plot. Sequences with underline in black indicate the insertion and its potential origin. Red arrows/letters, duplicated segments or sequences from duplicated segments; purple dots/letters, microhomology; green letters, insertion. FoSTeS, fork stalling and template switching. The black triangle denotes a mismatching nucleotide that arises *de novo* close to the breakpoint junction in BAB 8300. This observation is consistent with the "error-prone" feature of the MMBIR model [2].

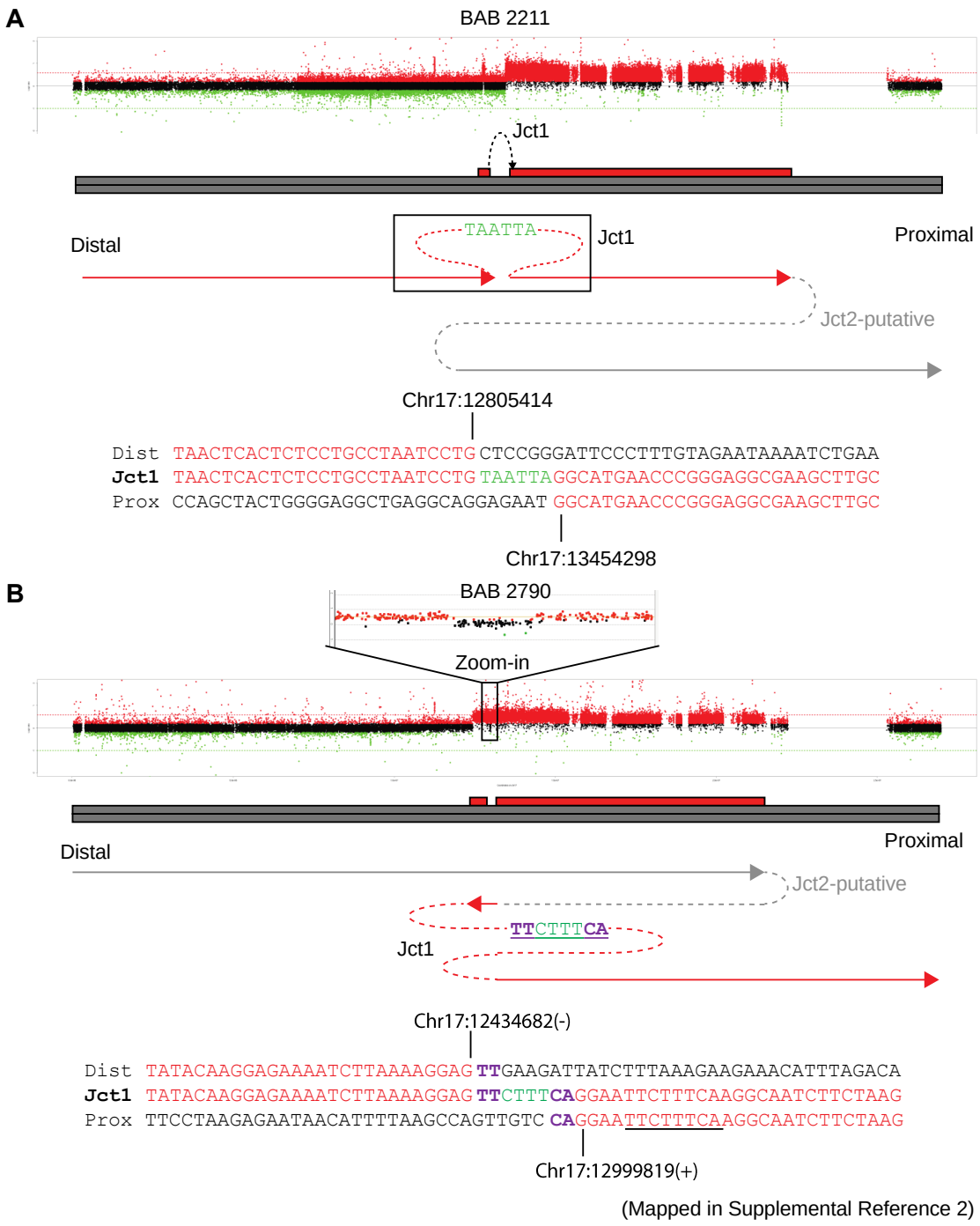

Figure S2 – Subjects with potential DUP-NML-DUP rearrangements. A. DUP-NML-DUP pattern identified in BAB 2211. Array CGH $\log_2$ ratio plot and the diagram indicating the dosage changes are shown. Breakpoint junction sequencing reveals Jct1, which connects the distal and proximal duplicated segments in direct orientation. Jct2-

putative is the unmapped, putative second breakpoint junction. Breakpoint sequence reveals a 6 bp (TAATTA) insertion. **B.** DUP-NML-DUP identified in BAB 2790. Array CGH $\log_2$ ratio plot and the diagram indicating the dosage changes are shown. Breakpoint junction sequencing reveals Jct1, which connects distal and proximal duplicated segments in an inverted orientation. Breakpoint sequence is previously reported [3]. Jct2-putative is the unmapped, putative second breakpoint junction. The model of the iterative process generating the breakpoint junctions is shown underneath the array CGH plot(s) in **Figure S2A** and **S2B**. The arrows and dashed lines in grey indicate the potential process involved in generating Jct2-putative. Sequences with black underline indicate the potential origin of the insertion at Jct1. Genomic coordinates of the breakpoint are annotated. Red arrows/letters, duplicated segments or sequences from duplicated segments; purple letters, microhomology; green letters, insertion.

