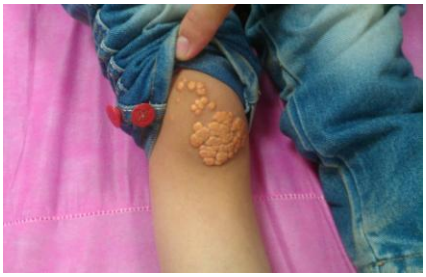
Unit IV – Problem 3 – Genetics: Familial Hypercholesterolemia



- Autosomal dominant familial hypercholesterolemia (FH) is an important cause of heart disease (5% of cases of MIs in patients younger than 60 years of age) → because plasma cholesterol levels are approximately twice as high as normal resulting in accelerated atherosclerosis and xanthomas (see the image: deposition of cholesterol in skin and tendons).
- 1:500 persons is a heterozygote for (FH) while 1:1,000,000 births is homozygous for (FH) → homozygotes are much more severely affected experiencing myocardial infarctions before 20 years of age (without treatment, most of these patient will die before the age of 30 years.
- Cholesterol is carried primarily by low-density-lipoprotein (LDL). In a process known as endocytosis, LDL-bound cholesterol is taken into the cell via LDL receptors on the cell's surface. (FH) is caused by a reduction in the number of functional LDL receptors on cell surfaces. Because the individual lacks the normal number of LDL receptors, cellular cholesterol levels increase.
- The LDL receptor gene is located on chromosome 19 and the mutations in this gene can be grouped into five broad classes:
  - **Class-I mutations**: no detectable protein product. Therefore, heterozygotes would produce only half the normal number of LDL receptors.
  - **Class-II mutations**: LDL receptor is produced but it cannot leave the endoplasmic reticulum and eventually will be degraded.
  - **Class-III mutations**: LDL receptor is produced and will migrate to cell surface but is unable to bind to LDL.
  - **Class-IV mutations**: LDL receptor is produced but cannot carry LDL into the cell.
  - **Class-V mutations**: producing LDL receptor that cannot dissociate from LDL particle after entry into the cell. The receptor cannot return to the cell surface and will be degraded.
- Dietary reduction of cholesterol (primarily through reduced intake of saturated fat) has only modest effects on cholesterol levels in (FH) heterozygotes because cholesterol is reabsorbed into the gut and then recycled through the liver (where most cholesterol synthesis takes place), serum cholesterol levels can be reduced by the administration of bile-acid absorbing resins (which is enhancing excretion of cholesterol). Therefore, liver cells will form additional LDL receptors which will lower circulating cholesterol levels. This treatment is much more effective when combined with one of the statins (which reduce cholesterol synthesis by blocking the enzyme HMG-CoA reductase → decreased synthesis leads to further production of LDL receptors).