1. Proband, a 50 years old man with sigmoid cancer, was counselled regarding Lynch syndrome suspicion. His younger brother (48) had a surgery for „gut cancer“ one year ago, his older sister (53) is healthy. Proband´s father died at 60 because of stomach cancer. Proband´s brother (75) suffers from asthma. his daughter (44) is healthy. Proband´s paternal grandmother died at 65 because of „womb cancer“. Since Lynch syndrome can be caused by mutation of several different genes, massively parallel sequencing of proband´s DNA was employed to confirm the diagnosis

   Lynch syndrome is a familial AD inherited susceptibility to cancer, especially colorectal, endometrial, less often gastric, liver and gall bladder, ovary, prostate and several others. Note that the cancer itself is not heritable, only the risk of developing it. – refer to practicals/lectures from tumor genetics

   a. **In a list of genetic variants that were identified by NGS, find the variant that is most likely the cause of the proband´s disease:**

variant number	Gene	chr	HGVSc (cDNA level)	HGVSp (protein level) or variant localization in a noncoding sequence	dbSNP ID	genotype	cover-age	alterna-tive allele cover-age	population frequency of alternative allele
1	gene1	3	NM_000249.3: c.9C>G	NP_000240.1: (p.Phe3Leu)	rs779759678	het	1522	761	0.002
2	gene1	3	NM_000249.3: c.67G>T	NP_000240.1: p.Glu23*	rs63750823	het	395	183	0.00002
3	gene1	3	NM_000249.3: c.1039-78A>G	intron 11	rs11129748	het	1650	879	0.345
4	gene2	2	NM_000251.2: c.1662-65G>A	intron 10	rs140439728	het	771	361	<0.00002
6	gene3	2	NM_000179.2: c.116G>A	NP_000170.1: p.Gly39Glu	rs1042821	het	2161	1023	0.2188
7	gene3	2	NM_000179.2: c.3646+35_3646+38delATCT	intron 7 (+29delCTAT)	rs2234731	het	1313	680	0.7
8	gene3	2	NM_000179.2: c.642C>T	NP_000170.1: p.Tyr214Tyr	rs1800937	het	1886	976	0.1053
9	gene3	2	NM_000179.2: c.540T>C	NP_000170.1: p.Asp180Asp	rs1800935	homo	2842	2836	0.2855

   b. **Which variant(s) would you confirm by Sanger sequencing?**

   c. **Which variant cosegregates with the disease in the family?**

Worked out by: …… Group:…… Checked by:……

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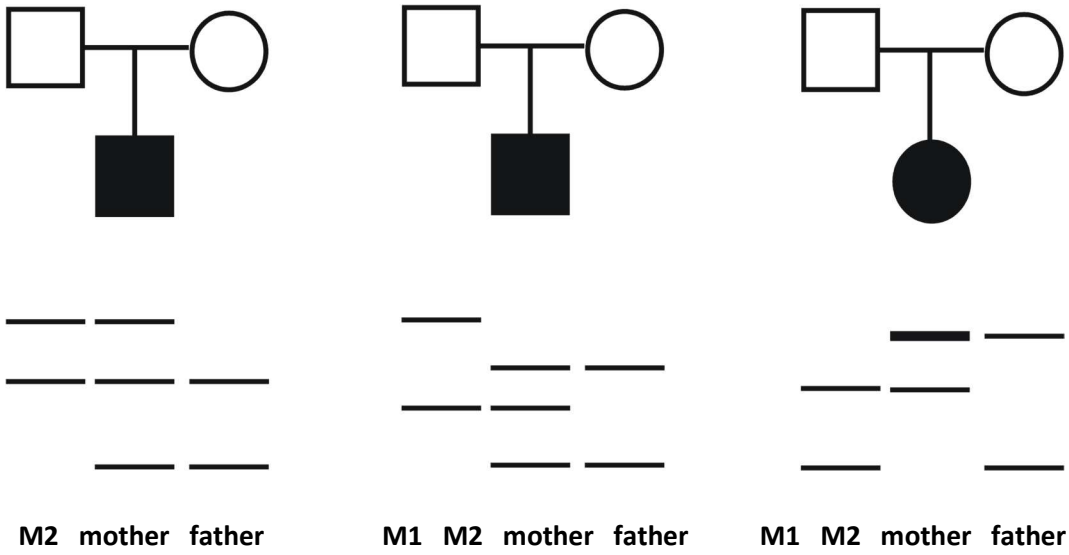
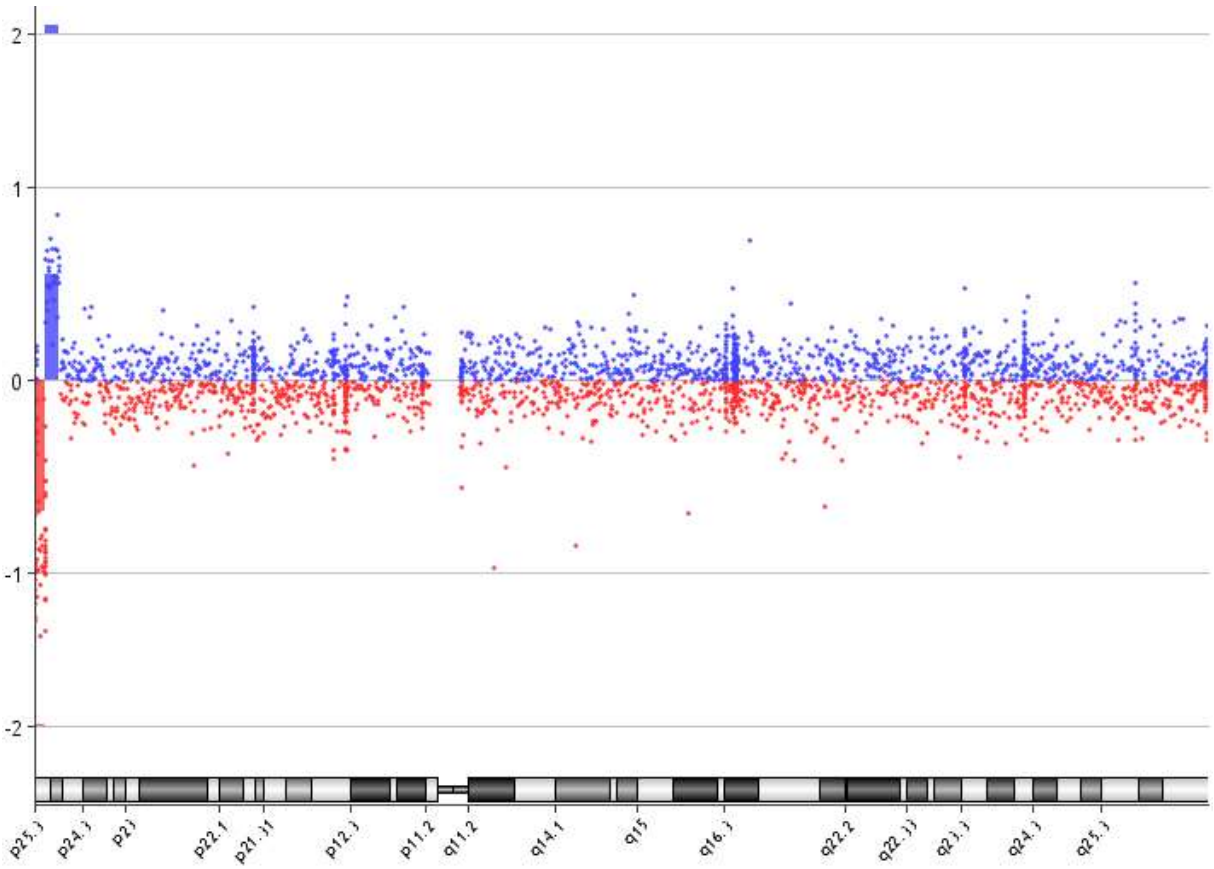
2. **From which parent the affected child inherited an extra chromosome 21; in which meiotic division nondisjunction occurred?**