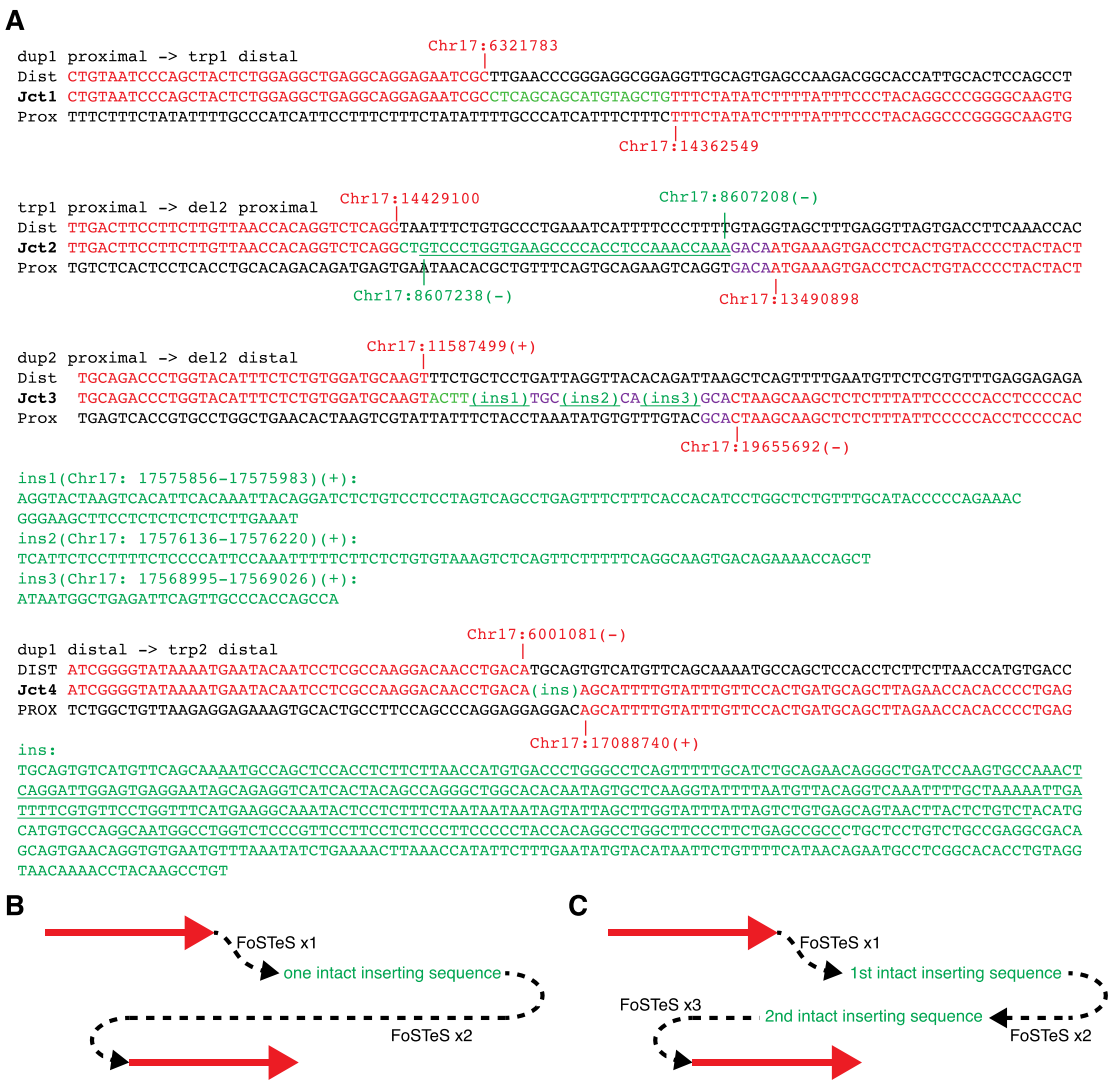

Figure S3 – Breakpoint junction sequences in BAB 2337. A. Breakpoint junction sequences mapped at Jct1, Jct2, Jct3 and Jct4. Letters in red, sequences from duplicated segments; green, insertion; purple, microhomology. Sequences in green with underlines are found with potential origin. The insertion in Jct4 can be partially mapped. **B.** A model showing the potential mechanism of FoSTeS to generate insertions at breakpoint junctions.