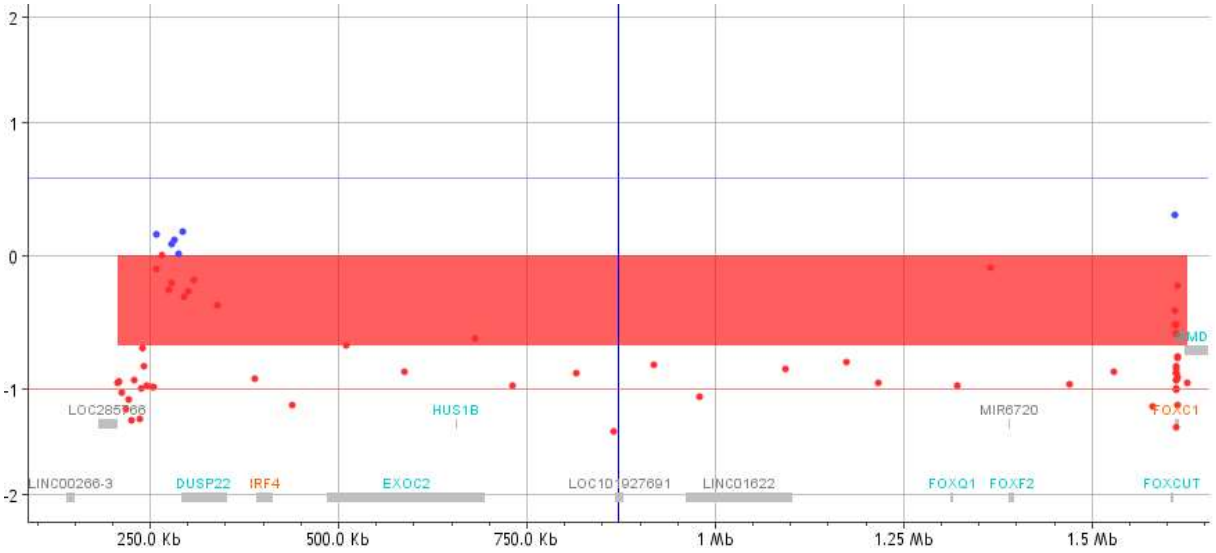


3. Proband is a 30 year old man seeking preconception counselling. He suffers from bilateral glaucoma and hypoplastic iris. He has hypoplastic maxilla. A peculiar symptom is excessive skin bulging from the umbilicus. In the past, plastic surgery was considered because of possible risk of umbilical hernia.

   The proband underwent ArrayCGH examination:



detail of the underrepresented region in the subtelomeric segment of chromosome 6:



a. Which gene from the region can be possibly linked to the patient´s symptoms?

Genes in the region: *LOC285766, HUS1B, miR6720, FOXC1; DUSP22, IRF4, EXOC2, LOC101927691, LINC01622, FOXQ1, FOXF2, FOXCUT*

b. What syndrome is associated with mutation in this gene?

c. What is the risk of transmission of the disorder to offspring?

Worked out by: …… Group:…… Checked by:……

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