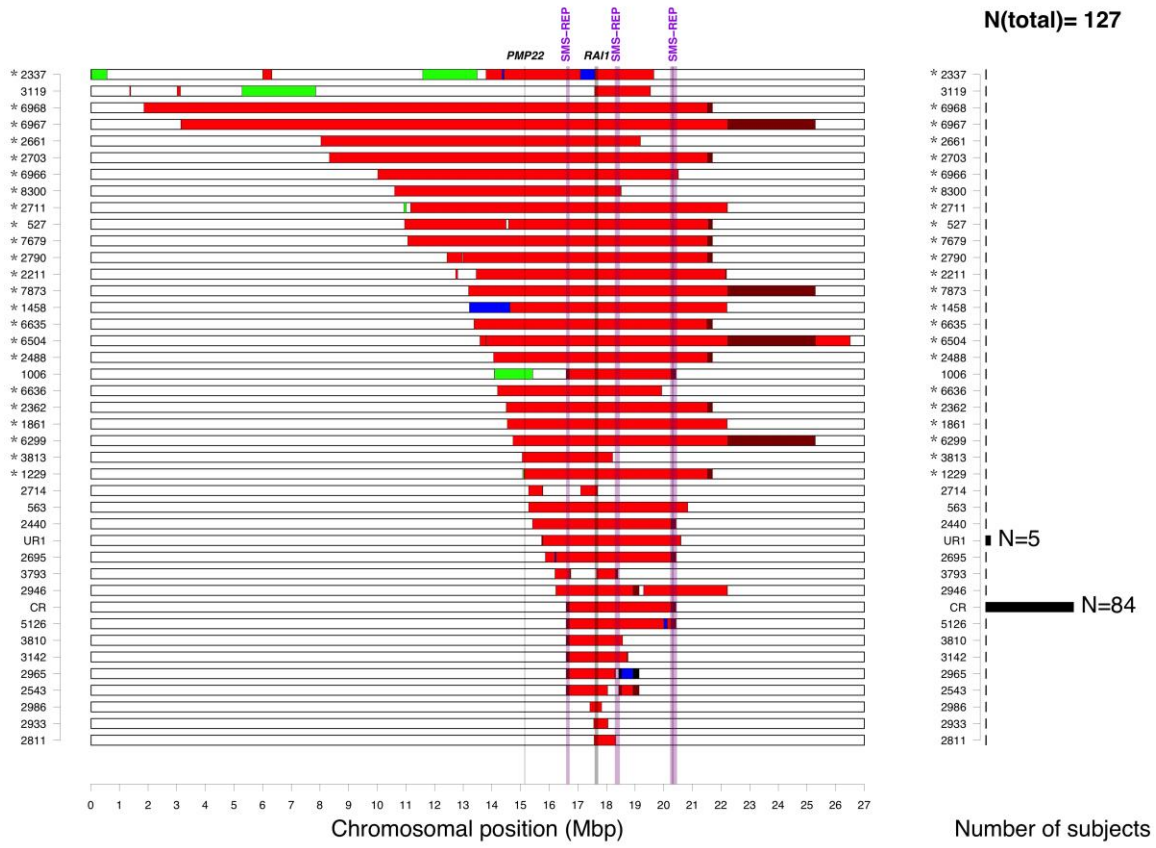

Figure S4 – Summary diagram of the genomic rearrangements encompassing *RAI1* identified in 17p in the entire cohort of 127 subjects. The genomic rearrangements identified in 127 subjects are shown. Subjects are identified with common recurrent PTLS duplication (N=84), uncommon recurrent duplication (N=5) and nonrecurrent duplications (N=38). The annotations in the figure are the same as **Figure 2**. The BAB numbers with asterisks harbor *PMP22-RAI1* duplications. The incidence counts of each genomic rearrangement are shown on the right panel. The incidence count is one for the rearrangements labeled with BAB numbers. CR, common recurrent PTLS duplication; UR1, uncommon recurrent PTLS duplication.

Supplemental Table

The Table S1 has been included as an Excel file.

Supplemental References

1. Zhang, F., Khajavi, M., Connolly, A.M., Towne, C.F., Batish, S.D., and Lupski, J.R. (2009). The DNA replication FoSTeS/MMBIR mechanism can generate genomic, genic and exonic complex rearrangements in humans. Nat. Genet. 41, 849-853.

2. Carvalho, C.M., Pehlivan, D., Ramocki, M.B., Fang, P., Alleva, B., Franco, L.M., Belmont, J.W., Hastings, P.J., and Lupski, J.R. (2013). Replicative mechanisms for CNV formation are error prone. Nat. Genet. 45, 1319-1326.

3. Zhang, F., Potocki, L., Sampson, J.B., Liu, P., Sanchez-Valle, A., Robbins-Furman, P., Navarro, A.D., Wheeler, P.G., Spence, J.E., Brasington, C.K., et al. (2010). Identification of uncommon recurrent Potocki-Lupski syndrome-associated duplications and the distribution of rearrangement types and mechanisms in PTLS. Am. J. Hum. Genet. 86, 462-470.